Bladder cancer
Diagnosis and clinical management
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EDITED BY

**Seth P. Lerner, MD, FACS**
Professor and Beth and Dave Swalm Chair in Urologic Oncology
Department of Urology
Baylor College of Medicine
Houston, TX, USA

**Mark P. Schoenberg, MD**
Professor and Chair
Department of Urology
Montefiore Medical Center and Albert Einstein College of Medicine
Bronx, NY, USA

**Cora N. Sternberg, MD, FACP**
Professor and Chair
Department of Oncology
San Camillo Forlanini Hospital
Rome, Italy

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List of contributors

Hikmat Al-Ahmadi MD
Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Andrea B. Apolo MD
Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Jessie L.S. Au PharmD, PhD
Chief Scientific Officer, Optimum Therapeutics, LLC, San Diego, CA, USA; Henry D & Ida Mosier Chair of Pharmaceutical Sciences, University of Oklahoma, Oklahoma City, OK, USA; Adjunct Professor of Surgery, Medical University of South Carolina, Charleston, SC, USA; Adjunct Professor of Medicine, Taipei Medical University, Taiwan; Distinguished University Professor Emeritus, The Ohio State University, Columbus, OH, USA

Dean F. Bajorin MD
Weill Cornell Medical College, New York, NY, USA

Rick Bangs MD, MS
BCAN, SWOG, and NCI Patient Advocate, Rochester Hills, MI, USA

Joaquim Bellmunt MD
Bladder Cancer Center, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA, USA; University Hospital del Mar-IMIM, Barcelona, Spain

Laura A. Bertrand MD
Department of Urology, University of Iowa, Iowa City, IA, USA

Bernard H. Bochner MD
Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Lior Z. Braunstein MD
Harvard Radiation Oncology Program, Boston, MA, USA

Fabio Calabró MD
Department of Medical Oncology, San Camillo Forlanini Hospitals, Rome, Italy

Eugene K. Cha
Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Kevin Chan MD
Division of Urology and Urologic Oncology, City of Hope National Medical Center, Duarte, CA, USA

G. John Chen
Division of Health Services Research, University of Kansas School of Medicine, Kansas City, KS, USA

Guido Dalbagni MD
Attending Surgeon, Department of Urology, Memorial Sloan-Kettering Cancer Center, and Professor of Urology, Weill Cornell Medical College, New York, NY, USA

Siamak Daneshmand MD
USC Institute of Urology, USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Maria De Santis MD
Ludwig Boltzmann Institute for Applied Cancer Research (LBI-ACR VIEenna) and Applied Cancer Research – Institution for Translational Oncology Vienna (ACR-ITR VIEenna) – KFJ Hospital, Vienna, Austria

Scott Delacroix, Jr MD
Assistant Professor, Department of Urology, Louisiana State University School of Medicine, New Orleans, LA, USA

Colin P.N. Dinney MD
Professor, Department of Urology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Jason A. Efstathiou MD
Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

André P. Fay MD
Bladder Cancer Center, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA, USA
Margit Fisch MD
Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Thomas W. Flaig MD
Department of Medicine, Division of Medical Oncology, University of Colorado Denver, and University of Colorado Cancer Center, Aurora, CO, USA

Georgios Gakis
Department of Urology, University Hospital Tübingen, Tübingen, Germany

Matthew D. Galsky MD
Associate Professor of Medicine; Director of Genitourinary Medical Oncology, Icahn School of Medicine at Mount Sinai, and the Tisch Cancer Institute, New York, NY, USA

Nilay M. Gandhi MD
James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD, USA

J.M. Gaya MD
Department of Urological Oncology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain

Scott M. Gilbert MD MS
Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Heather Honoré Goltz
College of Public Service, University of Houston-Downtown, and Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

John L. Gore
Department of Urology, University of Washington, Seattle, WA, USA

Ahmed Haddad MD
Department of Urology, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Noah M. Hahn MD
Associate Professor of Medicine, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, USA

Donna E. Hansel MD, PhD
Professor, Department of Pathology; Chief, Division of Anatomic Pathology, University of California, San Diego, La Jolla, CA, USA

Harry W. Herr MD
Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Gopa Iyer MD
Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Nicholas D. James MBBS, PhD
School of Cancer Sciences, University of Birmingham, Birmingham, UK

George J.S. Kallingal MD, MPH
Clinical Instructor, Department of Urology, University of Miami, Miami, FL, USA

Ashish M. Kamat MD
Associate Professor, Department of Urology, MD Anderson Cancer Center, Houston, TX, USA

Mark Kawachi MD
Division of Urology and Urologic Oncology, City of Hope National Medical Center, Duarte, CA, USA

Jaegil Kim MD
Broad Institute of Harvard and MIT, Cambridge, MA, USA

William Y. Kim MD
Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Tobias Klatte
Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

Badrinath Konety
Department of Urology, University of Minnesota, Minneapolis, MN, USA

Theresa Koppie
Department of Urology, University Hospital Tübingen, Tübingen, Germany

Marc A. Kowalkowski
Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

David J. Kwiatkowski MD
Broad Institute of Harvard and MIT, Cambridge, MA, USA and Brigham and Women’s Hospital, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
Donald L. Lamm MD  
Clinical Professor, University of Arizona; Director, BCG Oncology, Phoenix, AZ, USA

David M. Latini PhD  
Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA

Nathan Lawrentschuk MD  
University of Melbourne, Department of Surgery; Olivia Newton-John Cancer Research Institute, Austin Hospital and Peter MacCallum Cancer Centre, Division of Cancer Surgery, Melbourne, Australia

Cheryl T. Lee MD  
Department of Urology, University of Michigan, Ann Arbor, MI, USA

Seth P. Lerner MD, FACS  
Department of Urology, Baylor College of Medicine, Houston, TX, USA

Jeffrey J. Leow MD  
Center for Surgery and Public Health, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; Department of Urology, Tan Tock Seng Hospital, Singapore

Joseph C. Liao  
Department of Urology, Stanford University School of Medicine, Stanford, CA, USA

Fredrik Liedberg MD  
Department of Urology, Lund University, Malmö, Sweden

Jen-Jane Liu  
Brady Urological Institute, Johns Hopkins School of Medicine, Baltimore, MD, USA

Yair Lotan MD  
Department of Urology, The University of Texas Southwestern Medical Center, Dallas, TX, USA

David J. McConkey MD  
Departments of Urology and Cancer Biology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Edward M. Messing MD, FACS  
W.W. Scott Professor and Chairman, Department of Urology, University of Rochester, School of Medicine and Dentistry, Rochester, New York, USA

Matthew I. Milowsky MD  
Department of Medicine, Division of Hematology/Oncology, University of North Carolina at Chapel Hill, and Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

Nihal E. Mohamed  
Department of Urology and Oncological Science, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Andreas Neisius MD  
Department of Urology, University Medical Center, Johannes Gutenberg University, Mainz, Germany

Matthew Nielsen MD, MS  
Assistant Professor, Department of Urology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Michael A. O’Donnell MD  
Professor and Director of Urologic Oncology, Department of Urology, University of Iowa, Iowa City, IA, USA

Peter H. O’Donnell  
Department of Medicine, Section of Hematology/Oncology, The University of Chicago, Chicago, IL, USA

J. Palou MD, PhD  
Chief, Associate Professor, Department of Urological Oncology; Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain

Dipen J. Parekh  
Department of Urology, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

Kamal S. Pohar MD  
Department of Urology, Ohio State University, Wexner Medical Center, Columbus, OH, USA

Michael Porter MD MS  
Department of Urology, University of Washington; VA Puget Sound Health Care System, Seattle, WA, USA

Raj S. Pruthi MD  
Department of Urology, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

David I. Quinn MBBS, PhD, FRACP, FACP  
Head, Section of Genitourinary Medical Oncology; Co-Leader Developmental Therapeutics Program, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA
List of contributors

Michael Rink MD, FEBU
Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Jonathan Rosenberg MD
Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA

Arthur I. Sagalowsky MD
Department of Urology, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Mark P. Schoenberg MD
Department of Urology, Montefiore Medical Center and Albert Einstein College of Medicine, New York, NY, USA

Shahrokh F. Shariat MD
Professor and Chairman, Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, and Vienna General Hospital, Vienna, Austria

William U. Shipley MD
Chair, Genitourinary Oncology Unit, Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

Eila C. Skinner MD
Thomas A. Stamey Research Professor; Chair, Department of Urology, Stanford University School of Medicine, Stanford, CA, USA

Angela B. Smith MD
Assistant Professor, Department of Urology, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

Norm D. Smith MD
Section of Urology, The University of Chicago Medicine, Chicago, IL, USA

Eduardo Solsona MD
Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Guru Sonpavde MD
Associate Professor of Medicine, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL, USA

Ayman Soubra
Department of Urology, University of Minnesota, Minneapolis, MN, USA

Massimiliano Spaliviero MD
Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Cora N. Sternberg MD, FACP
Department of Oncology, San Camillo Forlanini Hospital Rome, Italy

Gary Steinberg
Department of Surgery, Section of Urology, University of Chicago Medical Center, Chicago, IL, USA

Arnulf Stenzl MD
Professor and Chair, Department of Urology, University Hospital Tübingen, Tübingen, Germany

Seth A. Strope MD, MPH
Division of Urologic Surgery, Washington University School of Medicine, St Louis, MO, USA

Robert S. Svatek MD, MSCI
Assistant Professor, Department of Urology, University of Texas Health Sciences Center, San Antonio, TX, USA

Keith Syson Chan MD
Department of Urology, Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA

George N. Thalmann MD
Department of Urology, University of Bern, Bern, Switzerland

Dan Theodorescu MD, PhD
Department of Surgery, Urology Division, University of Colorado Denver, and University of Colorado Cancer Center, Aurora, CO, USA

Joachim W. Thüroff MD
Department of Urology, University Medical Center, Johannes Gutenberg University, Mainz, Germany

Derya Tilki MD
Department of Urology, University of California, Davis, Medical Center, Sacramento, CA, USA

Levent N. Türkeri MD, PhD
Professor of Urology, Department of Urology, Marmara University School of Medicine, Istanbul, Turkey

Alon Z. Weizer MD, MS
Associate Professor, Department of Urology, University of Michigan, Ann Arbor, MI, USA
**Ryan Werntz**  
Department of Urology, University Hospital Tübingen, Tübingen, Germany

**M. Guillaume Wientjes PhD**  
Optimum Therapeutics, LLC, San Diego, CA, USA; Professor Emeritus, The Ohio State University, Columbus, OH, USA

**Timothy G. Wilson MD**  
Chief, Division of Urology and Urologic Oncology; Professor of Surgery, City of Hope National Medical Center, Duarte, CA, USA

**Fred Witjes**  
Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

**Kristina Wittig MD**  
Fellow, Urologic Oncology and Robotic Surgery, Division of Urology and Urologic Oncology, City of Hope National Medical Center, Duarte, CA, USA

**Diane Zipursky Quale**  
Bladder Cancer Advocacy Network, Bethesda, MD, USA

**Alexandre R. Zlotta**  
Department of Surgical Oncology (Urology), Mount Sinai Hospital and Princess Margaret Cancer Centre, Toronto, Canada
Urothelial cancer comprises diverse neoplastic diseases affecting the urethra, bladder, and upper urinary tract. Translational science and genomics are advancing our understanding of the biology of this complex disease. Technological advances in endoscopy, imaging, intravesical therapy, exenterative and robotic surgery, and urinary tract reconstruction have dramatically improved patient care and clinical outcomes. Despite effective cytotoxic chemotherapy, long-term cure can be elusive for patients with metastatic disease, offering opportunities for new drug development and application of targeted therapeutics and immunotherapy.

This textbook was conceived to bring a state-of-the-art comprehensive analysis of urothelial cancer to physicians at all stages of medical education. Leading authorities were brought together for each subject in order to provide multiple and often contrasting viewpoints. As with the previous comprehensive and clinical editions of our first book, each chapter is a collaborative effort between the co-authors who have been especially selected for their expertise and reputation as experts and thought leaders in the field. We also embrace and expect different points of view and interpretations of the literature among co-authors and are confident that this will be reflected in the text.

Urothelial cancer is a substantial world health problem. We hope this textbook proves informative, thought-provoking, and a valuable resource for physicians and scientists across many disciplines.
The editors wish to thank the nearly 100 authors who have contributed the outstanding manuscripts for 36 chapters to create a truly comprehensive textbook. We congratulate the team at Wiley-Blackwell and especially wish to acknowledge Oliver Walter and Jennifer Seward for their patience and guidance.
PART I

Diagnosis and treatment of non-muscle-invasive bladder cancer
Histopathological evaluation of bladder lesions represents one of the more challenging areas of pathology. In part, this reflects both the plasticity of the urothelium and the variety of processes that can affect the bladder. The frequent lack of objective ancillary markers to confirm or exclude a diagnosis contributes to the additional complexity in the analysis of bladder biopsies or resections. In this chapter we will outline common lesions that affect the bladder and highlight various challenges in their diagnosis.

**Benign urothelium**

Normal urothelium ranges from four to seven cell layers in thickness and contains a basal cell layer, intermediate urothelial cell layers, and a superficial umbrella cell layer (Figure 1.1). The overall thickness may be increased in the context of inflammation and reparative changes or may be diminished during a number of benign processes that induce denudation or expansion of the bladder. Normal urothelium is characterized by uniform nuclear size, nuclei oriented towards the luminal surface, nuclear grooves, and regular spacing between cells. Under normal conditions, cell layers of urothelium are relatively easy to identify. However, in instances where the morphology is disrupted or extensive inflammation is present, immunohistochemical stains may be helpful. Specifically, in normal urothelium, cytokeratin 20 stains the umbrella cell layer and p53 variably labels the basal and intermediate cell layers; [1, 2]. In contrast to the normal urothelium, neoplastic processes...
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may show full-thickness cytokeratin 20 expression, intense nuclear p53 expression in the majority of cells, and loss of CD44, although these findings are often variable and may not be especially helpful in individual cases [3–5].

**Reactive urothelium**

Although the description of normal urothelium appears relatively straightforward, physiologic variations can induce a spectrum of morphologic changes. Delineating reactive changes from early neoplastic processes in the bladder is a major challenge in pathology. The most common conditions that incite reactive changes include inflammation and prior chemotherapy or radiation therapy [6, 7]. In the former case, marked acute and chronic inflammation can increase the cellularity of the urothelium and thus decrease the organization of the background urothelial cells. Reactive changes, such as nuclear enlargement and the presence of pinpoint nucleoli may be identified (see Figure 1.1). The presence of inflammatory cells, however, does not per se render a benign diagnosis; a small percentage of urothelial carcinoma in situ cases may be associated with concurrent inflammation. In these instances, immunohistochemical stains may help with the final diagnosis. A second form of reactive change is associated with a prior history of radiation therapy, which itself is a risk factor for the development of bladder cancer [8]. Reactive changes associated with radiation include enlarged, hyperchromatic nuclei that appear more degenerative in nature. On occasion, reactive squamous metaplasia may also be present (see Figure 1.1). The underlying lamina propria in these cases may show fibrosis, inflammation, hyalinization of the blood vessels, extravasated red blood cells, fibrin thrombi in small vessels and occasional stromal cell atypia. When reactive changes are partially obscured by intense inflammation or when secondary processes are present, a diagnosis of “atypia of uncertain significance, favor reactive” may be rendered, which suggests

Figure 1.1 a) Normal urothelium. b) Reactive urothelium. c) Reactive urothelial atypia occurring after radiation.
the process is benign, although not all cells can be either definitely seen or characterized.

**Urothelial hyperplasia**

In urothelial hyperplasia, abnormal thickening of the urothelium is often evident at low magnification and often extends beyond ten cell layers [9, 10]. Despite the greater number of cells, the urothelium appears otherwise normal to slightly increased in cellularity with retained polarity and absence of nuclear atypia (Figure 1.2). Occasionally, mild nuclear enlargement may be present. This finding has been identified both in association with inflammation and adjacent to low-grade papillary urothelial carcinomas [11]. Given the latter association, subsequent follow-up of patients with a diagnosis of urothelial hyperplasia may be critical to exclude subsequent neoplastic processes.

A papillary form of urothelial hyperplasia has been described and is characterized by regular, repetitive ingrowth of blood vessels into the otherwise normal-appearing urothelium [12–14]. This subset of hyperplastic lesions may also be associated with the development of papillary neoplasms, which may be more likely if atypical cells or dysplasia are identified.

![Figure 1.2](image)

**Figure 1.2** a) Flat urothelial hyperplasia. b) Urothelial dysplasia/atypia. c) Flat urothelial carcinoma in situ.
Urothelial dysplasia

Urothelial dysplasia is one of the most subjective areas of bladder pathology. Urothelial dysplasia is defined as atypia of the urothelium related to underlying neoplasia that does not reach the morphologic criteria of flat urothelial carcinoma in situ [9, 15]. This definition includes a wide range of appearances that may include occasional hyperchromatic nuclei, hyperplasia with atypia, mild disorganization, and mild variation in nuclear size (see Figure 1.2). The criteria for the diagnosis parallel those of low-grade papillary urothelial carcinomas; however, the neoplastic process is more readily diagnosed when papillary cores are present (in contrast to similar atypia involving the flat urothelium). A subset of cases may show a background of papillary hyperplasia, in which case the terms “papillary hyperplasia with dysplasia/atypia” or “urothelial dysplasia with early papillary formation, consistent with an early low-grade papillary urothelial carcinoma” may be used [16]. Application of the immunohistochemical panel of CK20, p53, and CD44 may be employed to help in the diagnosis of urothelial dysplasia [17]. When the staining pattern matches that of neoplasia, the diagnosis is relatively straightforward. However, many cases have variability in the staining results (e.g., mild to moderate nuclear p53 or patchy full-thickness cytokeratin 20) that limits the utility of this panel. In these cases, clinical follow-up is often recommended, especially if there is a history of urothelial carcinoma or known risk factors for bladder neoplasia. These cases may be diagnosed as “atypia of uncertain significance, favor dysplasia” with a comment provided.

Flat urothelial carcinoma in situ (CIS)

CIS represents high-grade neoplasia of the bladder that often shows characteristic features such as markedly enlarged nuclei (often > 4x the size of a lymphocyte), hyperchromasia, disorganization and loss of nuclear polarity, loss of cohesion, and frequent mitotic activity that may be atypical and extends to the upper portion of the urothelium (see Figure 1.2). It is likely that the loss of cohesion explains the usefulness of cytology to detect high-grade lesions in the urine, as compared to other papillary neoplasms. CIS is often relatively straightforward to diagnose, although a number of variants may present challenges due to unusual morphology or only a limited number of cells present [18].

Papillary lesions

Exophytic (papillary) lesions of the bladder may be either benign or malignant. Neoplastic papillary lesions comprise the majority of papillary entities in the bladder and are graded according to the 2004 WHO classification scheme in the United States [19]. Using this model, papillary neoplasms are subdivided into urothelial papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma, and high-grade papillary urothelial carcinoma based on the cellularity and degree of atypia present. The morphologic parameters assigned to these lesions parallel the categories of flat lesions defined earlier in the chapter (Table 1.1). Generally, the highest grade component of the papillary lesion is assigned to neoplasm, although in instances in which only a minimal high-grade component is identified (<5%), one convention is often to label these lesions as “low-grade papillary urothelial carcinoma with focal high-grade features” [20]. Adoption of this four-tiered system of grading replaces the prior scheme of separating lesions into Grades 1, 2, and 3 based on the extent of cytologic atypia. This former system was limited in utility due to a lack of close correlation between the assigned grade and patient outcomes, as well as a tendency to group a large proportion of lesions into the intermediate Grade 2 category [21–23].

Table 1.1 Morphologic parallels between flat and papillary lesions.

<table>
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<tr>
<th>Morphology</th>
<th>Flat lesions</th>
<th>Papillary lesions</th>
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<td>Normal-appearing mucosa</td>
<td>Benign urothelium</td>
<td>Urothelial papilloma</td>
</tr>
<tr>
<td>Thickened but normal-appearing mucosa</td>
<td>Flat urothelial hyperplasia</td>
<td>PUNLMP</td>
</tr>
<tr>
<td>Hyperchromatic nuclei, mild disorganization</td>
<td>Urothelial dysplasia/atypia</td>
<td>Low-grade papillary urothelial carcinoma</td>
</tr>
<tr>
<td>Marked atypia, discohesion, disorganization</td>
<td>Flat urothelial carcinoma in situ</td>
<td>High-grade papillary urothelial carcinoma</td>
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</table>
Commonalities in papillary neoplasms include the presence of small vascular cores, branching morphology, and the ability to “invert” growth into underlying von Brunn nests [11]. Inverted growth reflects a neoplasm still contained within the basement membrane and is consistent with non-invasive behavior. Whereas the majority of cases are diagnosed with light microscopy, occasionally p53 and CK20 may be used to define high-grade neoplasia when focal or questionable on assessment.

The differential diagnosis of papillary lesions includes such entities as papillary nephrogenic adenoma, papillary cystitis, and ductal adenocarcinoma of the prostate (prostatic urethra) [24, 25]. These lesions can be ruled out either by using immunohistochemical stains (nephrogenic adenoma and ductal adenocarcinoma) or by limited atypia (cystitis).

**Urothelial papilloma**

Urothelial papilloma is characterized by normal-appearing urothelium lining thin fibrovascular cores (Figure 1.3). The umbrella cells may demonstrate prominent vacuolization in this lesion. These lesions are indolent, with only rare cases of recurrence and progression reported.

**Papillary urothelial neoplasm of low malignant potential (PUNLMP)**

PUNLMP is defined as fibrovascular cores lined by thickened, but otherwise normal, urothelium (Figure 1.3). Polarity is retained and few to no mitotic figures are identified. Although up to a third of these lesions may recur, progression to invasion is extraordinarily rare.

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**Figure 1.3**  
(a) Urothelial papilloma.  
(b) Papillary urothelial neoplasm of low malignant potential.  
(c) Low-grade papillary urothelial carcinoma.  
(d) High-grade papillary urothelial carcinoma.
Low-grade papillary urothelial carcinoma (LGpUC)

This lesion is defined by mild disorganization and mild atypia that includes hyperchromasia, some nuclear enlargement, and nuclear membrane irregularities. Mitotic figures may be frequently identified, but are generally not atypical (see Figure 1.3). No significant pleomorphism is present. Approximately half of these lesions recur and approximately 10% will progress.

High-grade papillary urothelial carcinoma (HGPUC)

HGPUC can demonstrate numerous overt features of malignancy, including pleomorphic nuclei, clumped chromatin, prominent nucleoli in some cases, loss of polarity, discohesion, and atypical mitotic figures high in the urothelium (Figure 1.3). In some cases, denudation may be so prominent that only minimal cells remain to render a diagnosis of high-grade disease. Similar to CIS, HGPUC is associated with a high risk of invasion in up to half of diagnosed cases; recurrence occurs in the majority of cases.

Invasive urothelial carcinoma

The histopathological features of invasive urothelial carcinoma (UC) are variable. Except for specific variants of UC, invasive UC has no specific histopathological features and shows cohesive nests of cells with moderate to abundant cytoplasm and large hyperchromatic nuclei. Nuclear pleomorphism is common, with irregular nuclear contours, occasionally prominent nucleoli and readily identifiable mitotic figures. Regardless of the morphologic appearance, assessing the depth of invasion is of paramount importance. There is, however, some confusion related to the use of some terminology such as applying the term “muscle invasion” without further qualification. This term does not distinguish between invasion of the muscularis mucosae or the muscularis propria. Also, the term “superficial bladder cancer” is vague and could be misleading as it groups three biologically different lesions: flat urothelial carcinoma (in situ), non-invasive papillary carcinoma (low- and high-grade), and carcinoma with lamina propria invasion.

There are several morphologic criteria useful in the determination of lamina propria invasion (Table 1.2). The presence of urothelial nests, clusters, or single cells within the lamina propria, sometimes with prominent retraction artifacts, is characteristic. The invasive tumor cells may show abundant eosinophilic cytoplasm at the advancing edge of the infiltrating nests (Figure 1.4). Another feature of invasive tumor is the presence of associated desmoplastic or inflammatory stromal response.

Attempts to subclassify T1 tumors based on their depth of invasion have been successful only in some cases in which a well-delineated muscularis mucosae or large vessels are readily identified in the deep lamina propria and which serve as anatomical landmarks to assess the depth of invasion (Figure 1.4). However, more work is necessary to arrive at criteria that can be universally adopted and applied to all transurethral resection and biopsy specimens.

Invasion into the muscularis propria should be diagnosed when a tumor is seen infiltrating thick, smooth muscle bundles (Figure 1.4), with all effort applied to distinguish that from muscle fibers of the muscularis mucosae within the lamina propria.

Table 1.2 Morphologic criteria for tumor invasion into lamina propria.

<table>
<thead>
<tr>
<th>Histologic grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasion is more common in high-grade lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of the invading epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular or absent basement membrane</td>
</tr>
<tr>
<td>Irregular nests or single infiltrating cells</td>
</tr>
<tr>
<td>Irregular invasive nests with more cytoplasm than the overlying non-invasive component (paradoxical differentiation of the invasive component compared to the overlying in situ disease)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of stromal–host reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of retraction artifact</td>
</tr>
<tr>
<td>Presence of stromal desmoplasia or myxoid stroma</td>
</tr>
<tr>
<td>Inflammatory reaction</td>
</tr>
</tbody>
</table>

Carcinomas with divergent (aberrant) differentiation

Urothelial carcinomas, particularly high-grade tumors, may show divergent differentiation. This feature is seen primarily in invasive tumors but may occasionally be present in non-invasive lesions as well [26]. In a series of 300 consecutive cystectomies performed at Memorial Sloan-Kettering Cancer Center, 27% of cancer-bearing specimens contained some form of
divergent differentiation. This incidence, however, was lower in transurethral resection specimens, at approximately 7%. When divergent differentiation is seen together with usual urothelial carcinoma, the pathology report should include the terminology “urothelial carcinoma with ____ differentiation,” inserting the type of differentiation observed (Figure 1.5).

**Squamous cell carcinoma**

The diagnosis of squamous cell carcinoma (SCC) should be reserved for urothelial tumors that exhibit exclusive or predominant squamous differentiation (Figure 1.5). For urothelial tumors with variable amounts of squamous differentiation, the term “urothelial carcinoma with squamous differentiation” should be used. Overall, squamous cell carcinomas constitute 2% to 7% of urothelial cancers except in West African regions and along the Nile Valley, where, as a consequence of the endemic schistosomal infections, they are the most common form of cancer [27–29]. Risk factors associated with the development of bladder squamous cell carcinoma include long-term indwelling catheterization, a non-functioning bladder, bladder calculi, and chronic infection with *Schistosoma haematobium* [30, 31]. Squamous carcinoma of the urothelial tract is thought to arise through a process of metaplasia of the urothelium. A large percentage of patients with SCC have squamous metaplasia of the adjacent

---

**Figure 1.4** Invasive urothelial carcinoma into superficial lamina propria. a) Small irregular clusters and individual cells underneath the basement membrane. b) Desmoplastic stromal reaction. c) Invasive urothelial carcinoma into deep lamina propria (note tumor adjacent to large caliber vessels and thin bundles of muscularis mucosae). d) Invasion of muscularis propria.
urothelium. Many have a history of severe, long-term chronic inflammation associated with stones, chronic infection, bilharziasis, and, in a few examples, prior systemic chemotherapy with cyclophosphamide [32]. A number of morphologic alterations in the urothelial lining have been associated with the development of bladder squamous cell carcinoma, including keratinizing squamous metaplasia, verrucous squamous hyperplasia, condyloma acuminatum, and squamous cell carcinoma in situ [33, 34].

Squamous cell carcinoma of the bladder tends to be sessile, ulcerated, and infiltrative at the time of diagnosis. The histologic hallmarks of pearl formation, intercellular bridges, and keratotic cellular debris are those of squamous carcinoma at any site. With the exception of the verrucous variant, most of these carcinomas are moderately or poorly differentiated and more deeply invasive at the time of diagnosis than the majority of transitional cell carcinomas, which may contribute to the generally poor prognosis of these tumors. When these tumors are evaluated stage for stage, however, the prognosis is similar to that of “usual” urothelial carcinoma [29, 35, 36].

**Adenocarcinoma**

Primary pure adenocarcinomas of the bladder are rare, representing no more than 2.5% of all malignant vesical neoplasms [37, 38]. By definition, the tumor should be composed entirely, or virtually entirely, of glandular elements. As with squamous carcinoma,
they arise through a process of metaplasia of the urothelium and frequently are associated with long-standing local irritation, a non-functioning bladder, and obstruction [39–45]. Up to 90% of carcinomas associated with bladder extrophy are of adenocarcinoma type and this tumor may also be encountered in a setting of bladder schistosomiasis [46, 47]. They can arise anywhere on the bladder surface, although a large percentage originates from the trigone and posterior wall. A major clinical difference as compared to usual urothelial carcinoma is that two-thirds of adenocarcinomas are single, discrete lesions, whereas TCC tends to be multifocal [39, 40]. Grossly, the tumors can be papillary, nodular, or flat and ulcerated. Microscopically, the tumor is most often composed of colonic-type glandular epithelium (Figure 1.5) and may contain abundant extracellular mucin. Regardless of histologic pattern, cystitis cystica et glandularis or surface glandular metaplasia is commonly present in the adjacent benign urothelium. At the time of initial diagnosis, most adenocarcinomas are locally advanced and deeply infiltrative, most likely accounting for their poor prognosis. Stage for stage, however, they appear to have similar survival to TCC [37, 43–45, 48, 49].

It is important to consider the possibility of metastasis or direct invasion from another primary site in the differential diagnosis of an adenocarcinoma involving the bladder. Tumors that directly invade the bladder and mimic primary vesical adenocarcinoma include those arising in the rectum, prostate, appendix, and endometrium [50–52]. For this reason, we have routinely added the following disclaimer to our pathology report of the biopsy specimen:

“We would accept as primary at this site if a metastasis or direct extension from an adjacent organ can be ruled out clinically.”

The treating clinician is in the best position to evaluate the patient and consider other primary sites.

**Clear cell adenocarcinoma**

This is another rare variant that is characterized by cuboidal tumor cells forming duct- or tubule-like structures that resemble its müllerian counterpart in the female genital tract. These tumors were initially thought to arise from mesonephric nests in the trigone area, but are now considered to arise through a process of metaplasia of the surface urothelium or from müllerian rests [53–56]. This tumor has a strong female predominance, which is unusual for urothelial tumors and suggests that müllerian origin may account for an even larger percentage of these cases [55]. Histologically, these tumors are characterized by tubular and papillary structures that are generally lined by flat, cuboidal, or rarely columnar cells, with hobnail cells present in most tumors. Clear cells are abundant in most tumors but cells with abundant eosinophilic cytoplasm are also common.

**Nephrogenic metaplasia (adenoma)**

This is a distinct metaplastic lesion that may mimic adenocarcinoma and is characterized by aggregates of cuboidal or hobnail cells with clear or eosinophilic cytoplasm and small, discrete nuclei without prominent nucleoli [57]. The architectural patterns include thin papillary fronds on the surface and tubular structures within the lamina propria of the bladder. This lesion is usually fairly well circumscribed and does not extend into the muscularis propria and the tubules are often surrounded by a thickened and hyalinized basement membrane. Usually, there is no stromal response to the lesion but a variable amount of acute and chronic inflammatory cells is commonly encountered. Nephrogenic adenoma is thought to be due to an inflammatory insult or local injury [58–60]. It is most commonly seen in the bladder but may occur in the prostatic urethra as well [57, 60].

**Plasmacytoid variant of urothelial carcinoma**

Plasmacytoid variant is a rare and aggressive variant of urothelial carcinoma which tends to infiltrate the bladder wall diffusely, giving it an indurated and thickened quality similar to the “limitis plastica” seen in gastric signet ring cell carcinomas (Figure 1.6). Most of these tumors exhibit morphology in which tumor cells have eccentrically situated nuclei and abundant eosinophilic cytoplasm, giving them the appearance of plasma cells and hence the term “plasmacytoid” urothelial carcinoma. Almost invariably, these tumor will exhibit cells with signet ring cell morphology. The tumor also commonly infiltrates extensively throughout adjacent soft tissue, which further complicates the attempted surgical resection of these tumors. In the differential diagnosis, one must rule out direct extension, usually from a rectal or prostatic carcinoma, or metastasis from stomach or lobular carcinoma of the breast or other organs [61–68].
Urachal carcinoma
Urachal carcinoma is a primary carcinoma of the bladder arising from urachal remnants, the vast majority of which is adenocarcinoma. Urachal remnants have been found in up to 35% of bladders at the time of autopsy; usually in the dome, but also along the anterior and rarely along the posterior bladder wall [69, 70]. Although their epithelial lining usually is transitional in type, it can be glandular in 33% of cases. Urachal carcinoma is rare and comprises 0.35% to 0.7% of all bladder cancers and 22% to 35% of vesical adenocarcinomas [70–72]. Most of these carcinomas have enteric features and may be mucinous; however, rare examples containing signet ring cell, micropapillary, squamous cell, small cell/neuroendocrine, lymphoepithelioma-like, usual urothelial and anaplastic carcinoma components have been reported [70, 73–75]. Adenomatous changes have been identified in the adjacent urachal remnant in 37% of cases in one study [70].

Although the criteria for a diagnosis of urachal carcinoma are somewhat controversial, most investigators agree with those set forth by Sheldon et al. [76] and Mostofi et al. [40]. These include (1) tumor in the dome of the bladder; (2) absence of cystitis cystica and cystitis glandularis; (3) predominant invasion of the muscularis or deeper tissues with a sharp demarcation between the tumor and surface bladder urothelium that is free of glandular or polypoid proliferation; (4) presence of urachal remnants within the tumor; (5) extension of tumor into the bladder wall with involvement of the space of Retzius, anterior abdominal wall, or umbilicus; and (6) no evidence of a primary neoplasm elsewhere.

A few staging systems have recently been proposed [75, 77], but the one commonly followed is that proposed by Sheldon et al. [76]: pT1 – no invasion beyond the urachal mucosa; pT2 – invasion confined to the urachus; pT3 – local extension to the (a) bladder, (b) abdominal wall, and (c) viscera other than the bladder; and pT4 – metastasis to (a) regional lymph nodes and (b) distant sites.

Because the urachus usually is found along the free surface of the bladder, urachal carcinomas frequently are amenable to partial cystectomy. The entire length of the median umbilical ligament may harbor urachal remnants that may develop carcinoma synchronously or metachronously [78]. For this reason the surgery of choice should include en bloc resection of the entire length of the ligament, including the umbilicus [75, 79].

The differential diagnosis includes metastatic adenocarcinoma and adenocarcinoma arising in the bladder surface. The latter usually is associated with an intraluminal mass and the diagnosis is established by finding CIS or extensive glandular metaplasia of the adjacent urothelium. Because these features are rarely seen on a TUR specimen of an ulcerated lesion, we include the following note in the pathology report of any solitary glandular lesion involving the dome of the bladder: “We would accept as primary at this site, including the possibility of urachal origin, if a metastasis or direct extension from an adjacent organ has been ruled out.” Once again, the urologist is in the best position to make this determination.

Small cell/neuroendocrine carcinoma
Small cell carcinoma is a malignant neuroendocrine neoplasm derived from the urothelium that histologically resembles its pulmonary counterpart [80–84]. It consists of small cells with nuclear molding, scant cytoplasm, and dark nuclei containing finely stippled chromatin and inconspicuous nucleoli (Figure 1.6). By immunohistochemical studies, most tumors express chromogranin and synaptophysin. In most cases they are associated with CIS of the urothelium and show microscopically foci of other divergent histologic patterns, usually transitional cell carcinoma, but also adenocarcinoma, squamous cell carcinoma, or spindle cell carcinoma [80, 85, 86]. Small cell or neuroendocrine carcinomas should be considered high-grade tumors. They usually present at an advanced stage; up to one-third of patients have metastases at the time of diagnosis.

Nested variant of urothelial carcinoma
This is a rare but important variant of urothelial carcinoma that follows an aggressive clinical course despite its very innocuous appearance. It was first described as a tumor with a “deceptively bland” appearance closely resembling Brunn’s nests but may be infiltrating deep into the bladder wall [87–91]. It is often confused with cystitis cystica, cystitis glandularis, nephrogenic metaplasia, and
Figure 1.6  
(a) Nested variant of urothelial carcinoma consisting of stacked nests of bland urothelial cells. 
(b) Urothelial carcinoma with deceptively bland tubules infiltrating deeply into the muscularis propria and perivesical tissue. 
(c) Urothelial carcinoma with micropapillary features. 
(d) Urothelial carcinoma with signet ring-cell and plasmacytoid morphology. 
(e) Small cell/neuroendocrine carcinoma. 
(f) Sarcomatoid carcinoma consisting of a mixture of epithelial and spindle malignant cells.
inverted papilloma but can be differentiated from these by the presence of poorly defined and confluent nests that may infiltrate deeply into the bladder wall, including the muscularis propria and beyond (Figure 1.6).

**Lymphoepithelioma-like carcinoma**

Another rare variant of urothelial carcinoma has been termed lymphoepithelioma [92, 93]. As the name suggests, this urothelial carcinoma is associated with a prominent lymphocytic infiltrate. The tumor cells have minimal cytoplasm and are of high cytologic grade, making their identification at low and intermediate magnification difficult. The main differential diagnosis is with lymphomas but immunohistochemical studies can easily resolve such a situation. When this morphology is present in a pure or predominant form, it has been reported that the prognosis for these patients is favorable, in contrast to those with only a focal component [94].

**Micropapillary carcinoma**

A rare variant of UC described by Amin *et al.* was termed “micropapillary carcinoma” and comprised a group of tumors that contained a micropapillary component resembling ovarian papillary serous carcinoma [95]. The micropapillary growth pattern was seen in the non-invasive and invasive components of the tumor as well as in the metastasis, confirming the high-grade nature of the tumor (Figure 1.6). In the invasive carcinoma, micropapillary carcinoma consists of tight clusters of infiltrating micropapillary aggregates situated within clear spaces, sometimes referred to as lacunae. In some cases, micropapillary growth may be focal whereas in others it could be extensive. It has recently been reported that the extent of the micropapillary component may be associated with advanced stage at presentation [96, 97].

**Sarcomatoid carcinoma**

It is preferred that the term “sarcomatoid variant of urothelial carcinoma” or “urothelial carcinoma with sarcomatoid differentiation” be applied to the group of malignant tumors of mixed epithelial and mesenchymal differentiation that have been described under different names by various authors, including: sarcomatoid carcinoma, metaplastic carcinoma, spindle and giant cell carcinoma, carcinosarcoma, malignant mesodermal mixed tumor, and tumors that exhibit recognizable heterologous elements. These tumors usually form large polypoid intraluminal masses and characteristically have dull gray appearance and infiltrative margins. Microscopically, the epithelial and mesenchymal components are present in variable proportions. The epithelial component may be of urothelial carcinoma with or without other divergent differentiation and the mesenchymal component may be in the form of undifferentiated spindle cell sarcoma or a recognizable heterologous component with osteogenic, cartilaginous, or rhabdomyosarcomatous morphology (Figure 1.6). The overlying and adjacent urothelium should be searched for CIS and the tumor examined carefully for a transition from epithelial to spindle cell pattern [98–102]. Some cases may be associated with a striking myxoid or sclerosing appearance mimicking an inflammatory pseudotumor [103]. Since true sarcomas of the bladder are very rare, it should be remembered that a bladder tumor with undifferentiated spindle cell pattern is more likely to be of epithelial than mesenchymal origin. Sarcomatoid carcinomas are high-grade tumors whose prognosis correlates with the depth of invasion.

**Useful web links**


**References**


CHAPTER 2

Risk stratification of high-grade Ta, CIS, and T1 urothelial carcinoma of the bladder

Tobias Klatte1, Fred Witjes2, Gary Steinberg3, and Shahrokh F. Shariat1

1 Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria
2 Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
3 Department of Surgery, Section of Urology, University of Chicago Medical Center, Chicago, IL, USA

Introduction

Urothelial carcinoma of the bladder (UCB) can be a highly aggressive and heterogeneous disease with high incidence, recurrence, and progression rates [1, 2]. At initial diagnosis, approximately 75% of patients have non-muscle-invasive bladder cancer (NMIBC) [1, 3]. This category of bladder pathology includes Ta (non-invasive epithelial), T1 (invasive subepithelial) tumors, and carcinoma in situ (CIS), representing approximately 70%, 20%, and 10% of NMIBC, respectively. Disease recurrence occurs in up to 80% of NMIBC patients and is the main focus in Ta UCB. Disease progression affects up to 30% of patients with high-grade (high-risk) Ta, T1, and/or carcinoma in situ (CIS) UCB [1, 3]. In a subset of patients with high-risk NMIBC and in almost all patients with muscle-invasive bladder cancer (MIBC), radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) is the standard treatment [4]. Despite advances in surgical technique, imaging, perioperative management, and chemotherapy, approximately 50% of patients treated with cystectomy for invasive UCB die from their disease [5, 6]. In this chapter we will review the risk stratification, management, and prognosis of NMIBC.

Risk stratification

Outcome prediction based on a physician's experience alone is subjectively influenced. NMIBC represents a heterogeneous disease with distinct prognoses, even within a similar stage and grade category. Assessment of all clinical and pathological prognostic factors reflecting this heterogeneity and subsequent stratification into groups according to the risk of recurrence and progression are essential for patient counseling and determination of the appropriate management strategy. Risk stratification is therefore imperative to avoid over- and under-treatment.

Within the last several years, there has been a plethora of reports describing different prediction tools relying on common pre- and post-operative pathologic parameters in UCB. These tools have been developed to facilitate and improve daily clinical practice through evidence-based decision-making [7–9]. The risk group is assigned when all clinical (e.g. age, gender, prior recurrence rate, numbers of tumors, size) and pathological information (e.g. tumor stage, grade, presence of CIS) is available. Online tools that facilitate risk stratification are available (http://www.eortc.be/tools/bladdercalculator/).

In a large study cohort of 1529 patients with NMIBC, Millan-Rodriguez et al. examined predictors of disease recurrence, progression, and cancer-specific mortality, and thus developed a risk stratification based on tumor multifocality, tumor size, intravesical bacillus Calmette-Guérin (BCG) therapy, and presence of concomitant CIS [10]. Tumor grade was the most powerful predictor of disease progression and cancer-specific mortality.

To predict separately the short- and long-term risks of both recurrence and progression in individual patients, a scoring system and risk tables were developed by the European Organization for Research and Treatment of
Risk stratification of high-grade Ta, CIS, and T1 UC

The EORTC database provided individual data for 2596 patients who did not have a second TUR or receive maintenance BCG therapy. The EORTC scoring system is based on the six most significant clinical and pathologic factors: tumor stage and grade, number of tumors, tumor size, concomitant CIS, and prior disease recurrence rate (Table 2.1). Although the final score is individual to each patient, risk group stratification is performed based on the separate scores for recurrence and progression. However, the study was limited by the low number of patients treated with BCG (7%) and single post-operative instillation of chemotherapy (less than 10%), and the fact that no second-look TUR was performed. Therefore, according to current treatment recommendations, especially in high-risk tumors, disease recurrence and progression rates may be overestimated in contemporary series.

The Club Urológico Español de Tratamiento Oncológico (CUETO) recognized these flaws and developed a scoring model which predicted disease recurrence and progression in 1062 patients with NMIBC from four CUETO trials that compared the efficacy of different intravesical BCG treatments [11]. The scoring system was built on seven factors including age, gender, prior recurrence status, number of tumors, tumor stage, tumor grade, and the presence of concomitant CIS (Table 2.2). Though patients included in these studies received 12 BCG instillations during five to six months, the study was limited by the fact that neither single post-operative instillation of chemotherapy nor second-look TUR was performed.

Despite the fact that these risk tables are incorporated into guidelines and ready for clinicians to use in daily practice [3], it has been shown that these treatment recommendations are not commonly used [12]. Chamie et al. [12] assessed practice patterns in 4545 patients with high-grade NMIBC according to established guidelines and found only one patient who received all the recommended diagnostic and treatment measures. Approximately 42% of physicians did not perform at least one cystoscopy, one cytology, and one instillation of immunotherapy for a single patient within their practice. Another problem is that only few studies have externally validated both of these scoring models [13–15].

### Table 2.1 EORTC scoring model.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recurrence score</th>
<th>Progression score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tumors</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 to 7</td>
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<td>3</td>
</tr>
<tr>
<td>≥8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Tumor diameter</td>
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<tr>
<td>&lt;3 cm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥3 cm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Prior recurrence rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 recurrence/year</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1 recurrence/year</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ta</td>
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<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>1</td>
<td>4</td>
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<tr>
<td>Concurrent CIS</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Grade (WHO 1973)</td>
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<td>G2</td>
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</tr>
<tr>
<td>G3</td>
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<td>5</td>
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</table>

### Table 2.2 CUETO scoring model.

<table>
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<tr>
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</tr>
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<td>Gender</td>
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<td>60–70</td>
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<td>&gt;70</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Recurrent tumor</td>
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<tr>
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</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Number of tumors</td>
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<tr>
<td>≤3</td>
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<td>0</td>
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<tr>
<td>&gt;3</td>
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<tr>
<td>T stage</td>
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</tr>
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<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Concurrent CIS</td>
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<td>0</td>
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<td>Yes</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Grade (WHO 1973)</td>
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</tr>
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<td>G1</td>
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</tr>
<tr>
<td>G2</td>
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<td>2</td>
</tr>
<tr>
<td>G3</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>
Xylinas et al. recently evaluated the discrimination of the EORTC risk tables and the CUETO scoring model in a large retrospective multi-center study of 4689 NMIBC patients [15]. The authors created Cox regression models for prediction of time to disease recurrence and progression, incorporating calculated risk scores as a predictor. The EORTC risk tables and the CUETO scoring system exhibited poor discrimination and overestimated the risk for both disease recurrence and progression in NMIBC patients.

The EORTC risk tables [7] and the CUETO scoring model [11] predict the short- and long-term probabilities of disease recurrence and progression in newly diagnosed patients or at the time of disease recurrence. These two prediction tools address and serve different, yet complementary clinical questions/problems. Incorporation of urinary biomarkers in standard prognostic models improves the prediction of outcomes [16], although use of urinary biomarkers is considered to be experimental and is not recommended for clinical routine.

Based on the most crucial prognostic factors, four distinct risk groups are distinguished by the European Association of Urology (Table 2.3). Risk-adapted use of perioperative chemotherapy, induction and maintenance therapy, or immediate cystectomy have been proposed in current guidelines (Table 2.3) [3]. The challenge in high-risk patients is clearly to identify those with the highest risk of progression for early RC, and to treat the rest with intravesical immunotherapy.

### Table 2.3 Risk group stratification and treatment recommendation according to the EAU guidelines.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Definition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Primary, solitary, Ta, LG/G1, 1, &lt; 3 cm, no CIS</td>
<td>One immediate instillation of chemotherapy</td>
</tr>
<tr>
<td>Intermediate</td>
<td>All tumors between low and high risk</td>
<td>One immediate instillation of chemotherapy followed by either chemotherapy for 1 year or BCG for 1 year</td>
</tr>
<tr>
<td>High</td>
<td>Any of the following: • T1 • HG/G3 • CIS • Multiple and recurrent and large (&gt;3 cm) Ta, G1, G2 tumors (all conditions must be present at this point)</td>
<td>BCG for 1–3 years</td>
</tr>
<tr>
<td>Highest</td>
<td>• T1, HG/G3 associated with concurrent bladder CIS, multiple and/or large T1, HG/G3 and/or recurrent T1, HG/G3, T1, HG/G3 with CIS in prostatic urethra, micropapillary variant • BCG failure</td>
<td>RC to be considered</td>
</tr>
</tbody>
</table>

### Ta high-grade urothelial carcinoma of the bladder

Ta tumors are non-invasive papillary carcinomas, i.e. they do not invade the subepithelial connective tissue (lamina propria). High-grade Ta tumors are relatively rare and incidence among all Ta tumors ranges from 2.9% to 18.0%, with an average of 6.9% in various series [17].

Various publications have revealed histological tumor grade to be the most important prognostic factor for progression to muscle-invasive disease [18] and tumor multifocality to be the most important prognostic factor for recurrence. Across multiple published series, the reported risk of progression for patients with high-grade Ta tumors is hampered by inaccuracies in pathological staging and grading, differences in the grading system used, i.e. WHO 1973 classification versus the WHO ISUP classification of 2004, varying frequency of concomitant CIS, different treatment approaches utilized after transurethral resection (TURBT), and by small series numbers. In addition, progression is not defined in various publications (lamina propria vs. muscle invasion). However, despite these limitations, progression to the lamina propria is observed in about 40% and progression to muscle-invasive disease is observed in 20–25% [17].

Since patients harboring Ta high-grade UCB have a 5% to 25% chance of progression to muscle-invasive disease [19, 20], they should be classified, treated, and monitored as high-risk NMIBC patients. Restaging TURBT four to six weeks following initial TURBT is recommended as well as intravesical immunotherapy utilizing a six-week induction course of once-weekly BCG.
instillations followed by three weekly instillations of full-dose or reduced-dose maintenance therapy every six months for up to three years [21]. A prospective randomized trial comparing full-dose BCG for one year to three years demonstrated that the former schedule is sufficient for reducing the risk recurrence in intermediate-risk patients, while the three-year schedule reduced the risk of recurrence in high-risk patients [22]. In case of disease recurrence and/or progression before maintenance BCG has been completed, radical cystectomy should be considered for Ta high-grade or CIS and should be recommended for high-grade T1. This may be classified as early cystectomy since it is performed in the absence of muscle-invasive tumor stages; however, a significant percentage of these patients are pathologically upstaged at radical cystectomy, with up to 10% having lymph node metastases. For other NMIBC recurrences, TURBT and continuation of maintenance BCG has been utilized; however, it is unlikely that patients will have a favorable response to additional intravesical BCG if they have previously received at least two courses of intravesical BCG (6+6 or 6+3) in the preceding 24 months. Alternative intravesical therapy such as intravesical chemotherapy or novel investigational agents may be utilized. The timing of response to intravesical BCG is important. If early failure occurs after maintenance BCG has been completed, radical cystectomy should be considered for patients with high-risk NMIBC.

### Carcinoma in situ

Carcinoma in situ (CIS or TIS) is a flat, high-grade, non-invasive urothelial carcinoma. It has been estimated that 5% to 10% of all patients with NMIBC have CIS or concomitant CIS [23]. CIS is stratified by three different clinical appearances: primary CIS, with no previous or concurrent papillary tumors; secondary CIS, which has been detected during follow-up surveillance in patients with a history of a papillary tumor; and concomitant CIS, i.e. CIS in the presence of papillary tumors. The diagnosis of CIS is made in most cases by a combination of cystoscopy, urine cytology, and bladder biopsies. Cystoscopically, CIS often appears as multifocal erythematous “cobblestone-like” patches. Photodynamic diagnosis (PDD) cystoscopy has been reported in multiple studies to significantly improve detection of CIS over conventional white-light cystoscopy.

CIS is a precursor lesion of invasive urothelial carcinoma, with many of the same molecular genetic perturbations. Concomitant CIS is a significant risk factor for disease progression despite intravesical therapy. The European Organization for Research and Treatment of Cancer (EORTC) risk score attaches significant importance to the presence of CIS [24]. Accordingly, all patients diagnosed with CIS are classified as high-risk.

Some data are available on CIS that is not associated with Ta or T1 tumors. Disease-specific survival ranges from 85% to 90% following radical cystectomy for CIS only. However, early radical cystectomy has been suggested as overtreatment in approximately 50% of patients [25], as they respond to BCG or other intravesical therapies [26]. If bladder preservation is pursued, TURBT of all concomitant papillary tumors is required for appropriate staging. Outcome data on intravesical treatment are limited by the small number of patients treated in randomized trials [17]. The standard induction schedule of six weekly instillations yields a complete response rate of approximately 70%. Roughly 40–60% of initially non-responding patients will respond to a second series of three to six weekly instillations [17]. Approximately 40–50% of patients with CIS eventually fail intravesical BCG, and patients recurring have a poor prognosis with a high risk of progression to muscle-invasive disease and cancer-related mortality.

### Key Points

- High-grade Ta tumors are relatively uncommon, accounting for approximately 7% of Ta tumors and 4% of all Ta and T1 tumors.
- Inaccuracies in staging and grading can result in the misclassification of 75% of patients thought to have high-grade Ta tumors.
- Restaging TURBT is recommended for accurate diagnosis and staging.
- Because high-grade Ta tumors have a 5% to 25% chance of progression to muscle-invasive disease, these patients should be treated and monitored as high-risk patients. Thus, a six-week induction course of BCG and maintenance for one to three years is recommended.
Bladder Cancer: Diagnosis and Clinical Management

**T1 urothelial carcinoma of the bladder**

T1 tumors are characterized by invasion into the underlying lamina propria (also referred to as submucosa) but without involvement of the muscularis propria, and constitute approximately 20–30% of all NMIBC. The initial treatment after radiological imaging (typically CT urogram plus either chest X-ray or CT) is complete TURBT if possible. Traditional factors used to predict the clinical outcome of T1 UCB include tumor grade, multifocality, lymphatic and/or vascular invasion, micropapillary or aberrant histology, tumor size, concomitant CIS, depth of lamina propria invasion, and response to intravesical therapy [27]. Additional prognostic information is obtained after the repeat TURBT performed four to six weeks after the initial TURBT. The pathologic findings at repeat TURBT provide important prognostic information for recurrence and progression despite intravesical therapy. Patients with T0 do best and patients with T1 at re-TURBT have the greatest likelihood of disease progression [28, 29]. Nonetheless, current prognostic factors and risk stratification systems are not sufficiently accurate to predict individual outcomes for patients diagnosed with T1 high-grade urothelial UCB. The two treatment options are immediate radical cystectomy or repeat TURBT for additional staging, prognosis, therapeutic, and surveillance reasons, followed by subsequent intravesical BCG immunotherapy and delayed radical cystectomy in the case of tumor recurrence or progression. Multiple series have evaluated immediate versus delayed radical cystectomy for patients with T1 high-grade urothelial cell carcinoma, with no consensus reached.

Intravesical BCG has been shown to be superior to chemotherapy or TURBT alone in preventing recurrence and progression of NMIBC. A meta-analysis by the EORTC demonstrated a 27% reduction of progression with BCG treatment. In addition, maintenance intravesical BCG provides a 37% reduction in the rate of progression [21]. However, the impact of BCG on progression was not confirmed in an individual patient data meta-analysis [30], and in any case the long-term risk of tumor progression remains significant despite BCG. In long-term follow-up, roughly 30% of patients undergo radical cystectomy, 30% die of UCB, and 30% remain free of recurrence; this phenomenon is dubbed the “rule of 30s” [31]. While bladder preservation is an attractive option for many patients with high-grade NMIBC, a subgroup of patients with the higher risk of progression may benefit from early radical cystectomy. This includes patients with multifocal T1 high-grade UCB, tumor size > 3 cm, and concomitant CIS. Patients with at least two of these factors and CIS should be considered for immediate radical cystectomy [32]. The most important advantageous prognostic factor is the absence of high-grade UCB in the first surveillance cystoscopy [33].

**Non-surgical treatment options for BCG failure**

Patients with high-grade NMIBC refractory (persistent high-grade NMIBC at six months) or relapsing (recurrent high-grade NMIBC within 18–24 months of the last dose of maintenance BCG) are recommended to undergo radical cystectomy, which is associated with the greatest likelihood of cancer-specific survival and is considered the gold standard. However, a significant number of patients may be reluctant to undergo major surgery due to concerns about morbidity, mortality, changes in body image, the need for urinary ostomy, loss of sexual function, and a lack of understanding of the significant potential of loss of life expectancy. Repeat BCG treatment may be utilized for both BCG-resistant disease (i.e. persistence at three months after the induction cycle) and BCG-relapsing disease (i.e. recurrence after disease-free intervals of six months). However, multiple

**KEY POINTS**

- CIS is a flat, high-grade carcinoma occurring in 5% to 10% of patients with NMIBC.
- Diagnosis is made by cystoscopy (if available with photodynamic tools), urine cytology, and bladder biopsies, with histology being the determining factor.
- Monitoring requires urinary cytology and cystoscopy.
- A six-week induction course of intravesical BCG instillation plus one to three years of maintenance BCG has been demonstrated in a number of US and European studies to be associated with decreased recurrence and progression rates and is recommended.
- For BCG failure, radical cystectomy has to be considered. This is an area of unmet need for intravesical treatment.
courses of BCG (more than two courses of 6+6 or 6+3) are rarely effective. BCG in this setting is over-utilized and different therapeutic interventions in this setting are necessary and, at present, lacking [34].

The combination of BCG and Interferon-alpha has been proposed in this setting [35]. However, in a large randomized study in BCG-naïve patients with high-risk NMIBC, intravesical BCG/Intron A was no more efficacious than BCG alone [36]. Thus, it is unclear what benefit there is to utilizing the combination of BCG/Intron A for BCG refractory/relapsing disease.

The SWOG S0353 phase II trial evaluated 47 patients with recurrent NMIBC after two prior courses of BCG, 89% of which were high risk. Patients received an induction course of two-gram intravesical gemcitabine weekly ×6 followed by monthly maintenance instillations for twelve months. At 3 months, 12 months and 24 months, 47%, 28%, and 21% of patients were free of disease, respectively [37]. In a retrospective study from MSKCC, 27 of 69 patients achieved a complete response. These patients had a delayed time to cystectomy and no MIBC at cystectomy [38]. In a non-comparative study on valrubicin instillations in 90 patients after at least one course of BCG, 19 (21%) achieved a complete response after six months, but only 7 (8%) remained disease-free [39]. Taken together, success rates of intravesical salvage chemotherapy with gemcitabine and valrubicin have been reported to be low, and such an approach is limited to small patient cohorts who refuse radical cystectomy or who are not candidates for major surgery.

There are several reports on thermo-chemotherapy in patients with recurrent UCB following BCG. Nativ et al. [40] evaluated the efficacy of bladder wall hyperthermia (42 +/- 2°C) and intravesical mitomycin-C on 111 patients with recurrent NMIBC. Treatment was administered weekly for six weeks, followed by six maintenance sessions at four to six-week intervals. The disease-free survival rate was 85% and 56% after one and two years, respectively. Progression occurred in 3% of patients. A prospective randomized phase III trial is currently recruiting patients (HYMN trial).

**Early radical cystectomy**

Although five- and ten-year disease-specific survival after radical cystectomy for patients with NMIBC approaches 90%, the benefit of surgery must be balanced against the associated morbidity and mortality. A retrospective multi-center cystectomy series for T1 UCB without neoadjuvant chemotherapy reported rates of upstaging to muscle-invasive disease to be almost 50%, although the impact of restaging TURBT could not be assessed in this study [41]. In addition, it has been suggested in retrospective studies that patients with high-risk NMIBC who undergo early rather than delayed radical cystectomy for tumor relapse after initial treatment with TURBT and BCG have a better survival rate [42, 43].

When contemplating radical cystectomy before pathologically confirmed progression into muscle-invasive disease because of the at least 50% likelihood of microscopic metastatic disease at the time of diagnosis of clinical stage T2 disease, immediate (immediately after NMIBC diagnosis) and early (after BCG failure) radical cystectomy can be differentiated. It is reasonable to propose immediate radical cystectomy to those patients with NMIBC who are at highest risk of disease progression. Indications for immediate or early radical cystectomy for selected patients with NMIBC according to the authors of the chapter are as follows:

- Multiple and/or large T1 (HG/G3) tumors;
- T1 (HG/G3) tumors with concurrent CIS;
- Recurrent T1 (HG/G3) tumors;
- Early recurrent T1 (HG/G3) tumors;
- LVI;
- T1G3 and CIS in prostatic urethra;
- Presence of unusual histology of urothelial carcinoma such as micropapillary or plasmacytoid variants;
- Non-functioning bladder.

It is recommended to discuss immediate radical cystectomy and conservative treatment with BCG instillations at the time of presentation of high-risk NMIBC. Patients should be informed about the benefits and risks of both approaches. Individual factors such as gender, age of the patient, and tumor location (difficult areas to resect completely or survey adequately) in (pseudo)-diverticulum should be considered because of potential worse prognosis and understaging in women, life-long risk of progression after BCG in high-risk tumors, and the potential risk of tumor dissemination in diverticula [44].

Radical cystectomy is strongly recommended in patients with BCG refractory tumors, as mentioned above. Delaying radical cystectomy and waiting until documented progression to muscle invasion might lead
to decreased disease-specific survival. In patients in whom radical cystectomy is performed at the time of pathological muscle-invasive disease, the five-year disease-free survival rate may be as low as 30–50% with surgery alone. A significant number of these patients are pathologically upstaged at surgery, and about 10–15% have lymph node metastases [45].

**KEY POINTS**

- T1 is tumor invading the lamina propria of the bladder.
- The initial management consists of TURBT, repeat TURBT, and subsequent intravesical induction and maintenance BCG instillation therapy.
- In patients with adverse risk profiles, early radical cystectomy should be considered.
- For patients with BCG failure, radical cystectomy remains the gold standard treatment.

**References**


CHAPTER 3

Utility of urine biomarkers

Derya Tilki¹ and Alexandre R. Zlotta²

¹ Department of Urology, University of California, Davis, Medical Center, Sacramento, CA, USA
² Department of Surgical Oncology (Urology), Mount Sinai Hospital and Princess Margaret Cancer Centre, Toronto, Canada

Introduction

Urinary biomarkers are needed to improve the care and reduce the costs of managing bladder cancer. Urine tumor biomarkers have been proposed as non-invasive diagnostic tools in patients who present with hematuria, for patients at high risk for developing bladder cancer, and for the early detection of recurrent disease in patients under surveillance following a diagnosis of bladder cancer. The performance of a valuable bladder cancer biomarker should ideally be characterized by high sensitivity and specificity both for the purpose of screening and monitoring. The use of such a biomarker might also be expected to reduce the number of cystoscopies for the surveillance of non-muscle-invasive bladder cancer. Currently, diagnosis and surveillance of bladder cancer consist of cystoscopy and cytology, but both have obvious limitations [1]. Cystoscopy identifies most (although not all) papillary and solid lesions, but is invasive. Urine cytology has reasonable sensitivity and specificity for the detection of high-grade bladder cancer (including carcinoma in situ), but sensitivity for detection of low-grade tumors ranges from only 4% to 31% [2].

The study of many urinary biomarkers has been possible due to the improved understanding of the underlying bladder cancer molecular alterations that drive bladder cancer initiation and progression, whether at the genetic, epigenetic, or proteomic level.

KEY POINTS

• As bladder cancer has a high rate of recurrence, non-invasive urine markers offer potential to improve the management of non-muscle-invasive bladder cancer.
• Marker performance can vary widely depending on the population that is tested, how the samples were stored, how the test was run, and how the results were analyzed.
• Positive predictive value (PPV) and negative predictive value (NPV) are often difficult to calculate accurately, as they are dependent on an unknown prevalence in the population.
• The comparison of biomarkers is imprecise and error prone, except within a given study.
• Some FDA-approved urine markers have been incorporated in the care of low-grade bladder cancer with reduced frequency of cystoscopies.
• The majority of investigated urine markers report equal or higher sensitivities for bladder cancer detection than cytology, but none of these tests meet the criteria of an ideal urine marker.
• Multiple potential markers have been investigated, but require further standardized testing and validation in different populations.
• Until reliable urine marker systems have been identified and validated, cystoscopy will remain the gold standard for bladder cancer detection, and cystoscopy with cytology will remain the standard for surveillance [1].
As of now, six urine markers have been approved by the US Food and Drug Administration (FDA) for clinical use in the detection of bladder cancer (Table 3.1). Several promising investigational urine-based bladder cancer marker systems demonstrate an ability to detect differences in the presence of cell surface antigens on exfoliated cells, soluble proteins, nuclear morphology, or gene expression. One of the greatest challenges facing effective biomarker development in this arena is the need to identify both high- and low-grade lesions which are often characterized by very different molecular and proteomic features. The “one size fits all” paradigm may have to be revisited for urinary biomarkers given the molecular heterogeneity of the disease.

### FDA-approved urine markers

#### Bladder tumor antigen (BTA) tests

The BTA stat is a qualitative point-of-care test with immediate result, whereas BTA TRAK is a quantitative test requiring trained personnel and a reference laboratory. These assays detect human complement factor H-related protein in the urine of patients with bladder cancer [3].

The reported overall sensitivity and specificity for the BTA stat test are 57% to 83% [4–6] and 60% to 92% [7, 8], respectively. In healthy persons, the specificity is 97%, but in patients with benign genitourinary conditions, the specificity is only 46% [7]. Hematuria unrelated to bladder cancer can lead to false-positive results [9, 10]. In a recent prospective, multi-center trial of over 500 patients, the reported sensitivity of BTA stat to monitor for bladder cancer recurrence was greater than that of cytology, particularly in Grade 1 lesions (47.9% vs. 12.5%) [11]. However, intravesical treatment, benign prostatic hyperplasia, kidney stones, and urinary tract infections caused a high false-positive rate, and the BTA stat test would have missed 46.6% of tumors detected on cystoscopy.

The BTA TRAK test is a quantitative sandwich immunoassay [12]. The cutoff limit of human complement factor H-related protein to detect bladder cancer is 14 U/mL [13]. Using this cutoff, the reported overall sensitivity is 62% to 91% [13–20]. However, with a set sensitivity of 90%, the specificity of BTA TRAK was only 24.8% [13].

### Table 3.1 FDA-approved urine marker assays for bladder cancer.

<table>
<thead>
<tr>
<th>Urine marker assay</th>
<th>Analyte</th>
<th>Technique</th>
<th>Sensitivity &amp; specificity</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTA Stat</td>
<td>Human Complement Factor H-Related Protein</td>
<td>Qualitative; Point-of-care, Colorimetric antibody–antigen reaction</td>
<td>57–83% &amp; 60–92%</td>
<td>Diagnostic &amp; surveillance [10/08/1999]</td>
</tr>
<tr>
<td>BTA TRAK</td>
<td>Human Complement Factor H-Related Protein</td>
<td>Quantitative; Sandwich immunoassay</td>
<td>62–91% &amp; 24.8% (Set sensitivity of 90%)</td>
<td>Diagnostic &amp; surveillance [04/15/1998]</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>Carcinoembryonic antigen and two bladder tumor cell-associated mucins</td>
<td>Cytology and immunofluorescence</td>
<td>50–100% &amp; 69–79%</td>
<td>Surveillance [02/23/2000]</td>
</tr>
<tr>
<td>NMP22</td>
<td>Nuclear Matrix Protein No.22</td>
<td>Quantitative; Sandwich-type, microplate, enzyme immunoassay</td>
<td>47–100% &amp; 60–90%</td>
<td>Surveillance [1/18/2000]</td>
</tr>
<tr>
<td>NMP22 BladderChek</td>
<td>Nuclear Matrix Protein No.22</td>
<td>Qualitative; Point-of-care, test cartridge with reporter and detector antibodies</td>
<td>50–90% &amp; 85.7%</td>
<td>Diagnostic &amp; surveillance [7/30/2002]</td>
</tr>
<tr>
<td>UroVysion</td>
<td>Aneuploidy in chromosomes 3, 7, and 17 as well as loss of the 9p21 locus of the P16 tumor suppressor gene</td>
<td>FISH</td>
<td>36–100% &amp; 89–96%</td>
<td>Diagnostic &amp; surveillance [10/24/2005]</td>
</tr>
</tbody>
</table>
As with the BTA stat test, benign genitourinary conditions may lead to false-positive results [13, 17, 19, 21]. Both tests are approved by the FDA only in combination with cystoscopy for monitoring of bladder cancer. Because of their high false-positive rates, they cannot be recommended without cystoscopy.

**ImmunoCyt**

ImmunoCyt (Scimedx Corp., Denville, NJ) combines cytology with an immunofluorescence assay [22]. It detects cellular biomarkers for bladder cancer in exfoliated urothelial cells using fluorescent monoclonal antibodies for a high molecular weight form of carcinoembryonic antigen and two bladder tumor cell-associated mucins. The test requires trained personnel, is expensive, and a large number of exfoliated cells are necessary to perform an accurate test [23, 24]. ImmunoCyt has a reported overall sensitivity of 50% to 100% [25–27]. Its specificity has been reported as 69% to 79%, with a higher false-positive rate in patients with benign prostatic hyperplasia or cystitis [26]. It has an improved sensitivity when compared to cytology, especially in low-grade tumors, but this is accompanied by a lower specificity and reduced positive predictive values (PPV) [28]. The test may be useful as an adjunct to cystoscopy and should be used only for monitoring patients with bladder cancer.

**Nuclear matrix protein 22 tests**

There are two marker tests for bladder cancer detecting nuclear mitotic apparatus protein 22 (NMP22) in voided urine: the original NMP22 bladder cancer test kit (Matritech Inc., Newton, MA), a laboratory-based, quantitative, sandwich-type, microplate enzyme immunoassay, and the NMP22 BladderChek (Matritech), a qualitative, point-of-care test cartridge containing the NMP22 detecting and reporter antibodies. Both are FDA-approved for use in bladder cancer surveillance. NMP22 BladderChek is also approved as a screening test for individuals who have symptoms of or are at risk for bladder cancer.

The sensitivity of the original NMP22 immunoassay has ranged from 47% to 100% and its specificity from 60% to 90% depending on the cutoff value [4–7, 17, 19, 29–33]. The specificity is significantly decreased in the presence of benign inflammatory or infectious diseases, renal or bladder calculi, a foreign body, bowel interposition, other genitourinary cancer, or instrumentation [5]. Intravesical bacillus Calmette-Guérin does not alter the performance characteristics of NMP22 [34]. Despite the promising data, the quantitative enzyme NMP22 immunoassay has not been widely used due to a high false-positive rate.

In a multi-institutional trial, the addition of the NMP22 BladderChek test to cystoscopy improved the detection rate of bladder cancer in patients with risk factors for bladder cancer [35]. The NMP22 BladderChek test sensitivity was 50% and 90% for non-invasive and invasive cancer, respectively, with an overall sensitivity of 55.7%. In contrast, cytology in this study performed particularly poorly, with comparable sensitivities of 16.7% and 22.2% in non-invasive and invasive bladder cancer, respectively, with an overall sensitivity of 15.8%. Overall specificity was still higher for cytology at 99.2% compared with 85.7% for NMP22 BladderChek.

In a recent study, the clinical benefit of NMP22 in the surveillance of patients with non-muscle-invasive bladder cancer and negative cytology was assessed by a decision-curve analysis [36]. The authors observed that NMP22 can help in decision making regarding immediate versus delayed cystoscopy; however, if a clinician would recommend cystoscopy even in the setting of a low risk of recurrence or progression, NMP22 would not add any clinical benefit to the surveillance algorithm. In other studies, NMP22 was shown to have potential as a cost-effective adjunct test [37, 38].

**UroVysion**

UroVysion (Abbott Molecular, Inc., Des Plaines, IL) is a multi-target, fluorescence in situ hybridization (FISH) assay that detects aneuploidy in chromosomes 3, 7, and 17 as well as loss of the 9p21 locus of the P16 tumor suppressor gene [39]. This test has been approved by the FDA both for monitoring patients with a history of bladder cancer and for bladder cancer detection in patients with hematuria. The FISH test combines assessment of the morphologic changes of conventional cytology with molecular DNA changes. Each probe is a fluorescently labeled, single-stranded DNA fragment complementary to specific target sequences of cellular DNA that are denatured to allow hybridization with the probe. A minimum of 25 morphologically abnormal cells is viewed. If four or more cells exhibit polysomy of 3, 7, or 17, or twelve or more cells exhibit loss of 9p21, the case is considered positive for tumor. However, no uniform criteria exist for a positive UroVysion assay at this time.

In the majority of comparative studies, FISH outperformed cytology across all stages and grades of bladder cancer [40–42]. The overall sensitivity of FISH was superior to cytology (74% vs. 48%), especially in high-grade
Utility of urine biomarkers

disease such as carcinoma in situ (100% for FISH vs. 67% for cytology) [43]. A recent meta-analysis of FISH reported that the overall performance of FISH was better than that of cytology (area under the curve: 0.87 vs. 0.63) [43]. This difference, however, was almost entirely attributable to the difference in performance in diagnosing Ta patients.

It has been suggested that some patients with a positive FISH result and negative cystoscopy might eventually develop urothelial cancer, because several studies have found that 85–89% of patients with a false-positive test had a positive bladder biopsy within 12 months of the test [44, 45]. However, others have found that the recurrence rate after a positive FISH result and negative cystoscopy can be less than 50% [46]. The real role of a positive FISH result remains unclear, because independent of risk stratification, most patients with non-muscle-invasive bladder cancer will experience disease recurrence.

Combining morphology with FISH may prove an alternative modality for cancer detection [47, 48]. Using the Duet automatic scanning system (BioView, Ltd, Rehovat, Israel), which examines both morphology and FISH scoring, an examination of voided urine specimens from 115 patients with negative or atypical cytology found that 44% of these patients did not have a prior diagnosis of bladder cancer. The combination of morphology and FISH resulted in 100% sensitivity and 65% specificity [47].

The high cost and the necessity of large urine volume or tumor burden as well as exfoliation of tumor cells have prevented wider use and approval as a standalone test [49]. Another limitation is that the FISH assay does not detect diploid cells without 9p21 deletions.

**Investigational urine markers**

Several recent reviews have discussed the current potential urine markers for bladder cancer under investigation [50–52]. A subset of these preliminary candidates is discussed below and in Table 3.2.

<table>
<thead>
<tr>
<th>Type</th>
<th>Targets</th>
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<tbody>
<tr>
<td>Epigenetic (methylation)</td>
<td>FGFR3 mutations</td>
</tr>
<tr>
<td></td>
<td>DAPK</td>
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<td></td>
<td>BCL2</td>
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<td>RAR-beta</td>
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<td></td>
<td>E-cadherin</td>
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<td></td>
<td>P16</td>
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<tr>
<td></td>
<td>TWIST1</td>
</tr>
<tr>
<td>Microsatellite</td>
<td>4p</td>
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<tr>
<td></td>
<td>11p</td>
</tr>
<tr>
<td>miRNA</td>
<td>200a,b,c/141/429</td>
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<tr>
<td></td>
<td>125b</td>
</tr>
<tr>
<td></td>
<td>126</td>
</tr>
<tr>
<td></td>
<td>199a</td>
</tr>
<tr>
<td>mRNA</td>
<td>uRNA</td>
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<tr>
<td></td>
<td>CxBladder</td>
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<tr>
<td></td>
<td>ETS2</td>
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<tr>
<td></td>
<td>MXRA8</td>
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<tr>
<td>Protein</td>
<td>Hyaluronic acid</td>
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<td></td>
<td>Hyaluronidase</td>
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<tr>
<td></td>
<td>Cytokeratins 8 &amp; 18 (UBC test)</td>
</tr>
<tr>
<td></td>
<td>IL-8</td>
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<td></td>
<td>MMP</td>
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<td></td>
<td>HAI-1</td>
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</tbody>
</table>
**AURKA**
The Aurora kinase A (AURKA) gene encodes a serine/threonine kinase associated with aneuploidy and chromosome instability. It has been explored in urine sediment by FISH. A training set was used to establish test conditions. A separate testing set of 100 patients with bladder cancer, 92 healthy individuals, and 56 patients with benign urologic disease reported a test sensitivity of 87.0% and a specificity of 96.6% [53]. A higher degree of gene amplification was associated with increasing grade of disease.

**BLCA-1 and BLCA-4**
BLCA-1 and BLCA-4 are nuclear transcription factors present in bladder cancer. BLCA-1 is not expressed in non-malignant urothelium [54], while BLCA-4 is expressed in both the tumor and adjacent benign areas of the bladder but not in non-malignant bladders [55]. BLCA-4 is measured in the urine using an ELISA assay; its reported sensitivity ranges from 89% to 96% and its specificity reaches 100% [56, 57]. Similarly, in a small study, BLCA-1 demonstrated good performance with 80% sensitivity and 87% specificity [54]. Tumor grade did not affect their expression. However, up to 19% of patients with spinal cord injuries have elevated BLCA-4 levels [58].

**CEACAM1**
Bladder tumor growth and progression depend on angiogenesis. Human carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is a cell adhesion molecule with proangiogenic activity. It has previously been observed that CEACAM1, which is ubiquitously expressed in the luminal surface of normal bladder urothelium, is downregulated in bladder cancer cells while it is concurrently upregulated in endothelial cells of adjacent blood vessels [59]. This differential switch in CEACAM1 expression is accompanied by an upregulation of proangiogenic and prolymphangiogenic factors. Tilki et al. constructed an ELISA assay for CEACAM1 and measured levels in voided urine specimens from patients with bladder cancer and control subjects without cancer, with common non-malignant urologic pathologies, or with past history of bladder cancer without present disease [59]. Higher urinary levels of CEACAM1 were associated with bladder cancer presence, advanced stage, and invasive tumor stage. Using ROC analyses, a cutoff of 110 ng/mL was established to yield a sensitivity of 74% and a specificity of 95%.

**Epigenetic urinary markers**
Epigenetic control of gene expression is fundamental to cancer biology and is key in bladder cancer. As a result, assays for epigenetic alterations have the potential to become accurate diagnostic biomarkers. Analysis of gene methylation has been shown to be feasible from voided urine [60, 61]. Friedrich et al. analyzed the methylation status of different markers in urine samples of patients with bladder cancer and found that methylation of DAPK, BCL2, and TERT (the human telomerase reverse transcriptase) in urine sediment DNA from bladder cancer patients was detected in the majority of samples (78%), whereas they were unmethylated in the urine sediment DNA from age-matched cancer-free individuals [61]. Microsatellite markers and gene promoter hypermethylation may help detect bladder cancer [62, 63]. Comparing a methylated gene panel from urine samples of bladder cancer and control patients, the sensitivity of the methylated gene panel was > 80% and specificity > 90%. In urine, hypermethylation of DAPK, RARbeta, E-cadherin, and p16 has been shown to have a good sensitivity and specificity for bladder cancer detection [64]. Renard et al., studying DNA extracted from non-cancerous and bladder cancer tissue, described frequent methylation of TWIST1 and NID2. They observed a sensitivity and specificity for this two-gene panel > 90% in urine samples collected from bladder cancer patients, compared to cytology (sensitivity 48% and specificity 96%) [65]. Scher et al. developed a small urine volume assay for the detection of BCa based on methylation-specific PCR of BCL2, CDKN2A, and NID2 with a sensitivity of 80.9% and 86.4% [66]. A panel combining several methylation markers (MYO3A, CA10, SOX11, NKX6-2, PENK, and DBC1) achieved 81–85% sensitivity and 95–97% specificity for detection of BCa [67].

**FGFR3 mutations**
Mutations (activating mutations) in the fibroblast growth factor receptor 3 (FGFR3) occur in 50% of primary bladder tumors and have been associated with good prognosis [68]. FGFR3 mutations are especially prevalent in low-grade/stage tumors, with pTa tumors harboring mutations in 85% of the cases [68]. Van Oers et al. described a simple assay for the simultaneous detection of nine different FGFR3 mutations in bladder cancer and voided urine [68]. In urine samples from patients with a mutant tumor, the sensitivity of mutation detection was 62%. Zuiverloon et al. evaluated
FGFR3 mutation in voided urine to detect recurrences during surveillance in patients with low-grade, non-muscle-invasive bladder cancer with a known FGFR3-mutant tumor. The sensitivity (58%) of the assay for detection of recurrence was higher than urinary cytology only, but still far from perfect [69].

**Hyaluronic acid and hyaluronidase**

Urine hyaluronic acid (HA), a non-sulfated glycosaminoglycan, has been shown to yield 92% sensitivity and 93% specificity for bladder cancer detection [70]. Hyaluronidase (HAase), an endoglycosidase, degrades HA into small fragments that promote angiogenesis [71]. There is a positive correlation between the secretion of HAase by bladder cancer cells and their invasive potential. A five- to eight-fold elevation of HAase in the urine of patients with Grade 2 or 3 bladder cancer could be detected [72].

The levels of HA and HAase are combined in the HA-HAase test [86]. In a study of 225 urine samples from 70 patients with known bladder cancer, the HA-HAase test performed better than the BTA stat test, with a reported sensitivity of greater than 90% across all tumor grades [73]. However, the accuracy of HA-HAase for detecting low-grade tumors was poor and lower than that of voided-urine cytology [74]. Further refinement of the assay and evaluation in larger clinical trials would help define the clinical applicability of this marker.

**Microsatellite analysis**

One of the most common genetic changes in bladder cancer is loss of heterogeneity in chromosome 9 [75]. Chromosomes 4p, 8p, 9p, 11p, and 17p also often display loss of heterogeneity in patients with bladder cancer [76, 77]. Several studies have analyzed voided urine with 17 to 20 microsatellite biomarkers [75, 78]. The overall sensitivity from these studies ranged from 72% to 97%, and overall specificity ranged from 80% to 100%. Microsatellite biomarkers outperformed cytology in low-grade, low-stage tumors. In a study of 228 patients, a sensitivity of 58% and a specificity of 73% were reported for this test [79]. Microsatellite analysis can predict recurrences of low-grade tumors in up to 80% of the cases, but lacks sensitivity [62].

**miRNA markers**

MicroRNAs (miRNAs) are non-coding RNAs that post-transcriptionally regulate gene expression [80]. They might serve as an ideal bladder biomarker as they are stable within urine and require little handling care [81]. MiRNAs are more stable against nuclease degradation due to their small size. Urine contains many nucleases, and assays to examine mRNA expression often fail due to target degradation or require stringent pre-laboratory handling of the urine sample. Urinary miRNA expression has been reported and the upregulation of miR-126/182/199a was found to discriminate bladder cancer patients from disease-free controls [82]. The combination of miR-126 and -182 identified up to 77% of bladder cancer cases, despite a lack of differential expression for any of these miRNAs in malignant and normal urothelium [83]. Puerta-Gil et al. verified that the differential expression of miR-143, miR-22, and miR-452 in urinary specimens showed promise as a non-invasive diagnostic test [84]. MiR-96 and miR-183 have been demonstrated to have stepwise expression increase with tumor grade and stage in addition to post-surgical reduction [85]. Miah et al. used a combination of miRs-135b/15b/1224-3p to detect bladder cancer with 94.1% sensitivity and 51% specificity which was correct in 86% of patients [86]. Recently, a pilot study demonstrated urinary miR-125b having an average 10.42-fold decrease (p < 0.01) and miR-126 showing an average 2.70-fold increase (p = 0.30) in the cancer samples compared to the normal controls [87]. Larger clinical trials are necessary to further define these markers.

**mRNA markers**

The analysis of gene expression in bladder cancer tissue to further characterize BC subsets and gain insight into its biology has been extensively studied [88]. As mRNA is unstable in many body fluids, the use of stabilizers for its detection in urine has been raised and may be a limiting factor to widespread use [89]. However, partially degraded RNA samples analyzed by cDNA microarrays seem to yield gene expression profiles comparable to those obtained using intact RNA [90]. Messenger RNA (mRNA) based commercial assays uRNA and Cxbladder developed by Pacific Edge Ltd have demonstrated increased sensitivity in detection of BCa in comparison to NMP22 assay in the setting of hematuria [91]. In a 485-patient study, uRNA had an increased sensitivity of 62.1% to NMP22 50% with a pre-specified specificity of 85% for the investigational assays. Cxbladder assay distinguished low-grade Ta tumors with a sensitivity of 91% and specificity of 90%. Currently, Cxbladder is forgoing FDA approval and anticipating launch in the United States after receiving CLIA registration in March of 2013. Other potential RNA targets for future assay
developments have been recently detected in a combination of transcriptome profiling and RT-PCR analysis, revealing confirmation of previously implicated genes to BCa, other cancers, and several new targets (TMEM45A, SYNGR1, and MXRA8) [92].

Mengual et al. have identified a 12+2 gene expression signature for BC diagnosis and prediction of tumor aggressiveness on urine samples. Overall, this gene set panel had 98% sensitivity and 99% specificity in discriminating between cases and control samples and 79% sensitivity and 92% specificity in predicting tumor aggressiveness. They then analyzed the efficacy of this 12+2 gene set in voided urine and observed sensitivities and specificities of 89% and 95%, respectively and of 79% and 91%, respectively for predicting tumor aggressiveness [93]. They validated their findings using an independent cohort. Their 12+2 gene expression signature has an overall sensitivity of 80% with 86% specificity (AUC 0.914) in discriminating between bladder cancer and control samples and 75% sensitivity and 75% specificity (AUC 0.83) in predicting tumor aggressiveness in the validation set of urines. Three new signatures composed of 2, 5, and 10 genes and a 12‐gene prior signature for diagnosis increased the area under the curve (AUC) to 0.913, 0.941, 0.949, and 0.944, respectively [94].

Survivin
Survivin, a novel member of the inhibitor-of-apoptosis gene family, is prominently expressed in many types of cancer. Survivin messenger ribonucleic acid (mRNA) is overexpressed in human cancers and can be detected in urine using a bio-dot immunoassay incorporating a rabbit polyclonal anti-survivin antibody [95]. Urinary levels of survivin gene activation, both at the protein and the mRNA level, are associated with bladder cancer presence, higher grade, and advanced pathologic stage [96–99]. In the first study to evaluate the diagnostic potential of survivin in bladder cancer, survivin protein and mRNA were detected in all of 47 patients with bladder cancer, but in only 3 of 35 patients with negative cystoscopic evaluation [98]. Another study showed a correlation of urinary levels of survivin with increased risk of bladder cancer presence and higher grade, but not tumor invasion [97]. In this study, survivin sensitivity was 64% and specificity was 93%. More recently, measurement of urinary survivin mRNA was evaluated in 50 patients with suspicion of new or recurrent bladder cancer prior to transurethral resection [100] to yield a sensitivity of 83% and a specificity of 88%. Although the results are promising, the lack of assay standardization and cutoff value must be resolved before possible clinical use [97].

Telomerase
Telomerase is a ribonucleoprotein enzyme that counteracts chromosomal instability by synthesizing telomeres [101–104]. Malignant neoplasms, including bladder cancer [105], have been shown to produce telomerase and thus to regenerate telomeres and prevent cell death [106]. The standard technique to measure telomerase activity is the telomeric repeat amplification protocol (TRAP) assay [106]. Another telomerase-based assay detects the catalytic subunit of telomerase, human telomerase reverse transcriptase, using the polymerase chain reaction. The human telomerase reverse transcriptase polymerase chain reaction has a higher sensitivity than the TRAP assay, ranging between 75% and 100% [107, 108]. The reported overall sensitivity of telomerase testing for the detection of bladder cancer is mostly in the range of 70% to 86% (7–100%) [4, 31, 109–117] with overall specificity mostly in the range of 60% to 70% (24–90%) [4, 31, 109, 111–114, 116–119]. In 2005, researchers who examined a range of TRAP cutoffs found good overall performance characteristics with a reported sensitivity of 90% and specificity of 88% for the arbitrary cutoff of 50 enzyme units [120]. The analysis of hTERT expression in exfoliated cells from patients with bladder cancer has been performed using quantitative PCR [121].

hTERT, SENP1, PPP1CA, and MCM5 transcripts have been investigated to predict and diagnose bladder cancer recurrences in 123 prospectively cross-sectional collected urine samples from 117 patients with bladder cancer and 111 controls. Sensitivity and specificity for hTERT were 63% and 73%, respectively. A positive hTERT result (p = 0.0001) was significantly associated with subsequent tumour recurrence [122].

Urinary UBC test
IDL Biotech AB (Bromma, Sweden) developed the UBC, a point-of-care qualitative assay, and the UBC enzyme-linked immunosorbent assay (UBC II ELISA), a quantitative assay that measures cytokeratins 8 and 18 in the urine [123, 124]. A study measuring UBC Rapid in the urine of 180 patients found an overall sensitivity of 66% and specificity of 90% [124]. In a comparative study, however, BTA stat and BTA TRAK outperformed the UBC Rapid test, particularly with regards to sensitivity [125]. Similarly, cytology showed
a better sensitivity and specificity than either UBC or UBC II ELISA [126]. Recently, investigators compared the sensitivity and specificity of cytology (19.8% and 99%), BTA (53.8% and 83.9%), and UBC (12.1% and 97.2%) [15]. For carcinoma in situ, UBC had a higher sensitivity (100%) compared to cytology (66.6%) and BTA (0%). The overall performance of the UBC test is not superior to cytology or other current biomarkers.

**Additional proteins and urinary proteomics**

Several groups have investigated other protein biomarkers to identify bladder cancer. Kelly et al. revealed that when Mcm5 is used in combination with NMP22, 95% of life-threatening diagnoses were identified (Grade 3, CIS, or stage ≥ pT1) [127]. Irmak et al. identified increased urinary orosomucoid (ORM) and human zinc-alpha2-glycoprotein (ZAG) in bladder cancer patients with the highest levels in invasive bladder cancer stages (pT2–3) [128]. Other groups have targeted inflammatory process proteins by evaluating a panel of interleukins and heat shock proteins with subsequent identification of significantly elevated IL-13 and HSP60 in BCa urine samples with an overall PPV of 74% and NPV of 76% [129]. The liquid chromatography-tandem mass spectrometry (LC-MS/MS) proteomic approach has identified analytes including calcium-signal transducer 2 (TACSTD2) from urinary micro particles [130] and glycoprotein A1TA with a sensitivity of 74% and specificity of 80% from BCa urine samples [131]. Additionally, Shinwell et al. explored a dualistic approach with combination of secretome-transcriptome analysis to identify Midkine and HAI-1, suggesting that avenues other than direct proteomic analysis of patient samples are viable in biomarker discovery [132]. Recently, a case-control phase II study of a panel of eight biomarkers (IL-8, MMP and 10, PAI-1, VEGF, ANG, CA9, and APOE) discovered through genomics and proteomics outperformed UroVysion with 74% sensitivity and 90% specificity [133]. Proteins have potential as robust biomarkers with advancement of detection and identification technology.

**Useful web links**


**Note**

This article has been adapted and reprinted (with modifications and updates) from Tilki D, Burger M, Dallagni G, et al.: Urine markers for detection and surveillance of non-muscle-invasive bladder cancer. *Eur Urol*. 2011Sep; 60(3): 484–492, with permission from Elsevier.

**References**


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Utility of urine biomarkers


Utility of urine biomarkers


CHAPTER 4

Novel endoscopic techniques for the detection of bladder cancer

Ayman Soubra1, Joseph C. Liao2, and Badrinath Konety1
1 Department of Urology, University of Minnesota, Minneapolis, MN, USA
2 Department of Urology, Stanford University School of Medicine, Stanford, CA, USA

KEY POINTS

• The gold standard for bladder cancer surveillance is white light cystoscopy. The shortcomings of this modality are its inability to detect subtle flat lesions, more specifically carcinoma in situ, which is a major prognostic factor, and its inability to differentiate benign from cancerous lesions.

• Photodynamic diagnosis is an improvement to WLC that uses a contrast agent and blue light cystoscopy to better detect bladder lesions.

• Narrow band imaging is a modification of WLC which uses light of two specific wavelengths. This enhances the visualization of mucosal and submucosal vessels to better detect and characterize lesions.

• Confocal laser endomicroscopy is fluorescent microscopic imaging of the bladder wall that provides information about cellular morphology as well as the tissue microarchitecture. This helps detect dysplastic changes in the mucosa.

• Optical coherence tomography is based on infrared light imaging of the bladder that aids in characterizing the different layers of the bladder wall and detecting any changes in them. This is mostly beneficial at sites found to be suspicious on surveillance cystoscopy.

• Photodynamic diagnosis and confocal laser endomicroscopy require the instillation of a contrast agent either into the bladder or intravenously. This adds to the complexity, cost, and time of the procedure.

• Randomized studies with long-term follow-up are needed to determine whether there is a survival benefit to these modalities over WLC, whether they stand alone as imaging techniques or will always need to be used with WLC, and if the increased complexity is cost effective when compared to WLC.

Bladder cancer is the second most common genitourinary cancer and the fifth most common cancer overall in the United States. In 2013, there were 72,570 new cases and 15,210 cancer-related deaths [1]. Bladder cancer is also the most expensive cancer in the US from diagnosis to death, mostly due to its high prevalence, high recurrence rate, and the need for close follow-up [2].

At presentation, up to 85% of patients are diagnosed with non-muscle-invasive bladder cancer (NMIBC), including Ta, T1, and carcinoma in situ (CIS) [3]. Up to 20% of NMIBC will progress to muscle-invasive disease [4]. While tumor size, multifocality, and tumor genetics affect the recurrence rate, little can be done about these factors. In contrast, complete resection should always be strived for and is the key in achieving a longer disease-free interval, especially since it is believed that most of what is considered early recurrence may be persistent lesions missed during the initial TUR [5]. Early diagnosis,
complete resection, and close surveillance reduce disease progression.

Modern white light cystoscopy (WLC), the standard approach to evaluating the lower urinary tract and managing NMIBC, has been the result of sequential landmark innovations over the last two centuries. The first report of endoscopic surgery concerned the extraction of a urethral papilloma by Desormeaux in 1853. This was followed by the invention of the cystoscope by Nitze in 1894, the development and refinement of the resectoscope by Stern and McCarthy in the early 1930s, and the introduction of flexible fiberoptic cystoscopes in the 1980s [6].

Despite significant advances, WLC has numerous limitations that can affect accurate detection and staging of bladder cancer. Up to 20% of flat CIS lesions may be missed [7], and benign inflammatory lesions cannot easily be distinguished from malignant ones. In the absence of proper diagnosis and treatment, 54% of patients with CIS will progress to muscle-invasive disease [8]. Complete resection of all visible tumors and the presence of muscularis propria in the resected samples are recognized benchmarks of successful TUR which are critical for accurate local staging. Data from numerous published series, however, showed the absence of muscularis propria in resected tumor samples ranging from 30–50%. This is associated with a higher risk of residual T1 tumors and understaging of T2 diseases in up to 40% of cases identified on repeat TUR. Improved optical imaging may lead to more complete initial TUR and decrease cancer recurrence and progression [9].

To address the shortcomings of WLC, several complementary endoscopic technologies have been developed and are under investigation. These technologies are not intended to replace, but rather to augment, WLC. They include fluorescence cystoscopy/photodynamic diagnosis (FC/PDD), narrow band imaging (NBI), confocal laser endomicroscopy (CLE), and optical coherence tomography (OCT). These technologies can be broadly categorized based on the field of view and the need for exogenous contrast agent (Figure 4.1). Macroscopic imaging modalities (PDD and NBI) can survey large areas of the bladder mucosa and are thus better at contrasting neoplastic lesions from surrounding benign urothelium. On the other hand, imaging technologies

<table>
<thead>
<tr>
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<th>Macroscopic</th>
<th>Microscopic</th>
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<tr>
<td>Photodynamic diagnosis (PDD)/fluorescence cystoscopy</td>
<td>Narrow band imaging (NBI)</td>
<td>Optical coherence tomography (OCT)</td>
</tr>
<tr>
<td>Field of view</td>
<td>Wide</td>
<td>Wide</td>
</tr>
<tr>
<td>Contrast agent</td>
<td>Yes – HAL</td>
<td>No</td>
</tr>
<tr>
<td>Scope/probe size</td>
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<td>Scope: 5–7 mm</td>
</tr>
<tr>
<td>Depth</td>
<td>Mucosal</td>
<td>Mucosal</td>
</tr>
<tr>
<td>Resolution</td>
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<td>mm</td>
</tr>
<tr>
<td>Commercially available?</td>
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<td>Yes</td>
</tr>
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</table>

Figure 4.1 New bladder-imaging technology: characteristics and specifications.
with microscopic field of view enable subsurface imaging and optical biopsy to reveal the tissue microarchitecture, cellular morphology, and potentially the depth of invasion. Some of the imaging modalities require exogenous imaging agents to enhance contrast enhancement, which does add to the cost and technical complexity of the procedure. NBI and PDD require specialized cameras while OCT and CLE are probe-based and compatible with the working channel of a standard WLC [10].

**Photodynamic diagnosis (PDD)**

Photodynamic diagnosis is the most extensively studied among the four endoscopic technologies. It is based on intravesical instillation of photoactive porphyrin analogues such as 5-aminolevulinic acid (5-ALA) and hexaminolevulinate (HAL). Although earlier PDD studies were performed using 5-ALA (which causes significant photosensitivity), HAL is more potent and approved for clinical use in Europe as Hexvix and in the United States as Cysview [11]. HAL is an ester of the heme precursor ALA. After intravesical instillation, HAL is taken up by bladder epithelial cells where it is used as a precursor in the formation of the photoactive intermediate protoporphyrin IX (PpIX) and other photoactive porphyrins (PAPs). These intermediates are reported to accumulate preferentially in neoplastic cells as compared to normal urothelium, partly due to altered enzymatic activity in the neoplastic cells. After excitation with blue light (375 to 440 nm), PpIX and other PAPs return to a lower energy level by fluorescing; this can be detected and used for cystoscopic detection of lesions. The fluorescence from tumor tissue appears bright red and demarcated, whereas the background normal tissue appears dark blue [12] (Figure 4.2).

The sensitivity of bladder cancer detection for PDD is higher than WLC (92%, 95% CI: 80–100% vs. 71%, 95% CI: 49–93%) but the specificity is lower than WLC (57%, 95% CI: 36–79% vs. 72%, 95% CI: 47–96%) [13]. In several prospective studies, PDD has a consistently higher detection rate for papillary tumors and CIS [10] (Table 4.1). Although CIS lesions typically appear as erythematous, velvety patches, they may also appear cystoscopically indistinct from surrounding normal urothelium. In a meta-analysis of 1503 patients, of whom CIS was present in 21.9%, the sensitivity of PDD for CIS was 92.4% compared to 60.5% for WLC [14]. In a European multi-center study, TUR under PDD guidance was found to result in more complete resection ($p < 0.0001$) [15]. When examining the difference in the diagnostic ability of each type of lesion separately, the benefit of PDD was most pronounced for CIS lesions, where 28% to 43% more lesions were identified by PDD compared to WLC. A less significant difference was found for detection of Ta lesions (94–97% by PDD compared to 83–88% by WLC) [16, 17]. A 10% higher detection rate by PDD for T1 disease has been reported in some studies [16, 18] with no difference for lesions in stage T2 or higher [18]. Hence, PDD's advantage lies mainly in the detection of NMIBC. It offers a more complete resection of NMIBC lesions regardless of their grade. In a second-look TUR study, significantly fewer lesions were found in the bladder: 4% CIS lesions compared to 28%, 15% PT1 lesions compared to 35%, and 17% for high-grade NMIBC compared to 37% were identified in patients who underwent PDD at the time of initial TUR versus conventional WLC respectively [19]. Studies examining recurrence after initial cystoscopy demonstrated that the rates are much lower when PDD is used during resection compared to WLC, and the recurrence-free survival is significantly longer (Table 4.2).

Currently, PDD is only approved for use with rigid cystoscopy. Studies that have looked at the use of PDD with flexible cystoscopy found that it is possible but not as convenient or effective as rigid cystoscopic PDD. However, comparative studies suggest that flexible cystoscopic PDD is superior to rigid WLC [20, 21]. It has also been shown that the accuracy of flexible cystoscopic PDD improves with experience and that there is a drop in the false-positive rate to as low as 1% [22]. The agent for PDD needs to be instilled intravesically by catheterization one to two hours prior to cystoscopy. A minimum of 30 minutes to 1 hour dwell time is required to provide adequate exposure to the agent. Moreover, white light should be used for only a short period of time and at low intensity before shifting to the fluorescence mode because of its photobleaching effect. This is particularly true for flat lesions where photobleaching is more rapid, limiting the time available for the procedure. PDD is approved only for a single administration since there are not enough data on potential drug hypersensitivity with repeat exposure, and bladder cancer usually requires repeated cystoscopies for follow-up. We have used intravesical Hexvix in about six patients more than once and have not seen any obvious toxicity or increased...
photosensitivity. Porphyria and allergies to 5-ALA and other agents limit the use of PDD in such patients [10]. It is recommended that PDD should be postponed nine to twelve weeks post TURBT and BCG if clinically feasible. This does not apply to patients receiving a single BCG (with the course being interrupted) or a post TUR mitomycin-C instillation [23]. Ray et al. reported that after six weeks there is no association between false-positive biopsies and the last BCG instillation [24] and there is no improvement in specificity after twelve weeks have passed. There appears to be less of a concern in using PDD after the use of mitomycin as it results in less inflammation compared to BCG. However, the use of HAL-based PDD should be avoided after any type of repeated intravesical therapy for up to 90 days, as it can increase the false-positive rate of PDD [23].

Despite the fact that PDD detects more high-risk tumors and leads to better resection, it is still debatable whether PDD improves survival or prevents progression. Four randomized controlled trials (RCTs) examined the clinical effectiveness of PDD and reported a prolonged recurrence-free survival. Yet there was no observed improvement in survival compared to WLC, partly because of the inconsistent administration of adjuvant
intravesical therapy which may have thus abrogated any benefit of the initial PDD-based resection [10, 25].

In summary, PDD is a technique that is fairly easy to use albeit requiring pre-operative preparation. PDD can detect more bladder tumors but it is unclear if it impacts long-term outcomes such as cancer-specific survival or progression. The principal benefit of PDD may be in ensuring a more complete resection, which may have particular advantages for those in training or those less experienced. Since overall survival in NMIBC is relatively high, but recurrences are common, a more relevant outcome measure may be prevention of disease recurrence. This would be important medically and from a patient's quality of life point of view.

### Narrow band imaging

Narrow band imaging (NBI) provides enhanced visualization of the mucosal vascular structures without exogenous contrast agents or dye. In NBI, white light is filtered to discrete blue (415 nm) and green (540 nm) light bands, which are strongly absorbed by hemoglobin. NBI can penetrate the mucosal surface to increase the visibility of capillaries and enhance the contrast with the rest of the mucosa. The blue light is reflected by the mucosal capillaries while the green is reflected by the deeper submucosal vessels. Thus, papillary tumors appear dark green because of the underlying vascular stalk and CIS lesions can be distinguished from normal mucosa because CIS lesions are rich in dense capillaries. Areas of tumor can appear persistently red as well. The easy switch between WLC and NBI modes using the press of a single button with the lack of need for instillation or injection of contrast material makes it easier to work with and handle (Figure 4.3).

NBI has been shown to improve the diagnosis of Barrett's esophagus [26], better differentiate between malignant and benign colonic polyps [27], and improve diagnostic sensitivity and negative predictive value in detecting squamous cell carcinoma of the head and neck [28].

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**Table 4.1 Sensitivity and specificity of PDD compared to WLC across different studies in the literature.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of study</th>
<th>Year</th>
<th>Patient numbers</th>
<th>PDD sensitivity</th>
<th>WLC sensitivity</th>
<th>p-value</th>
<th>PDD specificity</th>
<th>WLC specificity</th>
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<td>2006</td>
<td>298</td>
<td>92% (CIS lesions)</td>
<td>68%</td>
<td></td>
<td>82% (CIS lesions)</td>
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<td>39% false detection rate</td>
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<td>62</td>
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<td>Rigid cysto: 97.5%</td>
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</tbody>
</table>
When NBI was studied in the surveillance of bladder cancer patients, it increased the detection of lesions by 20% when compared to WLC [29]. Naselli et al. designed a prospective randomized clinical trial in 223 patients who underwent TUR under standard WLC or NBI. The one-year recurrence rate in the NBI group was 32.9% compared with 51.4% in the WLC group (OR = 0.62, \( p = 0.0141 \)) [29]. Similar results were reported by Herr et al. who found that NBI identified all malignant lesions (100%) as compared to WLC (87%, \( p = 0.05 \)). Moreover, NBI detected 100% of the CIS lesions versus 83% detected by WLC [26]. Results of meta-analysis of all prospective studies by Li et al. showed that NBI is superior to WLC, with 17% more patients and 24% more cancers being detected. More specifically, 28% of CIS lesions were detected by NBI and not WLC. Data from different studies conclude that there is no difference in the false-detection rate between WLC and NBI [27]. A second-look cystoscopy using NBI performed one month after tumor resection by WLC was able to identify 13% more patients with residual/recurrent disease and one case of undetected concomitant CIS when compared to a second look using WLC [30]. Patients followed for three years with WLC and then for another three years with NBI after the advent of this technique showed a recurrence rate of 94% in the first three years versus 62% in the second three years. A possible explanation for this difference is the natural history of the disease leading to fewer recurrences with time, but the authors argue that these subjects had multifocal disease and multiple recurrences previously and that the difference is attributable to more complete tumor identification and treatment with NBI [31]. In a small, single-institutional study, the same group found that there was a minimal learning curve for adopting NBI during surveillance cystoscopy among experienced and novice urologists [32]. A multi-center international study comparing NBI and WLC-assisted TUR has recently been completed, with the results pending [33].

NBI clearly appears to be an easily deployable technique that works with flexible cystoscopy to enhance real-time diagnosis and characterization of mucosal lesions. Further evaluation will allow us to better determine its precise applicability, particularly for resection of bladder tumors and perhaps to assess response to intravesical therapy.

### Confocal laser endomicroscopy

Based on the well-established principle of fluorescence confocal microscopy, confocal laser endomicroscopy (CLE) is an optical biopsy technology that enables *in vivo*
Novel endoscopic techniques for the detection of bladder cancer

high-resolution, subsurface imaging. CLE is approved for gastrointestinal and pulmonary endoscopic applications in Europe and the US. For urological applications, CLE recently received CE labeling in Europe and has been under investigational use in the US since 2009 [34, 35]. A 488-nm laser is used as the light source and fluorescein, an FDA-approved drug, as the exogenous contrast agent. For bladder applications, the fluorescein may be administered either intravenously or intravesically [34]. Tissue microarchitecture and cellular features can be resolved with images reminiscent of standard histopathology. The available clinical system (Cellvizio, Mauna Kea Technologies) utilizes miniaturized fiberoptic imaging probes ranging from 0.85 mm to 2.6 mm in diameter that can be passed through working channels of standard endoscopes [36]. The images are acquired as video

Figure 4.3 Optical imaging for bladder cancer diagnosis. Comparison of the same lesions as they appear on WLC and NBI. Histologically confirmed CIS resected tumor, visualized by NBI (b) better than by WLC (a); histologically confirmed bladder tumor not well visualized by WLC (c) and detected by BLC (d); histologically confirmed benign lesion of capillaries detected by WLC (e) and confirmed on NBI (f).
sequences at twelve frames/sec, thus enabling dynamic imaging of physiologic parameters such as vascular flow.

Real-time microscopy of normal urothelium, inflammation, CIS, low-grade and high-grade urothelial carcinoma has been demonstrated, with images comparable to conventional histopathology (Figure 4.4). Features of normal urothelium, such as the presence of umbrella cells and a relatively acellular lamina propria, are identifiable on CLE. Features characteristic of low-grade urothelial carcinoma, such as the presence of fibrovascular stalks bordered by monomorphic cells, and of high-grade tumors, such as distorted microarchitecture, and pleomorphic cells with indistinct cellular borders are identified on CLE. These criteria form the basis of optical diagnosis when differentiating between normal and malignant urothelium using CLE [35].

Since CLE has a limited visual field and because of the time limitation of the procedure, it has been investigated in conjunction with PDD, which offers a wider field of view. Suspicious lesions identified by PDD were further characterized by CLE and the results were compared to pathology. It was found that exposing the mucosa to blue light did not modify the CLE analysis; however, analysis by CLE could not be made using the HAL fluorescence that was instilled for PDD. Fluorescein, when added, masked HAL fluorescence and CLE analysis was not disrupted [37]. The rate of false-positive biopsies with PDD, which is greater than WLC [38], can potentially be reduced by combining PDD and CLE. One of the limitations of CLE is the optical depth, where visualization is limited to the lamina propria and invasion to muscularis propria cannot be assessed. However, in such cases CLE is useful in providing histologic information about the tumor area and edges to be resected, and the deep muscular layer can be visualized after lesion resection or during second-look resection [34].

At this juncture, it appears that CLE is a promising new technique that has already proven itself to some extent in the GI tract and which could potentially be utilized for real-time assessment of the depth of invasion in bladder tumors. The precise individual role of CLE in the diagnosis or treatment of bladder cancer vis-à-vis the other endoscopic techniques is yet to be determined.

**Optical coherence tomography**

Optical coherence tomography (OCT) enables cross-sectional imaging of tissue similar to clinical ultrasound but at a 10 times higher resolution [39]. It was developed...
in the early 1990s for ophthalmological applications [40, 41]. The first reports of OCT of the bladder characterized tissues \textit{ex vivo} [42]. As an optical equivalent of ultrasound, in which infrared light is used instead of sound to image the luminal surfaces of biological tissue with spatial resolution close to the cellular level at 15 to 20 \( \mu m \), OCT has the ability to visualize subsurface structures \textit{in vivo} deeper than that offered by CLE (Figure 4.5).

The three layers of the bladder include the urothelium, the lamina propria, and the muscularis propria. In healthy tissue, these layers are well defined and organized. On OCT, the urothelium appears as an area of low intensity, followed by high-intensity lamina propria, and low-intensity muscularis propria. The contrast between these three layers is lost in muscle-invasive bladder cancer wherein distinct layers or boundaries are disrupted [43, 44]. OCT has also been shown to detect NMIBC, CIS on the diagnostic cystoscopy, and recurrent tumors found on surveillance cystoscopy, rendering it a promising adjuvant optical biopsy [39].

Various studies of OCT have yielded similar values for sensitivity and specificity for the detection of tumors. The reported sensitivity of OCT approaches 98%, with a specificity of 72% for the detection of pathologically confirmed tumors [44]. A similar study in 24 patients characterized lesions as healthy, abnormal but not invasive, or invasive by OCT and found that the sensitivity was 100% and the overall specificity was 89%, with a negative predictive value of 100% [45]. In an \textit{ex vivo} study of 142 human bladder specimens, Hermes \textit{et al.} found that OCT was able to discriminate between normal, CIS, and invasive UCC with a sensitivity of 83.8%, specificity of 78.1%, and a false-positive rate of 5.7% [46] (this seems to be 46). Lerner \textit{et al.} looked at different stages of bladder UCC. Non-invasive disease (Ta) was detected by OCT with a sensitivity of 90% and a specificity of 89%, whereas the sensitivity for higher-stage disease (T1 and T2 tumors) was 75% and 100%, while the specificity was 97% and 90%, respectively [47].

One of the characteristic signs of chronic cystitis is the local accumulation of liquid under the epithelium as small bullae. Due to specific optical properties of liquid, OCT is able reliably to identify the accumulation of inflammatory exudate and thus not only identify invasion but also differentiate malignant lesions from inflammatory ones [48].

OCT is an emerging technology which can also enhance our ability to carry out real-time assessment of the depth of invasion of bladder tumors. This could enable more complete primary tumor ablation as well as leading to better decision making regarding optimal therapy for patients presenting with bladder cancer.

**Conclusions**

In summary, bladder cancer continues to be a challenge for urologists and patients because of its incidence, high recurrence rate, the need for frequent follow-up, and the high cost of surveillance. WLC is currently the reference standard for visualizing the bladder and in the diagnosis as well as follow-up of bladder cancer. However, WLC needs to be optimized to detect more

![Figure 4.5](https://example.com/f4_5.png) Images obtained using optical coherence tomography. a) The distinction between the normal layers of the urothelium. b) Loss of this distinction in muscle-invasive cancer. Source: Goh \textit{et al.} 2008 [47]. Reproduced with permission from Elsevier.
lesions. A variety of promising new techniques to assess the bladder endoscopically have recently been introduced into practice. Further study is required to determine the individual value or “niche” that one or more of these new techniques may occupy in our diagnostic armamentarium. NBI is more convenient than PDD as it requires no additional steps. PDD has the risk of hypersensitivity reactions and photosensitivity, although these complications are extremely rare in contemporary practice. In contrast, there are no contraindications to the use of NBI. It can be used repeatedly, there is no need for intravesical instillation, and it is a low-cost technology since only software modification of the WLC is required [30]. Other technical limitations with both PDD and NBI include decreased visualization in the case of inadequate hemostasis [10].

One of the major drawbacks of these technologies is that they can lead to unnecessary negative biopsies as a consequence of false-positive findings. The false-negative rate of NBI was reported to be 13% by Herr et al. They attribute this rate to their policy to resect any lesion, some of which were just denuded mucosa [49]. The same applies to PDD, where false-positive results are reported to be between 12% and 30%, and this is generally attributed to tangential application of the light source [49, 50], prior use of BCG, and use of the technique during the learning curve [51].

Of all the four technologies described above, CLE offers the highest resolution (2 to 5 μm). However, only OCT offers real-time bladder cancer staging [10]. One of the limitations of OCT is that although it improves the effectiveness of TUR by evaluating the resection margins, cautery at these margins can lead to problematic artifacts. Both techniques will add to the total operation time.

The costs of these modifications to WLC include instrumentation, contrast agents, more biopsies, and additional operative time. True cost-effectiveness for each of these techniques is lacking. Moreover, results with some of these techniques, particularly CLE and OCT, need further confirmation in large-scale trials before adoption into routine clinical practice.

Useful web link


References

Novel endoscopic techniques for the detection of bladder cancer


31 Herr HW and Donat SM: Reduced bladder tumour recurrence rate associated with narrow-band imaging surveillance cystoscopy. BJU Int. 2011 Feb; 107(3): 396–398.


CHAPTER 5

Transurethral resection of bladder tumors

Jen-Jane Liu¹ and Mark P. Schoenberg²

¹Brady Urological Institute, Johns Hopkins School of Medicine, Baltimore, MD, USA
²Department of Urology, Montefiore Medical Center and Albert Einstein College of Medicine, New York, NY, USA

KEY POINTS

• The majority of bladder cancer presents as non-muscle-invasive disease.
• Transurethral resection is the mainstay of therapy for non-muscle-invasive bladder cancer.
• Advances such as the Iglesias resectoscope with continuous flow and video TUR have improved the surgeon’s ability to adequately visualize and safely resect tumors endoscopically.
• The success of TURBT is dependent on complete resection of all visible tumor. Photodynamic diagnosis may improve the surgeon’s ability to identify flat tumors and CIS.
• Recurrence and progression after TURBT is influenced by pathophysiology (grade), completeness of resection, and use of intravesical therapy.
• New techniques such as bipolar vaporization and laser resection of bladder tumors may decrease morbidity from TURBT, while obtaining tissue for pathologic analysis.

Introduction

Approximately 70% of all bladder cancer patients present with non-muscle-invasive bladder cancer (NMIBC) [1]. The mainstay of treatment for NMIBC is transurethral resection of bladder tumor (TURBT). The transurethral resection of bladder tumors is one of the first examples of minimally invasive surgery. In this chapter we review the historical development of endoscopic instrumentation, as well as the contemporary technique and therapeutic efficacy of modern TURBT. We also examine new technologies available that have the potential to further improve the therapeutic value of transurethral bladder cancer surgery.

Endoscopy and visualization of the bladder

Prior to the 17th century, visual inspection of body cavities was limited by a lack of adequate instrumentation. Treatment of bladder tumors was limited to dilating the female urethra to visualize and remove tumors, or utilizing an open approach through the perineum or suprapubic area in males [2]. Phillip Bozzini, whose Lichtleiter or “Light Conductor” apparatus was described in 1804, was the first to introduce “endoscopic” instrumentation (Figure 5.1). A candle provided illumination, and a mirror projected the light through a funnel with an eyepiece at the other end [3]. The speculum on this device, however,
was too large to place into the male urethra and the light source was not bright enough, hampering visualization of the bladder. Maximilian Nitze is credited as the inventor of the cystoscope in 1877. His innovations included the incorporation of a series of lenses that enabled magnification of the image and illumination with a light bulb at the tip of the instrument, rather than outside the body, enabling visual endoscopic inspection of the bladder (Figure 5.2) [4].

Jose Iglesias made several important modifications to the Stern–McCarthy resectoscope. He designed a spring-mounted trigger that permitted one-handed operation of the cutting loop. Perhaps his most important contribution was the development of the continuous flow resectoscope in 1975 (Figure 5.4) [8]. This enabled improved visualization by allowing fresh inflow of clear fluid at the same time that bloody fluid was evacuated, and also allowed stable but low intravesical pressures to be used during resection. Advances in video chip technology facilitated the introduction of video-TUR in the mid-1980s [9]. Video-TUR improved the ergonomics of the procedure for the surgeon, protected the surgeon from contamination by bodily fluids, and facilitated intra-operative instruction.

**Patient preparation**

Patients scheduled for TURBT should be prepared for general or regional anesthesia, depending on the preferences of the surgeon and the anesthesiologist. General anesthesia is preferable, particularly for patients with large tumors or those near the lateral wall that may require neuromuscular blockade. Patients with coagulopathies or taking anticoagulants should have their coagulation factors corrected and checked prior to surgery. Patients must be able to be positioned in the lithotomy position. Currently, the AUA does not recommend pharmacologic thromboembolism prophylaxis prior to transurethral procedures [10]. Post-operative prophylaxis with early ambulation and pharmacologic prophylaxis based on patient risk factors is recommended. Antimicrobial prophylaxis is recommended. According to recent AUA guidelines, first-line antimicrobial prophylaxis is either a fluoroquinolone or trimethoprim-sulfamethoxazole. An aminoglycoside with or without the addition of ampicillin, first or second generation cephalosporins, or amoxicillin/clavulanate are considered second-line alternatives [11].
Surgical technique

A 24–28 French resectoscope is used with a 30-degree lens during the resection. Bimanual exam may be helpful in staging muscle-invasive bladder tumors, however, evidence suggests that it is accurate approximately half of the time, with a significant risk of understaging [12]. Sequential dilation of the urethra with sounds facilitates atraumatic passage of the resectoscope, preventing stricture formation, particularly in the region of the fossa navicularis in male patients. Initially, the entire bladder should be inspected systematically to identify the location of tumors or abnormal-appearing areas [13]. A formal bladder map can be created with this information that can be used as a reference on subsequent surveillance cystoscopy or resections. New imaging techniques such as photodynamic diagnosis (PDD) and narrow band imaging (NBI) can also help identify suspicious lesions [14]. PDD relies on preferential uptake of photosensitizer by tumors, whereas NBI filters light to the same wavelength as hemoglobin, enhancing the appearance of neovascularity in tumors.

Figure 5.2 Nitze cystoscope, ca. 1895. L&H Loewenstein, Berlin. Source: Didusch Center for Urologic History, American Urologic Association. Reproduced with permission.
Both technologies require special equipment, and PDD requires the intravesical instillation of the photosensitizer hexaminolevulinate (Hexvix, Cysview, Photocure, Princeton, NJ, USA) one to two hours prior to instrumentation.

Transurethral resection can be performed using either a monopolar or bipolar cutting loop. In cases in which a monopolar loop is used, a non-conducting solution such as water, glycine, or sorbitol should be chosen for irrigation. The properties of different irrigation fluids are noted in Table 5.1. For cases in which the bipolar loop is used, saline may be employed. Fluid absorption can occur through venous sinuses during resection of large tumors or in the setting of unrecognized bladder perforation. This can result in dilutional hyponatremia, known as the TUR syndrome (Table 5.2).

Currently available data suggest that bipolar resection is associated with fewer intraoperative complications such as hemorrhage. Tissue obtained using this technology appears to have less cautery artifact, which may improve the pathologic evaluation of the surgical specimen [15, 16]. The rate of urethral stricture is unchanged when compared to procedures performed using conventional monopolar instrumentation [15].

The goal of TURBT is complete resection of all visible tumor. When the resection is complete, an additional sample of the base can be sent to pathology separately to assess for involvement of the muscularis propria. Tumors located at geographically distinct sites should be submitted as separate specimens. Fulguration is acceptable for small, papillary lesions in which a diagnosis of low-grade, non-muscle-invasive disease has already been established. Random bladder biopsies should be performed in the case of positive cytology without evidence of bladder lesions, in cases of suspected carcinoma in situ, or when considering partial cystectomy [13, 17].

Care should be taken when resecting the lateral base of the bladder as this can stimulate the obturator reflex and result in bladder perforation. This is particularly relevant in female patients whose bladders are often thin-walled. The bladder should be approximately half to two-thirds distended to minimize perforation and spread of current to the obturator nerve. Using a tapping motion or reducing the cutting current when resecting near the lateral wall may help reduce the obturator reflex. Although some studies suggest that the obturator reflex is decreased with bipolar resection, its occurrence is still reported [18, 19]. The obturator reflex can occur with general or spinal anesthesia. Systemic paralysis can abolish the obturator reflex, however, this requires the administration of general anesthesia [20]. Obturator nerve block can also be utilized to abolish the obturator nerve reflex. The block can be achieved transvesically, or more commonly with ultrasound or nerve stimulation guidance inferior and lateral to the pubic tubercle [21, 22].
Small biopsies or resections may not require urethral catheter drainage, but the patient should void prior to discharge. Larger areas of resection may require admission to the hospital for continuous bladder irrigation and prolonged catheter drainage. Meticulous hemostasis is crucial at the time of TURBT. If intravesical therapy is to be administered, a catheter should be placed and the bladder emptied prior
to instilling medications. If perforation is suspected, intravesical therapy should not be given, as systemic absorption of chemotherapeutic agents can occur, resulting in severe side effects. Extraperitoneal perforation (lateral walls, anteriorly) can be treated with urethral catheter drainage. It is likely that sub-clinical extraperitoneal perforation occurs frequently (approximately 50%) after TURBT based on studies where a routine cystogram was performed [23]. The rate of symptomatic extraperitoneal perforation is estimated to be 1–3.5% [24, 25]. Perforation at the dome is often intraperitoneal. If the perforation is small, non-operative management with urethral catheter drainage can be considered [26, 27]. Larger perforations should be carefully evaluated and evidence of bowel injury should be sought. Laparoscopic or open repair may be required in cases of gross intraperitoneal extravasation. There is a risk of tumor seeding with bladder perforation during TURBT, although the exact rate is unknown. It is difficult to determine the true rate of perforation, and whether locally advanced disease observed during radical cystectomy results from tumor implantation at the time of perforation [28, 29].

### Special situations for TURBT

#### Tumors overlying the ureteral orifice

Urothelial cancer can obscure the ureteral orifices, and may cause obstruction. The ureteral orifice can be resected in these situations, using cutting current and minimizing cautery in the area. Indigo carmine or methylene blue can be given afterwards to assure patency of the ureter. Routine ureteral stent placement is generally not indicated. Ureteral obstruction or subsequent stricture are the major complications. In one study, where 84 resections of the ureteral orifice were performed, hydronephrosis persisted in 13% of patients at a median follow-up of 15 months [30]. Stricture was noted in three patients who required endoscopic intervention. No renal deterioration was noted in these individuals. When routine evaluation is performed post-operatively, vesicoureteral reflux has been reported in up to a third of patients undergoing ureteral orifice resection at the time of TURBT, although the clinical significance of this finding is unclear [31].

#### Tumors in bladder diverticula

Vesical diverticula are properly “pseudo-diverticula” because they do not possess all layers of the native bladder wall (urothelium, lamina propria, a muscularis...
The muscularis propria is most commonly absent, and this fact makes resection of tumors located in diverticula challenging from both a technical perspective and from the standpoint of post-operative analysis of the TUR specimen. In addition to the technical difficulty presented by resecting within a diverticulum, the risk of perforation is increased compared to resection performed within the bladder proper. Nonetheless, TURBT of diverticular tumors is both feasible and clinically valuable despite the additional difficulty associated with this particular intervention. In a study of 26 patients with disease confined to the diverticulum (Ta, Tis, or T1), five-year disease-specific survival was 83% for Ta or Tis disease, and 67% for T1 disease. Only four of the 13 patients with T1 disease underwent treatment with TURBT alone. Two were disease free and the other two died of their disease [32]. A thorough evaluation with cross-sectional imaging and cystoscopy is mandatory for evaluation of bladder cancer in diverticula, and close follow-up is warranted, particularly if endoscopic therapy is used as treatment. While TURBT is therapeutically important in appropriately selected patients with small non-invasive tumors involving diverticula, large tumors
and those with invasive characteristics are probably best managed by partial or, when necessary, radical cystectomy [32].

**Efficacy of TURBT**

The efficacy of TURBT is dependent on the grade and stage of the lesion being treated. Table 5.3 illustrates the probability of recurrence and progression for low- and high-grade NMIBC following TURBT [33]. Low-grade NMIBC progresses to muscle invasion relatively rarely (less than 3%); however, low-grade disease does recur frequently (approximately 50–70%) [34, 35]. Factors that have been shown to influence recurrence include tumor multiplicity and use of adjuvant therapy. In a multi-center study of over 1400 patients who did not receive adjuvant therapy, the rate of recurrence of bladder tumor at three-month cystoscopy ranged from 2% to 10% for single tumors, and from 6% to 62% for multiple tumors (N = 1009) [36]. The wide range in the recurrence rate suggests variability in the completeness of tumor resection.

New technologies to enhance detection of tumors may improve the efficacy of TURBT. Photodynamic diagnostic cystoscopy (PDD) using hexaminolevulinate (Hexvix, Cysview, Photocure, Princeton, NJ, USA) appears to result in the identification of more tumors (up to 20%) compared to white light cystoscopy alone, particularly for flat lesions and CIS (up to 30% more than white light alone) [37, 38]. Utilization of PDD results in more complete TURBT, reducing the odds of residual tumor by 28% [37]. PDD is associated with decreased recurrence rates in randomized trials, and a meta-analysis of available studies showed decreased recurrence (overall decrease of 11%) in Ta, T1, CIS, low-, and high-risk groups [38, 39]. There is no clear evidence that PDD reduces progression to muscle-invasive disease, although one study did show a trend toward decreased rates of cystectomy in long-term follow-up of patients undergoing PDD-guided TURBT [37, 40].

**Other techniques**

Alternative techniques to electrosurgical resection have been utilized for TURBT. The use of vaporization with the plasma bipolar button (Olympus, Central Valley, Pennsylvania) has been investigated in preliminary studies [41, 42]. Biopsy is performed prior to ablation to achieve pathologic diagnosis, and then the remainder of the tumor is vaporized. Preliminary results suggest that large tumors (>3 cm) can be successfully vaporized and that there may be less post-operative bleeding and a shorter duration of catheterization required. Various lasers have also been employed for tumor resection, most commonly the holmium:YAG laser. This laser can be used to fulgurate small bladder tumors in an outpatient setting with local anesthesia; however, the utility of laser ablation in the setting of large or invasive tumors is controversial and should probably be considered investigational [43, 44]. A separate biopsy must be taken prior to ablation for histopathologic diagnosis. Some investigators have reported “en bloc” resection of tumors with the holmium laser, although the tumors evaluated were small (<2 cm) [45]. Reduced morbidity and procedural costs make laser ablation of small tumors attractive for the management of appropriately selected patients [43, 46]. Additionally, the coagulative properties of laser ablation may be beneficial in patients who require anticoagulation therapy. Other lasers that are being explored include the potassium-titanyl-phosphate (KTP, Greenlight) and thulium:yttrium aluminum garnet (Tm:YAG) laser [47, 48]. The neodymium:YAG laser is no longer used for bladder tumor resection due to its deep

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Approximate probability of recurrence in five years</th>
<th>Approximate probability of progression to muscle invasion</th>
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</thead>
<tbody>
<tr>
<td>Ta, low grade</td>
<td>50%</td>
<td>Minimal</td>
</tr>
<tr>
<td>Ta, high grade</td>
<td>60%</td>
<td>Moderate</td>
</tr>
<tr>
<td>T1, low grade (rare)</td>
<td>50%</td>
<td>Moderate</td>
</tr>
<tr>
<td>T1, high grade</td>
<td>50–70%</td>
<td>Moderate–High</td>
</tr>
<tr>
<td>Tis</td>
<td>50–90%</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 5.3 Probability of recurrence and progression for non-muscle-invasive bladder cancer.
Transurethral resection of bladder tumors

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penetration and risk of bowel injury [49]. Table 5.4 lists properties of lasers that have been used for TURBT.

### Intravesical therapy

Perioperative instillation of mitomycin-C (40 mg in 40 mL of saline) within 24 hours of TURBT has been shown to reduce the recurrence of non-muscle-invasive bladder cancer [50–52]. Consideration of single-dose intravesical therapy after TURBT for low-grade bladder cancer is recommended by the European Association of Urology, the AUA, and the National Comprehensive Cancer Network (NCCN) [33, 53, 54]. Ensuring administration in an empty bladder and alkalinization of the urine with oral sodium bicarbonate can enhance the efficacy of mitomycin-C [55].

Immediate post-operative instillation therapy should not be performed in the setting of suspected bladder perforation, as serious side effects can occur from absorption, including myelosuppression, non-healing at the site of perforation, and chronic pain [56, 57]. Doxorubicin, epirubicin, and gemcitabine have also been used for single-dose intravesical prophylaxis after TURBT [58]. A recent meta-analysis of post-operative intravesical chemotherapy demonstrated a 38% improvement in recurrence-free interval in patients receiving immediate post-operative intravesical therapy [59]. Additionally, *neoadjuvant* intravesical mitomycin-C has been studied and has demonstrated a 70% complete pathologic response in patients with small, recurrent low-grade tumors following an intensive two-week dosing schedule [60].

An adequate resection should contain muscularis propria in the specimen and pathology reports should clearly document whether there is extension of tumor into the muscularis propria. Surgeon experience, tumor size and multifocality, and optimal visualization are all factors in completeness and adequacy of resection. Upstaging of T1 bladder cancer at subsequent cystectomy occurs in up to 40% of cases [61]. Additionally, 50–70% of patients will have residual tumor on repeat resection after initial TURBT for high-grade T1 disease [62]. There is a distinction between re-staging TURBT versus repeat-TURBT. In the former, the goal is improved diagnostic accuracy, whereas the latter is to improve cancer control by resecting additional disease not detected at the first resection. According to a study by Herr *et al.*, new information obtained on repeat-TURBT changes management in one third of patients [63]. Recently, a randomized trial concluded that repeat-TURBT was associated with lower recurrence (59% vs. 32%) and progression rates (6.5% vs. 24%), as well as improved overall survival in patients with T1 disease [64]. Repeat-TURBT may also improve response to adjuvant intravesical therapy with BCG or mitomycin-C [64–66].

A recent retrospective study of over 1000 patients who were treated with BCG and followed for at least five years showed that repeat-TURBT was the only significant predictor of recurrence on multivariable analysis. In that report, five-year progression-free survival was significantly better in patients undergoing repeat-TURBT compared to those who had only a single resection (67% vs. 82%) [65]. The performance of repeat-TURBT is not universally endorsed. Some investigators have suggested that routine repeat-TURBT is not required in patients with Ta disease since adjuvant intravesical BCG successfully limits disease recurrence in this population [67]. Additionally, repeat-TURBT is associated with morbidity and increased expense, although these costs would most likely be offset by reductions in recurrence and progression of the disease [68].

Patients with high-risk lesions (high-grade T1, or multifocal, high-grade Ta disease) should undergo repeat resection four to six weeks after initial TURBT to ensure appropriate staging and to remove any residual tumor. According to the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines) for Bladder Cancer, repeat-TURBT should be performed in cases of incomplete resection or strongly considered when no muscle is present in

### Table 5.4 Properties of lasers used for transurethral resection of bladder tumor.

<table>
<thead>
<tr>
<th>Laser</th>
<th>Wavelength (nm)</th>
<th>Power (W)</th>
<th>Depth of penetration (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmium:YAG</td>
<td>2120 (Absorbed by water)</td>
<td>20–100</td>
<td>300–500</td>
</tr>
<tr>
<td>KTP</td>
<td>532 (Absorbed by hemoglobin)</td>
<td>80–120</td>
<td>1–2</td>
</tr>
<tr>
<td>Thullium:YAG</td>
<td>2010 (Absorbed by water)</td>
<td>70–120</td>
<td>750</td>
</tr>
<tr>
<td>Neodymium:YAG*</td>
<td>1064</td>
<td>3.2</td>
<td>4–18</td>
</tr>
</tbody>
</table>

YAG: yttrium aluminum garnet

*No longer used for bladder tumors

Source: Hahn, 2006 [75]. Reproduced with permission from Oxford University Press.
high-grade Ta disease [33]. All patients with T1 disease (regardless of grade) should undergo repeat-TURBT (unless cystectomy is being considered). For low-grade disease, repeat-TURBT may help eradicate persistent disease, which can contribute to improved recurrence-free survival. There are few studies that examine repeat-TURBT in patients with low-grade disease.

**Radical TURBT and bladder-sparing for muscle-invasive disease**

Approximately 10–15% of patients who undergo cystectomy after TURBT for muscle-invasive disease will be classified as P0 at cystectomy [69, 70]. This observation coupled with studies of TUR monotherapy for invasive bladder cancer has bolstered the use of “radical TUR” in selected patients with ≥ T2 disease. “Radical TURBT” involves full-thickness resection of the bladder wall with a margin around the tumor. Risks include perforation, which could require partial cystectomy or bladder closure if the perforation is intraperitoneal, and persistent extraperitoneal urinary extravasation despite prolonged catheter drainage [71, 72]. Deaths have been reported in those who suffered intraperitoneal perforation. In a study of 99 patients treated with TURBT alone, ten-year disease-specific survival was 76%, and over half of patients retained their bladders [73]. Overall and progression-free survival were superior in those patients with no residual disease on repeat-TURBT. Eighteen percent of the patients with T0 disease on repeat-TURBT died of bladder cancer at ten years of follow-up. A more recent study examined 133 patients undergoing TURBT monotherapy with long-term follow-up. Overall survival was 25% at 15 years, although cancer-specific survival was 77% [74]. This poor overall survival is reflective of the significant baseline comorbidities that exist in the population of bladder cancer patients, as evidenced by the significant morbidity and mortality that are also seen after radical cystoprostatectomy. Fifty-eight percent of patients had an intact bladder at 15 years, and 62% were free of local disease [74]. Of those patients who progressed, 68% died of bladder cancer. Thus, radical TURBT alone for muscle-invasive bladder cancer can result in long-term survival in patients with favorable disease characteristics (Figure 5.6); however, progression is common and salvage therapy at the time of progression is not always successful. A complete resection of all disease results in better outcomes for both radical TURBT as monotherapy and when used with other bladder-sparing treatments such as chemotherapy and radiation.

![Figure 5.6 Cancer-specific survival after radical TURBT by age. Source: Solsona et al., 2010 [74]. Reproduced with permission from Elsevier.](image-url)
Conclusions

As the first example of minimally invasive, organ-sparing surgery in urologic oncology, transurethral resection of bladder tumors remains a cornerstone of therapy for NMIBC. TURBT as monotherapy or combined with other treatment modalities can produce long-term disease-free survival in appropriately selected patients with muscle-invasive disease. New technologies and surgical techniques have emerged to enhance the detection of cancer and improve the surgeon’s ability to perform complete resection of all tumor with minimal morbidity. Future research should be focused on ways to reduce the need for frequent resections and the morbidity of treatment.

Useful web links


References


CHAPTER 6

Intravesical chemotherapy

Levent N. Türkeri1, M. Guillaume Wientjes2, and Jessie L.S. Au2,3

1 Department of Urology, Marmara University School of Medicine, Istanbul, Turkey
2 Optimum Therapeutics, LLC, San Diego, CA, USA
3 Department of Pharmaceutical Sciences, University of Oklahoma, Oklahoma City, OK, USA

KEY POINTS

• Recurrence is common in non-muscle-invasive bladder cancer.
• The risk of recurrence (and progression) can be stratified according to clinical and histological parameters.
• The anatomical structure of the bladder is convenient for intravesical chemotherapy or immunotherapy.
• Early, single instillation of a chemotherapeutic agent significantly reduces recurrence in low-risk tumors.
• Minimizing drug dilution during intravesical therapy is important for therapeutic success.
• Device-assisted intravesical therapy may allow bladder sparing in some patients who would otherwise require cystectomy.
• The superiority of the sequential use of chemotherapy and immunotherapy compared to immunotherapy alone has not yet been established.

Introduction

Patients with non-muscle-invasive bladder cancer (NMIBC) remain vulnerable to later recurrences and progression after initial treatment by transurethral resection (TUR). Recurrence and progression rates of the disease within the first year can approach 60% and 17%, respectively [1, 2]. Recurrences are significant because they impose multiple burdens upon patients and society including the inconvenience, discomfort, and cost associated with multiple surgical procedures [3, 4]. Adjuvant, intravesical chemotherapy has proven to be effective in avoiding post-TUR implantation of tumor cells, eradicating residual disease, and preventing tumor recurrences [5–7]. The timing and number of instillations should be tailored according to the risk stratification of particular tumors. The effectiveness of sequential use and/or the combination of chemotherapeutic agents remain to be proven, while some patients may benefit from device-assisted, intravesical chemotherapy regimens.

History of intravesical chemotherapy

The effectiveness of intravesical therapy to reduce the recurrence of NMIBC was first recognized in the 1950s [8, 9]. A large number of immuno- and chemotherapeutic agents including thiotepa, mitomycin-C (MMC), doxorubicin and its analogs, gemcitabine, and taxanes have since been evaluated [10, 11]. Thiotepa, introduced in the early 1960s, was the first FDA-approved agent for papillary NMIBC [12]. The immunomodulatory agent bacille Calmette-Guérin (BCG) was approved in 1989 for treatment of carcinoma in situ.
Intravesical chemotherapy

Indications

The primary treatment for NMIBC patients is transurethral resection of bladder tumors (TURBT). Patients with a single low-grade Ta tumor are at low risk for recurrence and are frequently followed by surveillance [16]. For most other patients, intravesical therapy is indicated and is used in perioperative (within 6–24 hours after TURBT), induction (6–8 weeks), and maintenance (1–3 years) settings; the goals are to eradicate existing/residual tumor(s) and to prevent tumor recurrence and disease progression. Patients with intermediate and high risks of recurrence, e.g., patients with large, multiple, poorly differentiated, or recurrent tumors, or CIS, are advised to receive intravesical BCG or chemotherapy [15, 16]. BCG is given as induction and maintenance therapy, and not in a perioperative setting due to its potential to cause severe side effects as well as tuberculosis [15, 16]. Chemotherapy is indicated in patients who cannot tolerate BCG (~20%) or are BCG-refractory (~30%) [18].

Agents used in intravesical chemotherapy

Anthracyclines

Anthracyclines act by intercalating between DNA and RNA strands, thus preventing transcription. Doxorubicin, epirubicin, mitoxantrone, and pirarubicin show similar activity in NMIBC. Valrubicin is used in BCG-refractory CIS [19].

DNA alkylators

The major compounds are MMC, its structural analog apaziquone (EOquin®), and thiotepa. Meta-analysis suggests MMC is more effective compared to anthracyclines [11, 16, 20]. The most common MMC regimens use six or eight weekly treatments (40 mg dose) plus monthly maintenance for one to two years. Apaziquone showed promising pre-clinical activity in early clinical trials, but did not meet the primary endpoint of reduced recurrence at two years against a placebo in randomized phase III trials [21]. Thiotepa, due to its lower efficacy and myelosuppression, is less frequently used.

Antimetabolites

Antimetabolites typically interfere with the synthesis of DNA and/or RNA. Intravenous gemcitabine has activity against metastatic bladder cancer. Single-arm trials show that intravesical gemcitabine (1) is effective in NMIBC with a favorable toxicity profile, with activity similar to MMC, (2) has superior activity compared to BCG rechallenge in BCG-refractory patients, and (3) is not effective in the perioperative setting [11, 22].

Antimicrotubule agents

Antimicrotubules affect the polymerization and depolymerization of microtubules. The vinca alkaloid vinorelbine, an inhibitor of polymerization, shows activity in a phase I trial [23]. Taxanes such as docetaxel and paclitaxel, inhibitors of depolymerization, show good tolerability and efficacy in BCG-refractory patients in phase I/II studies [11].

Molecular targets

Loss of tumor suppressor genes p53 and RB, overexpression of oncogenes and peptide growth factors and their ligands, and alterations in cellular adhesion molecules and tissue microenvironment all play a role in bladder tumor formation, growth, and metastasis [24]. Several molecular targeted agents have been evaluated as intravenous treatments in advanced metastatic bladder cancer, including agents that interfere with the epidermal growth factor signaling pathway, FGFR3,
HRAS, and PI3-kinase [24]; early clinical trial results have been disappointing [24, 25]. A phase I intravesical trial with suramin, an inhibitor of multiple growth factors, showed good tolerability at cytotoxic doses [26]. Our laboratory recently established that suramin, at non-cytotoxic doses (but not cytotoxic doses) significantly enhanced the in vitro and in vivo MMC activity in xenograft and patient bladder tumors, without enhancing the host toxicity [27]. Another approach in pre-clinical development is to use siRNA gene therapy targeting survivin, a gene/protein associated with broad spectrum chemoresistance in animals and humans, to improve the MMC activity [28, 29].

**Immediate post-operative single-dose intravesical chemotherapy**

**Evidence from trials and meta-analyses**

Administration of adjuvant intravesical chemotherapy after TUR has been shown to reduce the high recurrence rate of NMIBC. Jones and Swinney in Europe and Veenema et al. in the USA demonstrated that intravesical thiotepa could eradicate residual tumors and apparently decrease the risk of tumor recurrence [9, 30]. Interestingly, the initial randomized studies of adjuvant thiotepa instillations had the greatest impact on tumor recurrence in patients treated with a single dose of intravesical chemotherapy immediately after surgery [31, 32], suggesting the eradication of the microscopic residual tumors missed during TUR and/or the free-floating tumor cells that carry the potential to re-implant [33, 34]. Subsequent trials have confirmed that immediate post-operative, single-dose chemotherapy was beneficial across all patient subgroups [35, 36]. A meta-analysis of seven randomized trials [35–41] conducted by the European Organization for the Research and Treatment of Cancer (EORTC) showed that this approach resulted in a 12% absolute reduction in tumor recurrence, corresponding to a 39% reduction in the odds of recurrence, favoring single instillation [42] (Table 6.1). Subsequently, another meta-analysis by the American Urological Association (AUA) indicated a statistically significant 17% decrease in median recurrence rate with a single dose of MMC compared to TUR alone [43]. Based on these data, an immediate post-operative single instillation of chemotherapy is recommended for all patients with NMIBC, ideally within the first six hours, except for those with (overt or suspicious) bladder wall perforation. However, the treatment effect appears to be dependent on patient characteristics and not all patients benefit from a single instillation to the same extent. Further analysis of data from studies providing the basis for guideline recommendations reveals that a single early post-operative instillation is most effective in patients with a fully resected primary, solitary tumor, as well as a solitary recurrent tumor and a previous recurrence rate of less than one tumor per year [44, 45].

**Choice of chemotherapeutic agent**

Meta-analysis by the EORTC revealed no significant difference in efficacy among chemotherapeutic agents (epirubicin, MMC, thiotepa, or pirarubicin) used for the immediate post-operative single dose of chemotherapy, rendering the choice of agent optional. However, in a more recent placebo-controlled trial of NMIBC, a single instillation of gemcitabine immediately after TUR was not superior in terms of recurrence-free survival [46]. It was speculated that the protocol-mandated continuous irrigation with saline for at least 20 hours might be responsible for the low and similar recurrence rates in the gemcitabine and placebo arms. It is noteworthy that intravesical chemotherapy should be instilled within 24 hours of TUR and left in the bladder for approximately one to two hours, as therapeutic benefits tend to fade if the instillation is delayed beyond 24 hours. Results of a randomized trial suggested that unless the first instillation was given on the day of TUR, the relative risk of recurrence more than doubled, irrespective of the rest of the instillation regimen [47]. The role of two early instillations instead of one was also investigated, albeit with variable results in published trials [33, 48].

**Role as an adjunct to further intravesical therapy**

An immediate post-operative single instillation may further improve the outcome of disease even in patients in whom subsequent intravesical chemotherapy is required. A significantly higher recurrence rate was observed in patients with multiple tumors after a single instillation (65.2% vs. 35.8%) in the EORTC meta-analysis, calling for the need of further treatment [42]. However, in patients requiring further serial intravesical chemotherapy, immediate post-operative single instillation appears to improve the overall treatment efficacy, as shown by two EORTC trials in which starting the treatment on the day of TUR was more effective than starting 7 to 15 days later [49]. This finding was further supported by a study revealing a two-fold increase in the risk of recurrence if the first of five weekly MMC instillations was not given within 24 hours of TUR [47].
However, all of these studies suffered from problems related to trial design and/or small patient numbers, leaving this issue unresolved for the time being [50]. Recent evidence suggests that the benefit of immediate post-operative single instillation of chemotherapeutic agents after TUR as the sole treatment modality is mainly seen in patients with low-risk disease with primary, small, solitary, low-grade tumors and the protective effect is limited to the first two years of follow-up [40, 51, 52].

In conclusion, immediate post-operative single instillation therapy is indicated in tumors at low risk of progression (single, primary, papillary lesions) as the only intravesical treatment and can also be considered as the initial step of further intravesical therapy in patients who are presumably at intermediate risk. In the

Table 6.1 Randomized controlled clinical trials included in EORTC meta-analysis (2004).

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Agent</th>
<th>No of pts</th>
<th>Median follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oosterlinck et al. MRC</td>
<td>1993</td>
<td>Epirubicin 80 mg/50 mL</td>
<td>431</td>
<td>24</td>
<td>Recurrence rate after a single Epirubicin instillation was decreased by approximately 50%</td>
</tr>
<tr>
<td></td>
<td>1994</td>
<td>Thiotepa 30 mg/50 mL</td>
<td>417</td>
<td>105</td>
<td>No difference in time to first recurrence, recurrence rates, or failure-free interval</td>
</tr>
<tr>
<td>Ali-El-Dein et al.</td>
<td>1997</td>
<td>Epirubicin 50 mg/50 mL (single vs. delayed maintenance)</td>
<td>168</td>
<td>32.2 (mean)</td>
<td>Significantly lower recurrence rate with early single instillation compared to controls (24% vs. 52%, p &lt; 0.001). Mean interval to recurrence was significantly longer in both treatment arms (16 and 18 months in single instillation and maintenance arms, respectively) compared to control arm (6.9 months, p &lt; 0.05). However, in patients with a previous history of bladder tumor, recurrences were lower with maintenance therapy (34.6% vs. 22.6%, respectively). No difference was observed in progression rates</td>
</tr>
<tr>
<td>Solsona et al.</td>
<td>1999</td>
<td>Mitomycin-C 30 mg/50 mL</td>
<td>121</td>
<td>94</td>
<td>Significantly longer recurrence-free survival (p &lt; 0.013) and lower recurrence rates with MMC at early follow-up. Difference maintained at long-term follow-up, however, it was at the limit of statistical significance</td>
</tr>
<tr>
<td>Tolley et al.</td>
<td>1999</td>
<td>Mitomycin-C 40 mg/40 mL Single vs. 5 instillations</td>
<td>452</td>
<td>84</td>
<td>Significant reduction in recurrence rates with Mitomycin-C (rate of decrease 48% and 62% in single vs. 5 instillation arms, respectively compared to control arm). Risk of subsequent recurrence was decreased by 35% with single instillation (p = 0.01) and 50% by 5 instillations (p = 0.0001).</td>
</tr>
<tr>
<td>Rajala et al.</td>
<td>2002</td>
<td>Interferon-α2b 50 MU/ 100 mL Vs. Epirubicin 100 mg/100 mL</td>
<td>200</td>
<td>72</td>
<td>Kaplan–Meier disease-free estimates were 23.7%, 31.4%, and 50.8% in groups 1 to 3, respectively (p = 0.002). Median time to first recurrence was not attained in Epirubicin group; it was 9 and 12 months in control and Interferon, respectively</td>
</tr>
<tr>
<td>Okamura et al.</td>
<td>2002</td>
<td>(2’S,R)-4’-O- tetrahydropyranly- doxorubicin (THP)</td>
<td>160</td>
<td>40.8</td>
<td>A significant difference in the recurrence-free curve between the two arms (log-rank test; p = 0.0026), with 92.4% recurrence-free rate at 1 year, 82.7% at 2 years, and 78.8% at 3 years in treatment arm (84 patients) and 67.0%, 55.7%, and 52.6%, respectively in control arm. The recurrence rate per year was 0.11 +/- 0.22 in arm A and 0.24 +/- 0.36 in arm B, with a significant difference (p = 0.007)</td>
</tr>
</tbody>
</table>
presence of high-risk tumors, an immediate instillation is an option because it appears to have a positive impact on recurrence. However, whether this type of treatment improves the outcome compared with a course of adjuvant treatment alone in the high-risk patient population remains to be determined [53].

Methods to improve the efficacy of intravesical chemotherapy
Pharmacokinetic interventions and delivery systems

Targets of intravesical therapy are (1) residual tumors not removed by TURBT, (2) dislodged tumor cells that may form new tumors, and (3) newly formed tumors from “at risk” urothelium. In intravesical therapy, the bladder is emptied via catheterization and the drug is instilled and maintained, usually for one to two hours. Our laboratory has been studying the pharmacology of intravesical chemotherapy since the late 1980s. The theoretical basis and the experimental results are detailed elsewhere [54] and are briefly summarized below.

There are two major causes of treatment failure [17, 55]. First, only 3–5% of the dose of MMC and doxorubicin penetrates across the bladder urothelium due to its highly specialized barrier function. After entering the bladder tissues, drug concentrations decline rapidly due to drainage into blood vessels. Second, the MMC concentrations required to produce anti-tumor activity increase with tumor stage, e.g., the 90%-effective concentration for T1 and muscle-invading tumors is, on average, 2.5 times higher than for Ta tumors [55]. For these reasons, the average clinically achievable drug concentrations at locations of Ta and T1 tumors are 6- and 30-fold below the 90%-effective levels [55]. These studies further revealed an up to 20-fold inter- and intra-patient variability in drug exposure, and that dilution of drug concentrations accounted for > 90% of the variability [56]. The drug concentration dilution was due to the presence of residual urine at the time of drug instillation and urine production during treatment. Taken together, these results suggested the efficacy of intravesical therapy may be improved by reducing the variability and maximizing the drug exposure.

Computational modeling has been employed to quantify the effects of various physiological and pharmacological parameters on drug delivery to bladder tissues; the results showed that several concurrent protocol changes aimed at increasing and preserving high drug concentrations in urine maximize the drug levels at locations of Ta and T1 tumors. These methods are (1) using MMC dosing solution at maximal water solubility (2 mg/mL), (2) voluntary dehydration with no fluid intake for eight hours prior to and during treatment, (3) ultrasound-guided removal of residual urine to < 10 mL immediately prior to dose administration, and (4) neutralizing the urine pH (1.3 g oral sodium bicarbonate the night prior to, the morning of, and 30 min prior to treatment), as MMC is ten times more stable at neutral pH compared to higher and lower pH [56]. The model further predicted that such improvement would significantly improve the recurrence-free cures. This prediction was tested and confirmed using intravesical MMC in a multi-center, randomized phase III trial (230 patients); the time to recurrence increased from 11.8 to 29.1 months and the five-year recurrence-free rate increased from 24.6% to 41.0% (relative risk of 78%, \( p = 0.005 \)) [17].

The clinical proof of concept that enhancing drug exposure improves treatment efficacy has motivated several new methods to enhance MMC penetration into bladder tissues using physicochemical methods (hyperthermia, electromotility). The combination of MMC with hyperthermia at 42 ± 2°C shows a 50% five-year recurrence-free survival in patients with high-grade tumors [57]. Applying an electric current (20 mAm for 30 minutes) enhances the bladder tissue penetration of MMC and improves the recurrence-free survival from 19.5 to 35 months in high-risk patients [58]. A more recent approach is to use hydrogel to extend the contact time of MMC with the urothelium; a phase I trial has been completed [59]. On the other hand, these methods may not be sufficient to overcome the limitation that MMC, because it induces apoptosis via the p53 pathway [60], is not likely to have activity against tumors with mutated and inactivated p53, which occurs with high frequency in patient tumors, i.e. 49% and 76%, respectively [61].

In view of the above, desirable properties of agents for intravesical therapy include:

1. Higher penetration across the urothelium and longer retention in tissues.
2. Efficacy against the more rapidly proliferating bladder tumors.

Our laboratory is currently developing a polymeric delivery system for intravesical therapy, i.e., paclitaxel-loaded gelatin nanoparticles [62]. Paclitaxel has activity
against metastatic bladder cancer, shows high penetration across the urothelium and tight binding to intracellular macromolecules (resulting in significant drug accumulation and retention in tumor cells), and can induce apoptosis through p53-dependent or -independent pathways [63, 64].

The nanoparticles are designed to release paclitaxel via a solubility-limited mechanism; this provides constant concentrations in urine and eliminates the 20-fold variability in drug delivery due to dilution by newly produced urine and residual urine. The nanoparticle system is currently undergoing NIH-sponsored IND-enabling studies.

**Combination therapy**

Combination chemotherapy, although commonplace in oncology for systemic disease, is seldom used in intravesical chemotherapy. Among the limited attempts, the addition of epirubicin does not improve the response to BCG [65] whereas the combination of the bleomycin analog peplomycin and doxorubicin shows improvement over single agents [66].

**Sequential therapy**

Conceptually, the sequential use of drugs with different mechanisms of action may be beneficial because of a possible synergistic effect. Initiation of therapy by immediate post-operative intravesical chemotherapy followed by weekly BCG instillations is one of these strategies which aims to reduce tumor re-implantation as well as induction of sloughing of the urothelium which then allows BCG to interact better with fibronectin and initiate a more robust immune response [67]. The reverse has also been suggested, i.e. BCG-induced inflammation might increase the permeability of the bladder mucosa such that MMC can reach the target tissue more easily and exert its anti-cancer effect, as shown in a randomized trial [68]. Two randomized trials comparing the efficacy of MMC alone versus MMC and BCG in patients with intermediate or high-risk NMIBC found no significant difference in terms of median time to recurrence, tumor recurrence rates, recurrence-free survival, and progression rates [69, 70]. Additional randomized prospective studies also showed no significant difference in efficacy between sequential BCG and epirubicin versus BCG alone [65, 71]. A Nordic study comparing sequential MMC and BCG instillations with BCG alone found no difference in CR rate in 304 patients with CIS [72]. At one year, 77.9% of evaluable patients in the monotherapy group and 78.9% in the alternating sequential group had CR. At a follow-up time of 60 months, the Kaplan–Meier disease-free estimates were 40.7% and 53.8% for the sequential and monotherapy groups ($p = 0.03$; log rank test). Thus, alternating monthly MMC and BCG was significantly inferior to BCG alone. This observation was partly explained by the fact that BCG instillations were given every two months in the alternating arm and this was “too wide” a time frame for producing an adequate response [73]; another potential cause is the severely suboptimal number of BCG instillations, i.e. patients in the sequential arm received only a total of five instillations and lacked the six-weekly induction of BCG whereas the patients in the monotherapy arm received 16 BCG instillations over a period of 12 months. Another study, Finnblander IV, which had a similar study design (11 versus 5 BCG instillations) revealed very similar results, with five-year recurrence-free rates of 67% and 22%, respectively, favoring the BCG intense treatment arm [47]. In a more recent randomized phase II EORTC trial comparing sequential MMC and BCG versus BCG alone, where both arms received a six-weekly induction BCG therapy and the monotherapy arm received three more BCG instillations, no significant difference was observed in CR rates in intent to treat and per-protocol analyses [73]. After a median follow-up of 4.7 years, 52.1% of the sequential treatment versus 45.8% of the BCG alone arm were disease-free.

Sequential gemcitabine plus MMC treatment appears effective in BCG failures and high-risk patients, but has not been evaluated in randomized studies [74]. Intravesical sequential therapy with epirubicin followed by BCG was found to be effective in a series of 81 patients with T1 high-grade tumors [75]. After a mean follow-up of 48 months, recurrence and progression rates were 23.4% and 7.4%, respectively. However, the absence of a control group precludes a meaningful conclusion. Another study reported a significant advantage for sequential treatment of BCG and MMC versus BCG alone [68]; however, because MMC was used with electromotive application, it is not clear if the favorable outcomes in the sequential therapy were, at least partly, due to the mode of MMC application.

In conclusion, available data from published studies comparing sequential intravesical BCG and chemotherapy versus BCG only do not provide unequivocal evidence to support the superiority of either approach.
**Treatment outcome**

Tumor-free recurrence rate is the most common endpoint, followed by time to recurrence. Data on disease progression, due to the low frequency (< 3%), are not as readily available.

Perioperative chemotherapy is effective in reducing disease recurrence in patients with Ta and T1 tumors from about 50% for a placebo to about 37% (relative risk factor of 67%) but does not significantly reduce disease progression; similar benefits are attained in patients with different risk factors (grade, stage, multifocal, recurrent) [15, 16, 76, 77]. Due to the fact that CIS patients were often excluded from data analysis, the benefits of perioperative chemotherapy in these patients are less well defined, although the two most-studied drugs, MMC and epirubicin, appear to have equal activity.

The results of studies examining induction and maintenance therapy reveal that (1) chemotherapy significantly reduces recurrence, but not disease progression or survival; (2) longer treatments give better results; (3) MMC is more efficacious compared to thiotepa and doxorubicin; (4) higher doses or more effective delivery to the bladder wall increase efficacy; and (5) BCG/chemotherapy combinations are not generally superior to BCG. Relative risk varies widely with different treatments [20, 78].

BCG-refractory NMIBC patients who are not candidates for cystectomy are treated with BCG plus interferon, MMC, gemcitabine, or valrubicin. Valrubicin yields 18% complete response at six months [79]. Gemcitabine (six weekly treatments plus one year maintenance) is superior to BCG rechallenge (47.5% vs. 12.5% recurrence-free at 12 months) [80]. Docetaxel is also under evaluation for this indication. In a single institution trial of 54 patients, 40% of those treated were disease free at 12 months following the completion of therapy [81].

**Device-assisted intravesical chemotherapy**

**Thermochemotherapy**

The combination of hyperthermia and various chemotherapy agents has shown a synergistic effect in decreasing proliferation in cell lines [82–84]. Based on such experimental observations, a combination of intravesical chemotherapy and hyperthermia, which is called thermochemotherapy, was introduced for the management of high-risk NMIBC. The most common form of hyperthermia is administered via direct microwave irradiation of the urothelium by means of a 915-MHz intravesical microwave applicator [85]. The target intravesical temperature is set between 41°C and 44°C and is measured by five thermocouples integrated in a 20-Fr treatment catheter. The urethra is continuously cooled to avoid any injury during the procedure [86].

In a prospective, multi-center, randomized trial comparing the efficacy and local toxicity of thermochemotherapy to MMC alone in intermediate- to high-risk NMIBC patients, reported recurrence rates were 17.1% versus 57.5% (p = 0.0002) after a minimum follow-up period of 24 months [87]. Also, tumor recurrence in the chemotherapy alone group was significantly earlier and more frequent, with a hazard ratio of 4.821 (95% CI: 1.953–11.899). The ten-year disease-free survival rates for thermochemotherapy and chemotherapy alone were 53% and 15%, respectively (p < 0.001) [88]. A recent meta-analysis indicated 59% less recurrence after thermochemotherapy compared to MMC alone and a pooled bladder preservation rate of 87.6% [85]. However, the optimal treatment schedule and whether maintenance treatment is required as part of a routine schedule are still unknown. In addition, adverse events associated with thermochemotherapy appear to be more common than with chemotherapy alone. The efficacy of thermochemotherapy in patients failing previous BCG therapy is currently inconclusive [89–91]. An interim analysis of a multi-center trial reported almost 30% poorer recurrence-free survival rates at two years with thermochemotherapy in patients who failed a previous intravesical therapy compared to de novo patients [85]. Overall, the results of thermochemotherapy in patients that have previously failed other intravesical treatments are heterogeneous. However, the possibility that a significant number of patients could be salvaged with thermochemotherapy certainly warrants further research.

**Complications/side effects**

The rationale for intravesical therapy is to expose tumors to high drug concentrations and to minimize systemic exposure. The major form of toxicity of doxorubicin and MMC is local, including chemical cystitis, dysuria, frequent urination, hematuria, and skin rash. These side effects usually resolve upon cessation of therapy. Systemic toxicity is rare, with the exception of thiotepa, which, due to its extensive systemic absorption, causes myelosuppression [54].
**Electromotive drug administration**

The epithelium of the bladder is a strong barrier between the intravesical compartment and submucosal tissues of the bladder. However, electrokinetic forces increase drug delivery into and across biological membranes by four- to seven-fold compared to passive transport [58, 92]. Thus, the idea behind electromotive drug administration (EMDA) is to enhance the transport of intravesical chemotherapeutic agents by applying a current gradient between the bladder wall and the drug, which should, theoretically, increase the treatment efficacy [58, 93].

In a study comparing intravesical application of EMDA-MMC with MMC alone and standard BCG, the peak plasma concentrations of MMC were 5.5 times higher (43 ng/mL vs. 8 ng/mL) with EMDA compared to standard intravesical instillation [58]. These plasma MMC concentrations are below the threshold concentration associated with bone marrow suppression (i.e., 400 ng/mL; [56]). The initial response rates at three months were 53%, 28%, and 56% and the median times to recurrence were 35, 19.5, and 26 months for EMDA-MMC, passive MMC, and BCG, respectively. The efficacy of EMDA-MMC was similar to BCG in terms of recurrence in patients with treatment-naïve, high-risk NMIBC. In comparison to BCG alone, sequential application of BCG and EMDA-MMC showed a longer disease-free interval (69 months vs. 21 months; \( p = 0.0012 \)) after a median follow-up period of 88 months, a lower recurrence (42% vs. 58%; \( p = 0.0012 \)), lower progression (9.3% vs. 21.9%; \( p = 0.004 \)), lower disease-specific mortality (5.6% vs. 16.2%; \( p = 0.01 \)), and lower overall mortality (21.5% vs. 32.4%; \( p = 0.045 \)) [68].

**Photodynamic therapy**

Photodynamic therapy (PDT) involves the administration of a photosensitizer and its subsequent activation by light at the appropriate wavelength to destroy the malignant cells containing the photosensitizer [94]. Light absorption by the photosensitizer initiates a photochemical reaction that generates short-lived reactive oxygen species (ROS), in particular singlet oxygen, producing cell death and tissue damage [95–97]. Toxicity and treatment selectivity of PDT results from differential drug accumulation and/or retention between tumor and normal tissues. Endogenous aminolevulinic acid (ALA) is a natural precursor of the photoactive intermediate protoporphyrin IX. Intravesical hexaminolevulinic acid (hexaminolevulinate; HAL), a lipophilic hexyl ester of 5-aminolevulinic acid (5-ALA), leads to the accumulation of protoporphyrin IX in malignant cells [96–98]. Although the initial clinical studies indicated a favorable response by PDT with orally administered 5-ALA as an organ-preserving procedure for the treatment of NMIBC, hemodynamic and cardiac side effects, especially in patients with known cardiovascular disease, precluded its widespread use [94]. The side effect profile was more favorable with intravesical ALA-based PDT in patients with NMIBC in whom multiple transurethral resections and/or intravesical BCG immunotherapy alone had failed. The side effects of intravesical ALA-based PDT were mainly dysuria due to urinary tract infection in 14% of cases and hematuria in 22% [99]. At an average follow-up of 23.7 months, one-half of the patients were free of tumor recurrence. The safety and feasibility of intravesical HAL-based PDT in intermediate- to high-risk NMIBC as an adjuvant treatment after TUR were evaluated in a phase I study in which tumor-free rates at 6, 9, and 21 months were reported as 52.9%, 23.5%, and 11.8%, respectively [100].

Recently, the effectiveness of PDT with radachlorin (a complex natural photosensitizer that accumulates in tumors, efficiently destroying them upon photoactivation by a laser) was evaluated in 34 patients with high-grade NMIBC refractory to or intolerant of BCG therapy [98]. After a median follow-up of 28 months, tumor-free rates were 90.9%, 64.4%, and 60.1% at 12, 24, and 30 months, respectively. No severe adverse events were observed and overall, results suggested that this approach may be a promising alternative to spare the bladder.

**Useful web links**


**Note**

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References


Intravesical chemotherapy


51 Berrum-Svennon I, Granfors T, Johnson S, et al.: A single instillation of epirubicin after transurethral resection of


Intravesical chemotherapy


**CHAPTER 7**

**Intravesical immunotherapy**

Nilay M. Gandhi1,*, Laura A. Bertrand2,*, Donald L. Lamm1, and Michael A. O’Donnell2

1 James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD, USA
2 Department of Urology, University of Iowa, Iowa City, IA, USA
3 BCG Oncology, Phoenix, AZ, USA

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**KEY POINTS**

- The majority of urothelial carcinomas are non-muscle-invasive bladder cancers (NMIBC), a high proportion of which will either recur or progress to muscle-invasive disease despite complete resection.
- Bacillus Calmette-Guérin (BCG) intravesical immunotherapy is a standard of care and now recommended for high- and intermediate-risk NMIBC with complete response rates of 55–65% for Ta/T1 tumors and 70–75% for CIS.
- BCG is known to trigger a variety of local immune responses including inducing a Th1 immune response.
- Maintenance BCG therapy is recommended after induction therapy using the SWOG schedule of a six-week induction course followed by three weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months.
- Side effects of BCG include local cystitis-like symptoms as well as the risk of disseminated disease in the immuno-compromised or those with urothelial mucosal trauma.
- BCG toxicity rates have decreased overall to less than 10% with the use of dose-reduction (1/3, 1/10, 1/30, and 1/100 as needed), fluoroquinolone antibiotic, decreased bladder dwell time, and delay of treatment with signs of hematuria or urinary tract infection, although reduced doses may be less efficacious in patients with high-risk disease.
- Failures of BCG immunotherapy require aggressive follow-up and prompt cystectomy due to a poorer prognosis than patients proceeding directly to cystectomy.
- Interferon-α may be beneficial when combined with BCG following initial failures.

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**Introduction**

More than 70% of bladder cancer patients present with non-muscle-invasive disease. Approximately 40–80% of these tumors will recur within the first year, of which 10–25% will progress to muscle-invasive disease [1]. For urothelial carcinoma (UC), which accounts for over 90% of bladder cancers, intravesical treatments have become the mainstay following transurethral resection (TUR), allowing for the destruction of residual microscopic disease with cytotoxic chemotherapy and the prevention of new tumors with immunotherapy. There is no established role for immunotherapy in non-urothelial mixed variants.

In this chapter we discuss the development of bacillus Calmette-Guérin (BCG) immunotherapy as a standard of care therapy for high-grade, non-muscle-invasive bladder cancer (NMIBC) and we address the utility of combination therapy with interferon (IFN) and other cytokines. Current practices aimed at the reduction of local and systemic toxicity will be covered along with the debate surrounding maintenance therapy and treatment failure.

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*Drs. Gandhi and Bertrand share first authorship as both contributed equally.*

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Intravesical immunotherapy

History/development

Widespread implementation of the BCG vaccine for the prevention of tuberculosis (TB) began in the early 1920s following the work of Albert Calmette and Camille Guérin. Around this same time, autopsy studies showed patients who died of TB seldom harbored malignancy, suggesting a potential anti-neoplastic effect of TB infection [2]. In 1976, Morales first demonstrated BCG's efficacy against bladder cancer with a 12-fold reduction in tumor recurrence for nine patients with recurrent bladder cancer treated with intravesical and percutaneous BCG administration [3]. Knowing that a treatment minimum of three weeks was necessary to establish a delayed hypersensitivity reaction and that the side effects resolved within one week, Morales established the currently utilized schedule of six weekly induction bladder instillations. Lamm and Pinsky independently conducted the first randomized controlled trials (RCT) in the early 1980s, investigating the effects on tumor recurrence and progression in patients undergoing TUR without BCG against patients who received both percutaneous and intravesical BCG following resection [4, 5]. A significant difference in recurrence was noted among the BCG group (22% vs. 42%, \( p = 0.03 \)) at one-year follow-up. Additionally, higher-risk patients treated with intravesical BCG demonstrated a significant reduction in recurrent tumors \( (p < 0.01) \), a longer disease-free interval \( (p < 0.01) \), and time to progression \( (p < 0.03) \) compared to no treatment. With prolonged follow-up, the waning immune response to BCG was identified: anti-tumor benefit persisted for up to 10 years, but was lost at 15 years (53% progression, 34% cancer-specific mortality), suggesting a role for lifelong maintenance therapy [6]. BCG has been validated as being superior to intravesical chemotherapy for high-grade NMIBC in regard to both tumor recurrence [7] and progression when incorporated with maintenance therapy [8].

BCG mechanism of action

BCG is a live, attenuated strain of *Mycobacterium bovis* that elicits a variety of local immune responses which appear to correlate with its anti-tumor activity. The initial activating step for the inflammatory cascade is binding of BCG to fibronectin expressed on the urothelium [9]. BCG is then internalized by both normal urothelial and malignant cells and presented on the surface of antigen-presenting cells (APCs) such as macrophages and dendritic cells via major histocompatibility complex (MHC) class II. CD4+ T cells are activated, inducing a Th1 immune response leading to the influx of neutrophils, lymphocytes, natural killer (NK) cells, macrophages, and dendritic cells within the bladder wall along with a massive, transient influx of cytokines [10]. Release of a Th1 cytokine profile (IFN-\( \gamma \), IL-2, IL-12) is necessary for successful therapy, while elevated levels of Th2 cytokines (i.e. IL-10) have correlated with BCG failure [11].

One of the major BCG-induced cytokines, IFN-\( \gamma \), is known to induce expression of MHC class II molecules on bladder cancer cells, increasing the sensitivity to BCG by activating lymphokine-activated killer cells and APCs, including macrophages [12]. Macrophages serve as the initial line of defense, allowing for cytokine production, BCG antigen presentation, and function in an anti-neoplastic manner against bladder cancer cells [13, Figure 7.1]. Along with anti-mycobacterial effects, macrophages also exhibit tumoricidal activity via both direct cell-to-cell contact and the release of cytotoxic cytokines (TNF-\( \alpha \), IFN-\( \gamma \)) and apoptotic nitric oxide [14]. Neutrophils also become activated and elicit production of tumor necrosis factor-related apoptosis-induced ligand (TRAIL) which specifically targets the malignant bladder cells. A significantly higher level of urinary TRAIL is seen in patients responding to BCG therapy than in non-responders [15]. A systemic immune response is also seen in the form of elevated serum cytokines and cellular and humoral BCG reactivity [16].

Induction

Due to the increased risk of live bacterial intravasation, instillation is performed two to four weeks following TUR via a urethral catheter under gravity drainage [17]. Following complete TUR, an induction course of six weekly instillations is given. This regimen was established by Morales based on immunological studies and the pre-packaged dosing provided by Armand Frappier [18]. An intravesical dose of 10^8 to 10^9 colony-forming units is required for effective treatment. Interestingly, the Southwest Oncology Group (SWOG) noted it may take up to six months for an initial induction course of BCG to have full effect. Twenty-four percent of patients with residual CIS at three months
after induction were found to be disease free at six months without further BCG. However, when an additional three BCG instillations (maintenance) were administered, the number of complete responders increased to 64%. This number declined when a second six-week treatment course was used instead, suggesting the last three instillations of a six-week course may be immunosuppressive [19]. Persistence of disease following two six-week cycles or after six months on the three-week maintenance schedule is considered a poor prognostic sign and patients are classified as BCG refractory [20].

**Figure 7.1** Immune response cascade induced by intravesical BCG. Source: Rangel, L (ed.) *Cancer Treatment – Conventional and Innovative Approaches* [13].

**BCG and carcinoma in situ**

BCG is currently approved by the US Food and Drug Administration (FDA) for the treatment of CIS as well as papillary UC. For CIS, FDA approval was based on Lamm’s study which reported a 70% complete response rate with BCG compared to 34% with chemotherapy ($p < 0.01$). The median times to treatment failure were 5.1 months (doxorubicin) versus 34 months (BCG), with BCG having a 45% five-year disease-free survival probability [21]. When incorporating three-week BCG maintenance, the overall response rate for CIS approaches 84% [19]. A meta-analysis of 700 patients with CIS (345 BCG, 355 chemotherapy) demonstrated a 47% reduction in treatment failure with BCG (OR 0.53, $p = 0.02$) along with a 53% reduction in tumor recurrence only in studies involving BCG maintenance therapy [22].

**BCG prevention of recurrence**

A meta-analysis of six RCTs totaling 585 intermediate- and high-risk patients (281 TUR alone versus 304 TUR+BCG) demonstrated a 56% reduction in tumor recurrence attributable to BCG ($p < 0.01$) [23]. Comparisons with
mitomycin-C (MMC) showed BCG superiority in tumor reduction across all risk groups (OR 0.56, 95% CI: 0.38–0.84, p < 0.001), however, the benefits were limited to studies involving BCG maintenance [24], confirming findings from an earlier SWOG trial [25]. Recent RCTs found a statistically significant reduction in tumor recurrence with maintenance therapy [26–28]. Similar reductions in tumor recurrence with BCG therapy have also been identified in direct comparisons with epirubicin [29], doxorubicin [21], and thiotepa [30].

**BCG prevention of progression**

The SWOG 8507 RCT studied 384 patients randomized to receive either maintenance BCG or no maintenance following an induction course [19]. A significant improvement in recurrence-free survival (RFS) was noted (five-year 60% versus 41%, p < 0.01) and a longer time to progression or death (76% versus 70% five-year worsening-free survival, p = 0.04) with maintenance therapy (Figure 7.2). A suggestion of survival benefit was also noted, with an 83% five-year survival (p = 0.08). An analysis of 24 RCTs published prior to 2002 comparing TUR ± BCG or chemotherapy found a reduction of 27% in the odds of progression (OR 0.73, p = 0.01) between BCG and non-BCG comparison groups [31]. Bohle and Bock [32] showed a significant effect on progression in comparing BCG (7.7%) to MMC (9.4%). In these studies, the effects on progression were limited to patients receiving maintenance therapy.

**BCG maintenance**

Immune responsiveness to BCG wanes over time, supporting the use of maintenance therapy [33]. High-risk patients require lifelong treatment and surveillance and both the American Urological Association and the European Association of Urology guidelines recommend maintenance therapy for these patients [34, 35]. SWOG 8507 was the first maintenance study to demonstrate a significant reduction in tumor recurrence and disease progression as well as a possible survival benefit. Utilizing various maintenance schedules (not three-week), RCTs have failed to find any advantage of maintenance versus induction alone (Table 7.1). More recent, larger RCTs incorporating the SWOG maintenance protocol have confirmed that three-week maintenance, unlike other schedules, reduces disease progression [26–28]. The current protocol following induction calls for three-weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months.

In the largest RCT of maintenance BCG, Oddens concluded that full-dose (FD) three-week BCG maintenance for three years is recommended in high-risk patients (HR 1.61, p = 0.0087) versus 1/3 dose for one year. Overall, a 56.7% disease-free rate (DFR) was noted (five-year DFR: 64.2% FD, three year; 62.6% 1/3 dose, three year; 58.8% FD, one year; 54.5% 1/3 dose, one year) [28]. The advantage of three years of maintenance over one year is consistent, but one year maintenance is recommended for intermediate-risk patients. We emphasize caution with shortening the schedule in intermediate-risk patients however, as this group had the greatest reduction in metastasis and mortality with three-year/three-week maintenance in the EORTC 30911 study [27]. While concern has been raised that prolonged BCG maintenance may delay cystectomy and reduce survival, Lerner surprisingly showed a 63% reduced risk of death in patients who failed three-week maintenance BCG and required cystectomy compared to those who had early cystectomy following induction BCG (HR 0.37, p = 0.017) [36]. The explanation for this survival benefit may relate to the systemic immune stimulation induced by BCG. Patients with hyperplastic pelvic lymph nodes at cystectomy have better survival than those with unstimulated or depleted nodes [37]. Duration of maintenance should be guided by patient and disease characteristics, with the preference toward longer treatment courses in patients with higher risk disease and those able to tolerate the treatments, but remembering that the reduction in progression, metastasis, and mortality has been found to be highest in intermediate-risk patients [27].

**BCG toxicity and treatment**

One drawback of BCG therapy is its propensity to induce local and systemic side effects. Increasing knowledge of BCG use allows for effective management of these once debilitating side effects. The majority of patients will still experience cystitis-like symptoms to some degree, including urinary frequency (71%), cystitis (67%), fever (25%), and hematuria (23%) [20]. Symptoms generally resolve within 48 hours and are more common
Up to 20% of patients receiving BCG will develop a conventional bacterial urinary tract infection (UTI) at some point during treatment. Local infection can also spread to the epididymis or prostate, and up to 75% of patients had granulomatous prostatitis and/or an elevation in prostate-specific antigen (PSA) levels, although the vast majority was asymptomatic [39, 40]. While the PSA returned to normal levels within three months, this can cloud the results of men undergoing concomitant screening for prostate cancer during BCG treatments.

The most serious and feared complication of BCG intravesical instillation is sepsis. Patients may present with fevers, rigors, and hypotension but progress to disseminated intravascular coagulopathy and respiratory failure [41]. High levels of cytokines are released directly into the bloodstream as part of a hypersensitivity response (“cytokine storm”) [42]. While this typically occurs soon after BCG instillation, delayed cases have

Figure 7.2  
(a) Recurrence-free survival, (b) overall survival and (c) worsening-free survival in months by arm for eligible patients with no evidence of disease at randomization. Source: Lamm et al., 2000 [19]. Reproduced with permission from Elsevier.
Table 7.1 Comparison of randomized controlled trials investigating maintenance BCG. All studies not using the SWOG three-week maintenance studies fail to show any significant advantage, while all studies using three-week maintenance show statistically significant advantage. Source: Gandhi NM, Bohle A, and Lamm DL. Reproduced with permission.

<table>
<thead>
<tr>
<th>Trial</th>
<th># patients</th>
<th>Comparison groups (#)</th>
<th>Restaging TUR after induction</th>
<th>BCG Maintenance schedule</th>
<th>Withdrawal from BCG toxicity (%)</th>
<th>Recurrence-free survival</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCG NON 3-WEEK MAINTENANCE SCHEDULES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Badalament <em>et al.</em> (1987) [90]</td>
<td>93</td>
<td>Maint (47) vs Non-maint (46)</td>
<td>Yes</td>
<td>120mg monthly for 2 years</td>
<td>21 (45%)</td>
<td>~45% at 2 years for both</td>
<td><em>p = 0.77</em> NS</td>
</tr>
<tr>
<td>Hudson <em>et al.</em> (1987) [91]</td>
<td>42</td>
<td>Maint (21) vs Non-maint (21)</td>
<td>No</td>
<td>Every 3 months for 2 years</td>
<td>n/a</td>
<td>67% vs 71%</td>
<td>NS</td>
</tr>
<tr>
<td>Tachibana <em>et al.</em> (1989) [92]</td>
<td>77</td>
<td>BCG (44) vs Adriamycin (33)</td>
<td>No</td>
<td>Monthly for 1 year or monthly for &gt; 1.5 years</td>
<td>n/a</td>
<td>73% vs 27.3% at 3 years</td>
<td><em>p &lt; 0.01</em> vs chemo</td>
</tr>
<tr>
<td>Akaza <em>et al.</em> (1995) [93]</td>
<td>107</td>
<td>Maint (52) vs Non-maint (55)</td>
<td>No</td>
<td>40mg monthly for 1 year</td>
<td>n/a</td>
<td>77.6% vs 74.2% at 3 years</td>
<td>NS</td>
</tr>
<tr>
<td>Palou <em>et al.</em> (2001) [94]</td>
<td>126</td>
<td>Maint (65) vs Non-maint (61)</td>
<td>No</td>
<td>6 weekly every 6 months for 2 years</td>
<td>32 (49%)</td>
<td>85% at 20 months vs 74% at 24 months</td>
<td><em>p = 0.07</em> NS</td>
</tr>
<tr>
<td>Koga <em>et al.</em> (2010) [95]</td>
<td>51‡</td>
<td>Maint (24) vs Non-maint (27)</td>
<td>No</td>
<td>80mg every 3 months for 4 total doses</td>
<td>5 (20.8%)</td>
<td>95.8% vs 74.1% at 2 years</td>
<td><em>p = 0.078</em> NS</td>
</tr>
<tr>
<td><strong>BCG 3-WEEK MAINTENANCE SCHEDULES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamm <em>et al.</em> (2000) [19]</td>
<td>384</td>
<td>Maint (192) vs Non-maint (192)</td>
<td>No</td>
<td>3 weekly at 3 and 6 months then every 6 months for 3 years</td>
<td>161 (84%)</td>
<td>75% vs 46.9% at 8 years</td>
<td><em>p &lt; 0.01</em></td>
</tr>
<tr>
<td>Sylvester <em>et al.</em> (2010) [27]</td>
<td>789</td>
<td>BCG (266) vs BCG+INH (256) vs Epi (267)</td>
<td>No</td>
<td>SWOG protocol for 3 years</td>
<td>99 (18.9%)</td>
<td>63.3% vs 60.3% vs 47.3% at 3 years</td>
<td><em>p &lt; 0.01</em></td>
</tr>
<tr>
<td>Hinotsu <em>et al.</em> (2010) [26]</td>
<td>110</td>
<td>Maint (36) vs Non-maint (42) vs Epi (32)</td>
<td>No</td>
<td>SWOG protocol for 1.5 years</td>
<td>21 (58.3%)</td>
<td>92.7% vs 65.4% vs 33.2% at 2 years</td>
<td><em>p = 0.02</em> (maintenance vs induction)</td>
</tr>
<tr>
<td>Duchek <em>et al.</em> (2010) [96]</td>
<td>250</td>
<td>BCG (126) vs Epi+IFN (124)</td>
<td>Yes</td>
<td>SWOG protocol for 2 years</td>
<td>11 (8.7%)</td>
<td>~65% vs 50% at 2 years</td>
<td><em>p = 0.01</em></td>
</tr>
<tr>
<td>Oddens <em>et al.</em> (2013) [28]</td>
<td>1355</td>
<td>BCG 1/3, 1yr (341) vs BCG FD, 1yr (339) vs BCG 1/3, 3yr (337) vs BCG FD, 3yr (338)</td>
<td>No</td>
<td>SWOG protocol for 1 and 3 years</td>
<td>24 (7.2%), 23 (7%), 16 (5%), 30 (9.1%) [total 103 (7.8%)]</td>
<td>54.5%, 58.8%, 62.6%, and 64.2% at 5 years</td>
<td><em>p = 0.04</em> (1yr vs 3yr stratifying dose and risk group)</td>
</tr>
</tbody>
</table>
been reported and may be triggered by systemic glucocorticoids many years later. There have also been case reports of patients developing early or late granulomatous hepatitis, renal granulomas, pneumonitis, spinal osteomyelitis, psoas abscesses and mycotic aneurysms [43–45].

The incidence of osteoarticular side effects after intravesical BCG, either reactive or septic arthritis, ranges from 0.5% to 1%, with arthralgia being the most common presenting symptom [46]. Reactive arthritis typically presents with symptoms in more than one joint, predominately in the lower extremity, arising within two weeks after instillation. In one review, 53% of patients tested positive for HLA-B27 and 19% complained of axial pain, consistent with a spondyloarthritis picture [47, 48]. Suspicion should be increased for septic arthritis, either due to bacterial infection or less commonly to _M. bovis_ infection, in the setting of monoarthritis in conjunction with fevers following intravesical BCG instillation [47]. Patients with joint inflammation should undergo arthrocentesis for synovial fluid examination, including cell count, differential WBC count, gram stain, bacterial culture, and AFB smear with mycobacterial culture. In the absence of any evidence for infection, treatment with NSAIDs may be sufficient.

Despite the risk of disseminated infection and osteoarticular side effects with intravesical BCG, there is no evidence to suggest that patients with prosthetic devices (pacemakers, artificial heart valves, and orthopedic hardware) are at an increased risk of complications. In a multi-center series of over 1000 patients treated with intravesical BCG plus interferon, there were no unexpected complications in the 143 patients with prosthetic devices [49]; 2% developed uncomplicated fevers, but all defervesced within 24 hours. In patients who do develop disseminated disease, their prostheses are at risk of being seeded, possibly necessitating removal, but the prosthesis alone should not be considered a contraindication to intravesical BCG therapy (Table 7.2). Given the rarity of prosthetic seeding, antibiotic prophylaxis is not recommended, however an inflamed, painful joint at any time point following BCG administration should alert the physician to the possibility of joint infection and lead to prompt, aggressive therapy.

Intravesical BCG should never be administered immediately after TUR, after traumatic catheterization, or with gross hematuria, as disruption of the mucosal barrier will increase the risk of absorption and sepsis [50]. Other relative contraindications include: a personal history of TB (although only a theorized risk, not applicable to patients with only a positive skin test), active UTI (nitrites or bacteria, not leukocytes), poor performance status, and advanced age. In one series of 58 patients, approximately 50% of those aged 70 and older developed complications from BCG [51]. Additionally, they demonstrated a lower disease-free rate, a result that may be predicted with skin test reactivity to purified protein derivative (PPD) prior to intravesical BCG administration to assess response [52]. BCG in patients with significant liver disease is also cautioned as hepatic dysfunction precludes use of isoniazid (INH) should they develop BCG sepsis. Intravesical BCG should be used cautiously in immunosuppressed or immunocompromised patients in order to minimize the risk of local and systemic infectious complications.

A study of 14 solid organ transplant patients undergoing intravesical BCG for subsequent NMIBC found that 75% did not require any modification to their immunosuppressive regimen and 70% experienced no side effects [53]. Additionally, Herr _et al._ identified that transplant patients have a higher rate of progression and should be considered for early cystectomy if BCG fails [54]. To date, there are insufficient data on administering BCG in patients on anti-TNF medications (monoclonal antibodies infliximab and adalimumab used in the treatment of rheumatoid arthritis, theoretically

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**Table 7.2** Retrospective analysis of complication rates in 2602 patients being treated with intravesical BCG for NMIBC.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;103°F)</td>
<td>2.9</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>1</td>
</tr>
<tr>
<td>Granulomatous prostatitis</td>
<td>0.9</td>
</tr>
<tr>
<td>Pneumonitis and/or hepatitis</td>
<td>0.7</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0.5</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.4</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>0.4</td>
</tr>
<tr>
<td>Rash</td>
<td>0.3</td>
</tr>
<tr>
<td>Ureteral obstruction</td>
<td>0.3</td>
</tr>
<tr>
<td>Contracted bladder</td>
<td>0.2</td>
</tr>
<tr>
<td>Renal abscess</td>
<td>0.1</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>0.1</td>
</tr>
</tbody>
</table>

predispose to BCG sepsis), or on statins (HMG CoA reductase inhibitors are known to have immunosuppressive effects).

Patients who develop mild symptoms of cystitis even with low-grade fever usually do not require specific treatment aside from analgesics and anticholinergics; these symptoms most commonly resolve within 48 hours. However, fevers higher than 39°C (102.5°F) may indicate an infectious etiology. The cardinal sign of BCG infection is a relapsing fever with drenching night sweats persisting beyond 48 hours [46]. Empiric therapy with a fluoroquinolone antibiotic should be initiated until the etiology of the fever is determined, as this will treat the majority of non-BCG bacterial UTIs and has reasonable anti-mycobacterial coverage. In patients with either acute, severe symptoms or those that persist beyond 48 hours, antituberculous therapy should be initiated according to the following recommended guidelines [46, 55–57]:

- Moderate to severe cystitis persisting beyond 48 hours: Fluoroquinolone (levofloxacin 500 mg daily) or INH (300 mg daily) should be initiated.
- If symptoms progress or fail to resolve within one to two weeks: INH should be continued and rifampin (600 mg daily) added; if symptoms respond quickly, two additional weeks of treatment are usually sufficient but otherwise continue treatment for three months.
- Patients with disseminated infection: Multi-drug antibiotic therapy is recommended for three to six months depending on the severity of symptoms and organ systems involved.
- Alternative anti-TB regimens, including ethambutol and/or amikacin have been used in elderly patients when INH and/or rifampin were avoided due to concerns over liver toxicity.
- M. bovis is typically resistant to pyrazinamide and cycloserine and should be avoided.
- Patients with BCG sepsis or disseminated infection should be treated empirically with systemic steroids, although caution should be exercised and an infectious disease consultant involved.

Patients with symptoms severe enough to warrant anti-TB therapy should generally not receive further BCG treatments. For those badly needing BCG, heat-killed BCG is being researched [58].

A more recent randomized trial assigned 155 patients with NMIBC to either six weekly instillations of standard dose (81 mg) or 1/3 dose BCG following complete endoscopic resection [59]. At a median follow-up of 61 months, there were no differences between the groups with regard to disease recurrence, time to recurrence, need for deferred cystectomy, or disease-specific survival. Rates of Grade 3–4 toxicity were lower with the reduced dose (local: 37% vs. 50%; systemic: 4% vs. 16%). A four-arm EORTC RCT of full dose or 1/3 dose BCG administered in a three-week maintenance schedule over one or three years showed that treatment at full dose for three years significantly improved the risk of recurrence for high-risk patients compared to a reduced dose for one year (HR 0.75, 95% CI: 0.59–0.94) although there were no significant differences in the toxicity profile between the full and reduced doses [28].

The EORTC 30911 study demonstrated no differences in local or systemic toxicity with prophylactic isoniazid therapy [27], but a significant decrease in class II adverse events was noted with ofloxacin (p = 0.017) [39]. The CUETO group reported on the significant difference in local (p < 0.05) and systemic (p < 0.01) toxicity reduction when utilizing 1/3 dose with no subsequent decreased effectiveness [59]. A recent RCT reported 92% of patients as able to complete three-week maintenance BCG [28].

**Alternative forms of immunotherapy**

Interferons (IFN) are glycoproteins long valued for their anti-viral properties. IFN-α is now known to stimulate NK cells, induce MHC class I response, and increase antibody recognition [60]. Its anti-neoplastic properties are attributed to both direct anti-proliferative and complex immuno-modulatory effects, including stimulating the expression of TRAIL by neutrophils [61, 62]. In vitro evidence suggests that IFN-α, specifically IFN-α2b, augments and prolongs the Th1 response by inhibiting IL-10, a Th1 inhibitory cytokine [63].

Because of its ability to augment the Th1 immune response, IFN-α2b has primarily been studied in conjunction with BCG. The only published randomized trial comparing BCG alone to BCG+IFN in this pre-immunotherapy population showed no significant difference in RFS at two years, although the IFN group did exhibit a higher incidence of constitutional symptoms and fever [64]. For patients who have failed to respond to an initial course of intravesical BCG therapy, however, the
addition of IFN-α may play a role. A study of 40 patients failing one or more courses of BCG showed a DFR of 53% at 24 months when they went on to receive six to eight weekly instillations of low-dose BCG plus IFN-α [65]. A multi-center trial including 467 patients with previous BCG failure demonstrated a DFR of 45% after being treated with reduced-dose BCG and IFN-α [66]. Risk factors for recurrence were stage T1, tumor size > 5 cm, multifocality, more than one prior BCG failure and age > 80, which may be explained by the natural decline in immune system function that comes with aging.

In BCG failure patients, the timing of recurrence may play a role in the subsequent outcomes after combination therapy. Patients with recurrence > 12 months after initial BCG treatment who were treated with low-dose BCG plus IFN-α had a DFR of 53–66% at 24 months, comparable to the DFR of 59% seen in BCG-naïve patients [67]. However, patients with recurrence within one year did poorly, with a DFR of 34–43% at two years. It appears that combination therapy with both BCG and IFN-α may have a salvage role in patients with single-course BCG failure or late relapse, while those who recur quickly after initial BCG treatment may be destined to failure and better served by radical cystectomy.

Interleukin (IL)-2 is another cytokine of interest in the treatment of bladder cancer. IL-2 enhances the production of cytotoxic lymphocytes capable of lysing tumor cells while leaving benign cells unharmed; these IL-2 activated lymphocytes became known as “lymphocyte-activated killer” or LAK cells [68, 69]. Additionally, it was noted that IL-2 functions to augment the cytotoxic activity of NK cells and monocytes and serve as a Th1 cytokine [69, 70]. This last observation spurred interest in IL-2 as a therapy for bladder cancer in combination with BCG. Poor tolerance to systemic IL-2 prompted a shift to intravesical administration with a much improved side effect profile [71, 72]. In a small cohort, intravesical IL-2 administered after incomplete TUR of low-grade T1 papillary UC demonstrated regression of the “marker lesion” in 8 of 10 patients [73]. Although studies in humans are so far limited, animal models with recombinant IL-2-secreting strains of BCG have shown an enhanced anti-tumor cytotoxicity and a mounted Th1 cytokine profile, including increased IFN-γ production, compared with native BCG [74–76].

IL-12 has been the subject of considerable cancer research since it was first noted in the 1980s to be synergistic with IL-2. While primarily involved in T-cell regulation, IL-12 also has a role in inducing IFN-γ, enhancing T-cell response to mitogens, and augmenting NK cell toxicity [77, 78]. Multiple animal studies have shown tumor responsiveness to IL-12, including bladder cancer models [79–81]. Although initial studies looked at systemic administration, intravesical therapy has shown good success in mice both alone and in combination with BCG. Orthotopically placed bladder cancers responded to intravesical treatments of IL-12 and BCG in mice and the levels of urinary IFN-γ were noted to be significantly increased after therapy [82, 83]. BCG is a potent stimulus for IL-12 expression and IFN-γ levels were dampened when IL-12 was neutralized in vivo, suggesting a synergistic effect of IL-12 and BCG on induction of IFN-γ [84]. Although this continues to be an important area of research, a recent phase I monotherapy trial with intravesical IL-12 failed to show any clinical effectiveness [85].

Current research has focused on the use of an IL-10 blocker in conjunction with intravesical BCG. IL-10 inhibits the production of several cytokines produced by Th1, including IFN-γ [86]. Several initial studies demonstrated an improved BCG and local immune response in IL-10 knockout mice after being inoculated with bladder cancer, with increased bladder mononuclear infiltrate, enhanced delayed-type hypersensitivity responses, greater anti-tumor activity, and prolonged survival [70, 87, 88]. More recent research has focused on the IL-10 receptor and its blockage. Mice treated with BCG and an anti-IL-10 receptor antibody showed increased urinary IFN-γ production along with improved overall and tumor-free survival when compared to BCG controls, although not all of these differences reached statistical significance [89]. Further testing showing more confirmatory results is necessary but these initial results are promising.

**Conclusion**

Intravesical administration of BCG for NMIBC represents one of the most successful immunotherapies for any solid malignancy. Using the three-week maintenance schedule, BCG immunotherapy has been demonstrated by large, multi-center RCTs to reduce recurrence, progression, and metastasis, and improve cancer-specific and overall mortality in intermediate- and high-risk patients. Improved
administration techniques have reduced adverse events, resulting in better patient tolerability and therefore more widespread and prolonged use. However, BCG is ineffective in a significant proportion of patients and can be associated with significant side effects. Therefore, multiple Th1-stimulating cytokines (IFN-α, IL-2, IL-12) have been investigated both as adjuncts to BCG and as solo replacement therapy. To date, there are multiple in vitro and murine studies showing promising results but no clinical data that are compelling enough to change the standard of care. Many practitioners continue to use adjunctive immunotherapy based on basic science data and theoretical benefit with anecdotal success. Given the morbidity and mortality associated with UC along with the significant cost of treatment, additional basic science and clinical research is needed in order to better understand the tumor biology and host immunology that goes along with this disease.

**Useful web links**


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Overview

Approximately 75–80% of all patients with bladder cancer (BC) have disease confined to the urothelium (stage Ta or stage carcinoma in situ) or lamina propria (stage T1). The high-grade stage T1 (HGT1) group represents about 20% of the patients who present with non-muscle-invasive bladder cancer (NMIBC) [1].

These tumors are at high risk of recurring and progressing to muscle-invasive bladder cancer (MIBC). The depth of tumor invasion within the lamina propria, associated carcinoma in situ (up to 15–20%), lymphovascular invasion (LVI), associated rare pathological variants (e.g. micropapillary, nested variant), female gender, prostatic urethral involvement, tumor size, and multifocality have been shown to be important risk factors for progression of HGT1 disease [2]. Long-term studies of treated HGT1 tumors reveal recurrence (55–67%) and progression (4–24%) rates at one year and (73–84%) and (35–50%), respectively, at five years of follow-up [3–6].

Diagnosis

The primary diagnosis of HGT1 bladder cancer usually occurs because of symptoms and signs, with hematuria being the most frequent finding. T1 tumors rarely cause bladder pain and/or present with lower urinary tract symptoms (LUTS). In patients who do complain of these
symptoms, particularly in those with irritative LUTS refractory to symptomatic treatment, CIS should be suspected. The diagnosis of recurrence is primarily based on cystoscopy during follow-up. The diagnosis of HGT1 bladder cancers, as with other papillary tumors, depends upon cystoscopic examination of the bladder and histological evaluation of the resected tissue.

**Transurethral resection**

Risk stratification is important for the future management of patients with HGT1 tumors. Transurethral resection (TURBT) is required to achieve a histological diagnosis and is also the primary treatment. This procedure must be systematically and meticulously performed. Larger tumors should be resected separately in fractions that include the exophytic part of the tumor, the underlying bladder wall with the muscularis propria, and the edges of the resection. It has been demonstrated that a wide and deep initial resection decreases the rate of persistence and understaging [7, 8]. Specimens from different layers of the lesion should be sent for pathologic assessment in separate containers with the correct identification. The TURBT specimen should include muscularis propria. The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and understaging [9, 10]. The analysis of 2410 patients from seven phase III trials by the EORTC showed substantial variations in early recurrence rates among different institutions. The frequency of three-month recurrences ranged from 0% to 46%. This variation cannot be attributed solely to clinical features of the tumor, and was considered, in large part, the result of differential quality of TURBT performed [11], confirming the importance of a well-performed initial resection.

**Multiple random biopsies**

According to international guidelines, mapping/random bladder biopsies are not routinely recommended in patients with T1 tumors because the likelihood of detecting CIS, especially in low-grade tumors, is extremely rare (<2–5%) [12]. These should only be performed in patients with positive urinary cytology, suspicious mucosal abnormalities, and/or evidence of a high-grade tumor in the bladder. They are mandatory in patients with positive cytology and absence of visible tumor in the bladder, and normal upper tract examinations [7]. Since involvement of the prostatic urethra and ducts has been reported to occur in 11.7% of HGT1s [13], biopsy of the prostatic urethra is also recommended when bladder CIS is suspected or abnormalities of the prostatic urethra (PU) are visible. In this situation, a prostatic urethra tissue sample should be taken using a resection loop from the prostatic urethra (between the 5 and 7 o’clock position). In primary NMIBC without suspicion of prostatic stromal invasion, a biopsy of the prostatic urethra using cold-cup biopsy forceps is sufficient [14].

**Substaging of T1**

In 1990, Younes et al. [15] were the first to use the muscularis mucosae (MM) in TURBT specimens to substage clinical T1. The MM is comprised of scattered muscular fibers that are formed as a continuous or interrupted layer running along large blood vessels in the lamina propria, between the epithelium and the detrusor muscle. These authors developed a subclassification of T1 tumors based on dividing the lamina propria into three regions: (a) the zone between the basal membrane and the MM; (b) the zone corresponding to the MM; and (c) the zone between the MM and the muscularis propria. The tumors invading the first zone were referred to as T1a lesions; those invading the second as T1b lesions; and those reaching the deepest zone were classified as T1c lesions. The authors demonstrated differences in survival after five years depending on substaging.

Since this publication there have been multiple revisions, all showing a close relationship between deep invasion (i.e., into the MM and beyond, T1b/c) and progression. Compared with the 20% progression rate for all T1 Grade 3 tumors without substaging (WHO classification of 1973) [16], most of the publications report differences between T1a (of which about 10% progress) and T1b and T1c (of which 29–53% progress) [17–19]. It is clear that we can differentiate between low-risk (T1a) and high-risk (T1b and T1c) HGT1 cancers. This, in turn, justifies modification in the management of these patients, with the adoption of differentiated treatment and follow-up protocols.

The criticisms to substaging include difficulty in identifying the MM and inter-pathologist variation and disagreement. These difficulties are thought to be due to uneven distribution, misorientation, or thermal injury of resection fragments (possibly exaggerated by using high-current bipolar resectoscopes) [20]. Therefore, the accuracy of T1 substaging could be improved through more careful endoscopic resection, the practice and
experience of the pathologist, by immunohistochemistry, and through the use of validated molecular markers [18].

**Follow-up**

The diagnosis of recurrence is based on routine cystoscopic and cytologic surveillance during follow-up. In patients treated conservatively, it is mandatory to undergo strict, frequent, and costly follow-up [21].

The current standard of care for follow-up of treated HGT1 cancers consists of cystoscopy and cytology every three months for a period of two years, every six months thereafter until five years, and then yearly. If, during follow-up, a positive cytology occurs without visible tumor in the bladder, random biopsies or biopsies directed by protoporphyrin derivatives instilled into the bladder and fluorescent cystoscopy, and investigation of extravesical locations (upper track evaluation, prostatic urethral biopsy) are recommended [7].

The first cystoscopy after TURBT at three months is a very important prognostic indicator for recurrence and progression [22–24]. The prompt detection of MIBC and high-grade NMIBC recurrence is crucial because a delay in diagnosis and therapy can be life-threatening [25].

The risk of upper urinary tract recurrence increases in patients with multiple HGT1 tumors [2]. Thus, regular upper tract imaging (CT-IVU, IVU, or retrograde urography) is recommended [25].

Several clinical risk factors such as: size, multifocality, location, associated carcinoma in situ, prostatic urethra involvement, and female gender have been reported to predict recurrence and progression [26, 27]. While these factors have a predictive value on a population-wide basis, no parameter can reliably predict how an individual patient’s tumor will behave. In recent years, many markers have been described in order to improve patients’ comfort, decrease the number of cystoscopies performed, and aid clinicians in the primary diagnosis and follow-up of NMIBC. To date, no non-invasive biomarker has proven to be sensitive and specific enough to replace cystoscopy, either for diagnosis or follow-up. On the other hand, promising results have been reported for potential biomarkers to predict recurrence, early progression, and poor response to bacillus Calmette-Guérin (BCG) therapy. Potentially, these markers could identify those patients with HGT1 cancers who would benefit from immediate radical cystectomy so that critical time is not wasted with futile, conservative management approaches, and which tumors require more intensive follow-up. Recently, different biomarkers, involved in diverse cellular functions, have been evaluated as predictors for recurrence and progression to MIBC in patients with NMIBC. These molecules include: Karyopherin-α2, a nuclear and cytoplasmatic protein which is thought to play an important role in nucleo-cytoplasmatic transport and has also been suggested to be a transporter of tumor suppressors [28]; HMOX 1, one of the three isoforms of HMOX that catalyzes the degradation of heme to biliverdin, carbon monoxide and free iron [29]; GSTM1 and GSTT1, both polymorphisms of the glutathione S-transferase enzyme [30, 31]; C16orf74, a gene involved in inflammatory processes and strongly associated with an anti-TNFα response and with hypoxia [32]; and the better-known HRAS, KRAS, p53, and Her-2 [33–35]. Her-2 protein expression has recently been published as Ezrin protein expression, and the methylation status of TSGs was able to distinguish patients who respond to BCG from those who do not [36–38]. The p53 mutation and p53 protein status was one of the first markers to show promising results for predicting outcomes of patients with NMIBC, but this marker has recently been abandoned in clinical practice, even though many studies continue to show a significant association of p53 status with recurrence, progression, and survival [39, 40].

Although several biomarkers obtained from these and other studies have shown promising results, it is unlikely that any single marker will be able to improve prognostication for patients with HGT1 tumors. As has happened with clinical risk factors, many authors recommend that a combination of multiple molecular markers be used to predict outcome. Although multiple markers have been studied, no combinations have yet been included in guidelines to help clinical decision-making. Thus, clinical risk factors are still the only tools to guide recommendations for conservative management versus radical cystectomy in high-risk NMIBC.

Clearly, efforts to validate these results and to define new markers are needed.

**Treatment**

HGT1 bladder cancer is a heterogeneous disease that offers challenges for the patient and the physician, as treatment paradigms are continually evolving.
As mentioned earlier, TURBT is the initial and critical step in the treatment of HGT1 bladder tumors. A well-performed technique is of crucial importance to reduce the rate of recurrence and progression. TURBT alone has been recognized as inadequate treatment, with 20–50% of patients progressing to stage cT2 or greater disease in less than three years [41].

In order to improve disease-free survival and cancer-specific survival rates as well as to decrease the risk of recurrence and progression, many options have been proposed.

**Re-TUR**

Even though TURBT is a well-standardized procedure, significant risk of residual disease after this procedure has been demonstrated in many series [11]. In HGT1 tumors, persistent disease is frequently observed (33–53%), almost always (81% of cases) at the initial tumor site [42]. A major concern is the high rate of understaging (4–25%) [11] in series utilizing a second TURBT. Due to the high risk of harboring residual disease, guidelines from the European Association of Urology (EAU), The Société Internationale d’Urologie (SIU), and the American Urological Association (AUA) recommend a repeat TURBT to confirm complete tumor resection and to exclude understaging. While it has been demonstrated that re-TUR can increase recurrence-free survival [43], it is not exempt from complications (12.6%), as has been reported recently [44]. Patients must undergo a second anesthesia and operation, sometimes unnecessarily. Additionally, up to one-third of patients with HGT1 cancers treated with BCG never have a recurrence of their disease. Some authors, after analyzing their own TURBT results, recommended that re-TUR should be performed only in selected cases: after recognized incomplete initial TURBT, when there is no muscle in the specimen after initial resection (cT1x), and especially in T1b,c tumors. Most authors agree that re-TUR should be performed between two and six weeks after initial TURBT and that it ought to be done by a surgeon experienced in performing TURBTs.

**Intravesical therapy**

**Instillations of BCG**

The addition of intravesical BCG immunotherapy following TURBT has been shown in randomized trials to reduce cancer recurrence by 40% and significantly improve both progression-free and disease-free survival rates compared with TURBT alone. This combination now constitutes the standard, first-line therapy. Although adjuvant, intravesical BCG therapy after TURBT for HGT1 cancer is effective, Shahin postulated that BCG may only delay the time to recurrence and cystectomy, concluding that BCG does not affect cancer-specific survival in the long term [45]. However, this study did not include maintenance therapy. All additional supporting evidence highlights the importance of maintenance BCG in intermediate- and high-risk disease. An EORTC meta-analysis of 24 trials (N = 4863) showed BCG maintenance to be associated with a 37% reduction in the risk of tumor progression [21]. Moreover, two meta-analyses comparing BCG with mitomycin-C showed that BCG maintenance is superior to mitomycin-C for the prevention of progression and recurrence [46, 47]. BCG instillations are classically administered according to the empiric six-weekly induction schedule of Morales [48]. There is no consensus on the optimal BCG maintenance schedule. The EAU recommends at least one year [7].

Two publications which may have practical as well as theoretical implications have recently appeared. In one, subcutaneous immune priming with BCG was shown to speed up the anti-tumor response in mice. This finding was supported in a non-randomized prospective series in 55 patients, where a positive purified protein derivative (PPD) skin test before initiating BCG therapy predicted response (recurrence-free survival at 36 months of 75% for PPD + patients and 44% for PPD neg patients) [49]. Prospective randomized controlled trials of BCG priming are now being initiated in Europe and the United States.

The second report addresses a worldwide BCG production shortage in which producers of the Connaught strain, which had been more commonly used in Europe and North America, could not meet orders for the medication. Many urologists have switched to using Tice strain BCG, although in one prospective randomized trial reported in 2012, patients receiving Connaught BCG (1.5–5.0 x 10^8 colony-forming units (CFU)s in 50 mL saline) had significantly (p < 0.002) fewer recurrences (five year RFS = 75%) vs. 46% for those randomized to Onco Tice (5 x 10^8 CFU/50 mL/saline) [50].

**Other intravesical agents**

Although BCG is the most effective treatment, roughly 50% of patients with HGT1 cancers will experience a recurrence within five years [51]. The EORTC has
recognized accompanying CIS as the most significant factor associated with risk of recurrence and progression at five years after BCG therapy. With each BCG failure, the risk of progression rises; failing two or more courses of BCG increases the risk of developing MIBC from 7% to 30% [52]. If patients do not respond to BCG or later recur, the most reliable treatment option is cystectomy. For those who are unwilling or unable to undergo this significant procedure, there is a multitude of alternative intravesical therapies. Of all of them, valrubicin [53], gemcitabine [54, 55], and taxanes [56] are the agents that have shown better results and tolerability. Actually, valrubicin is the only intravesical agent currently approved by the Food and Drug Administration (FDA) for the treatment of BCG-refractory NMIBC; however, with the existing evidence, it is difficult to recommend one agent over another, or over cystectomy, because none has proved itself reliably effective. Further work needs to be done to determine the risk profile of each BCG-failure patient, and to establish durable and successful treatments for this high-risk group.

**Methods to improve drug delivery**
Electromotive drug administration (EMDA) involves enhancing membrane permeability and drug transport by way of an electrical current [57]. MMC is non-ionic at most urinary pHs, and thus requires a salt-containing solution to aid with transport across urothelial membranes [58]. EMDA-MMC has also been evaluated in conjunction with BCG in a randomized trial of 212 patients, and was shown to be more effective in reducing recurrence, progression, and all-cause and cancer-specific mortality than BCG alone [59]. Also, it has been shown to be safe and effective immediately before TURBT in a BCG-naïve population [60].

Additionally, local hyperthermia via a microwave antenna Foley catheter with MMC instillations (“chemothermotherapy”) has shown success in ablating existing tumors as well as being more efficacious in randomized studies than standard MMC instillations following endoscopically complete TURBT for intermediate- and high-risk NMIBC (two-year recurrence rate = 17% for chemothermotherapy vs. 57% for standard MMC) [61, 62]. Others have found it effective following TURBT for HG Ta, T1 bladder cancer, reporting a 62.5% recurrence-free rate at nearly three years mean follow-up [63]. Finally, while these techniques require special equipment and are not readily available to many patients, the efficacy of MMC instillations can be “optimized” by encouraging overnight fasting before instillations, increasing the concentration to 40 mg in 20 mL diluent compared to the standard 40 mg in 40 mL, and using oral Na HCO₃ to raise the urinary pH to prevent MMC degradation. Au and colleagues [57] demonstrated a doubling in the tumor-free rate for patients with intermediate- and high-risk NMI urothelial cancer compared with standard MMC in a randomized prospective trial, and there’s little reason to think this would not also improve MMC’s efficacy in BCG failures.

**Radical cystectomy**
Unfortunately, a significant proportion of patients with HGT1 cancers (~20% of all HGT1 cancers) will not respond and will progress to MIBC despite appropriate therapy [40]. Several studies have reported radical cystectomy is only curative in 50% of patients who progress from NMIBC to MIBC, compared to 90% when this is performed in patients with HGNMI tumors [64]. On the other hand, 50% of this latter group will receive overtreatment [65]. Moreover, no matter how skilled the surgeon and whether this treatment is performed by minimally invasive means (usually robotic) or open surgery, this operation is associated with a 15–20% serious complication rate and a 20–30% re-admission rate at 90 days [66, 67]. Moreover, while single-institution series report 1–3% mortality rates [66, 67], this increases to 7–10% using population-wide databases, particularly in patients aged 75 and older [68, 69]. So when we should perform RC in patients with HGT1 cancers remains controversial. The risk of overtreatment must be balanced against the potential benefit of aggressive therapy. Risk stratification of patients with bladder cancer based on pathologic features at initial TURBT or at the time of recurrence can select those most appropriate for early RC. However, risk stratification is insufficiently specific to define which patients should be treated immediately with RC. It is therefore critical to identify molecular markers that can help clinicians to achieve individualized, risk-stratified decision-making.

A distinction should be drawn between radical cystectomy immediately after HGT1 cancer is first diagnosed at TURBT and early radical cystectomy (ERC), when radical surgery is performed after BCG failure. The major reasons to consider RC for selected patients
with HGT1 tumors are the high rate of understaging as well as the risk of progression to MIBC. In the case of immediate radical cystectomy (IRC), it is recommended that all aspects be discussed with the patient, including the benefits and risks of both IRC and conservative management with BCG treatment. The information provided must include the good results of BCG induction and maintenance therapy, the possibility of undergoing re-TUR in order to decrease the risk of understaging and residual disease, the necessity of strict follow-up when conservative management is applied, the morbidities associated with BCG therapy and with RC, and the possibility of constructing an orthotopic neobladder. Thereafter, it is reasonable to propose IRC to those patients with HGT1 cancers who are at very high risk of progression or who are not candidates for or cannot tolerate BCG. The former are patients with multiple and large HGT1 tumors, concurrent CIS, CIS in the prostatic urethra, females, associated micropapillary or nested variant tumor in the TUR specimen, or those who, for technical reasons, cannot undergo complete endoscopic resection of visible tumors.

It has been reported that poor outcomes for the micropapillary variant are related to the percentage of the micropapillary component in the TUR specimen. We have found that management with BCG can achieve a good outcome in cases in which the percentage of micropapillary component associated with HGT1 urothelial cancer is less than 50% [70, 71]. However, others have reported less optimistic results with this treatment [71].

Other candidates for IRC include young persons, owing to the life-long risk of progression after BCG in the case of high-risk tumors. Kurkani and co-workers modeled that for patients under the age of 60, IRC was more effective, particularly in preserving quality-adjusted life years (QALY) compared with initial BCG treatment (9.46 vs. 9.36 QALY) and saved lifetime bladder cancer costs ($37,600 for IRC vs. $42,400 for initial BCG); however, by age ≥ 70, both of these factors reversed (with BCG being more effective and costing less) [72].

On the other hand, in patients with BCG-refractory tumors, ERC is strongly recommended. Currently, there is no standardized definition of BCG failure, but the general opinion is that RC should be performed before progression occurs [73]. With each BCG failure, the risk of progression rises; failing two or more courses of BCG increases the risk of developing MIBC from 7% to 30%. The same happens with early recurrence (persistence) at the first cystoscopy after induction BCG (roughly three months after the index TURBT or re-TUR), increasing the risk of MIBC up to 40% [23, 52]. Several studies have shown a particularly poor prognosis despite radical treatment in the group of non-responders who develop MIBC. This worse outcome in patients treated with delayed RC occurs because some patients experience subclinical progression to non-organ-confined disease ($p > T2$ and/or $N+$) at the final pathologic stage after RC [74], and modeling supports ERC in almost all patients, at most ages, who fail BCG [75].

### Useful web links


### References


CHAPTER 9
What to do when bacillus Calmette-Guérin fails

Massimiliano Spaliviero¹, Guido Dalbagni¹, and Matthew Nielsen²
¹ Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
² Department of Urology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

KEY POINTS

- BCG-refractory UC is defined as persistent carcinoma in situ (CIS) after two consecutive BCG courses; or within less than six months of complete response to BCG; or during maintenance therapy. Relapse with T1 disease is also considered BCG-refractory UC.
- BCG-refractory disease portends a poor prognosis, and the disease-free interval is an important prognostic factor.
- Radical cystectomy is the gold standard for the management of BCG-refractory UC.
- Valrubicin is FDA-approved for the management of BCG-refractory CIS in patients refusing cystectomy.
- Intravesical gemcitabine is an efficacious and well-tolerated agent for intravesical management of UC, including BCG-refractory patients. Local and systemic toxicity is minimal.
- Taxanes have shown promising preliminary results in phase I studies in BCG-refractory patients. Phase II studies are currently ongoing.
- The combination of BCG plus interferon α is a reasonable option for patients with BCG failure.
- Photodynamic therapy and other alternative therapies warrant further investigation prior to inclusion in the clinical armamentarium.

Introduction

Intravesical bacillus Calmette-Guérin (BCG) is a highly effective therapy for the management of high-risk, non-muscle-invasive bladder cancer (NMIBC), with complete response (CR) rates that can be as high as 83% [1]; however, recurrence may occur within one year in up to 50% of patients with high-risk disease, and within five years in as many as 90% of these patients [2]. BCG failure is also associated with an approximately 50% chance of disease progression and poor prognosis [3–5]. When intravesical BCG therapy fails, radical cystectomy is the standard treatment. Despite good overall health-related quality of life post-operatively [6], patients are sometimes reluctant to undergo major surgery for a condition that does not pose an immediate threat to their lives. Furthermore, radical cystectomy is not suitable for a subset of patients with severe comorbidities. After discussing the definition of BCG failure, we will review several currently available treatment alternatives.
Definition of BCG failure

In evaluating salvage therapies for use after BCG failure, comparisons between therapies have been hampered by the lack of standard definitions for BCG failure and BCG-refractory bladder UC, which accounts for the wide disparity (21% to 67%) in reported favorable response rates to salvage immunological and chemotherapeutic regimens used for BCG-refractory UC [7]. Some series have defined BCG failure after a single induction course of BCG [8,9], others after two courses [10]. The latter is preferable, since it is known that patients do respond to a second cycle of BCG. Haaff et al. reported the overall response in 61 patients treated with one or two six-week courses of intravesical BCG [11]. The 25 patients in whom the initial induction cycle failed were treated with a second six-week course. Overall, 79% of patients responded when both treatment courses were considered. Individual cumulative response rates were assessed after dividing the patients into three groups depending on the indication for intravesical BCG therapy, which was given as additional treatment for CIS or residual papillary UC, or as prophylaxis. After a mean follow-up of 13.5 months, the cumulative response rate of 19 patients with CIS was 68%, including 8 patients (42%) who responded to the initial induction course and 5 of 9 patients (56%) who became free of tumor after the second course. The 13 patients with residual papillary UC had a cumulative response rate of 69%, including 6 of 13 (46%) who were rendered disease-free after the initial course of BCG, and 3 of the remaining 7 (43%) who responded to the second treatment. Nine of the 29 patients treated for prophylaxis after complete resection had a recurrence after a mean follow-up of 11.8 months. An additional induction course rendered 67% (6 of 9) of these patients tumor free. The cumulative response rate in the prophylaxis group at a mean follow-up of 12.8 months was 90% (26 of 29). Okamura et al. reported the effect of repeated courses of BCG (Tokyo strain) as a prophylactic agent in patients with Ta/T1 cancer. Seventeen of 75 patients (23%) developed recurrences after a single course, and 12 received additional courses after a transurethral resection of bladder tumor (TURBT). The overall success rate was 90.7% [12]. Bui and Schellhammer reported the clinical outcome of 11 patients who received a second course after initial CR [13]. All patients were followed for a minimum of five years, and the median interval to tumor recurrence after the initial treatment was 17 months (range 9–74 months). Nine of the 11 patients achieved a second CR after receiving a second induction course; 5 of them were free of disease at a median follow-up of 87 months (range 64–110 months). Overall, 42% to 82% of patients who did not respond to an induction course responded to a second cycle [5,13–15]. These data suggest that a second course of BCG is warranted. These results also argue against defining BCG as failure to respond to a single induction course.

CIS after two cycles of BCG portends a poor prognosis. Patients whose disease recurs after a second cycle are less likely to respond to additional BCG [13]. These patients are also at increased risk of progression. Catalona and colleagues found that, among patients in whom two or more courses of BCG failed, the risk of developing muscle-invasive tumors or metastatic disease was 30% and 50% respectively [5]. In their study, only 20% responded to additional BCG therapy. A 7% actuarial risk of progression was associated with each additional course of BCG after BCG failure. Sarosdy et al. reported a 28% progression and metastasis rate among patients in whom BCG and bropirimine failed and who subsequently underwent non-surgical treatment [10].

Patients with persistent UC after two cycles of BCG fare worse than patients with recurrence after an initial response. At a median follow-up of 32 months, Harland et al. reported a disease progression rate of 10% in patients who responded to one or two courses of BCG vs. 48% in those who failed to respond [16]. The long-term outcomes of patients with CIS, treated as part of a randomized study comparing mitomycin-C against two strains of BCG, have been reported by the Dutch South East Cooperative Group [17]. Disease progression occurred in 18% of the 65% of patients who achieved a CR, and in 67% of the non-responders. The cumulative response rate for the initial and repeated six-week course was 56%. Ovesen et al. reported a progression rate of 26% vs. 77% in complete responders versus non-responders, respectively, at a median follow-up of 46 months [18].

The disease-free interval is an important prognostic variable. Bretton et al. reported clinical outcomes of 28 patients who received a second course of BCG [19]. Progression occurred in 13 patients (46%). Of the 15 patients (54%) without progression, 10 (36%) had CR and 5 (33%) had new tumors, and they were rendered
free of disease after transurethral resection. The median duration of response to course 1 of BCG was 15 months for the patients with disease progression after course 2 and 27 months for those with no progression \((p = 0.05)\). Ten \((77\%)\) of the 13 patients with progression responded to course 1 for less than 21.6 months compared to only 4 \((27\%)\) of 15 without progression. The conclusion of this study was that a second course of BCG was useful in patients who had a prolonged response to the initial treatment. Merz et al. reported a high progression rate after a second course of BCG among patients whose initial response to induction BCG was followed by a recurrence within nine months, compared to no recurrences after the second course among patients who developed recurrences after more than twelve months [20]. Gallagher and co-workers evaluated the impact of previous BCG failure patterns in patients with NMIBC on the subsequent response to intravesical BCG + Interferon-Alpha (IFN-\(\alpha\)) [21]. At a median follow-up of 24 months, the cancer-free rates of BCG-naive and BCG-failure patients were 59% and 45%, respectively \((p < 0.0001)\). When stratified by patterns of BCG failure, patients with immediate recurrence (BCG-refractory disease), within 6, 6 to 12, 12 to 24, or longer than 24 months had a cancer-free rate of 34%, 41%, 43%, 53%, and 66%, respectively \((p = 0.005\) for trend). Patients with failure after remission of 12 months’ duration and BCG-naive patients had similar responses. No statistically significant difference was found in the cancer-free rates between patients with failure after 12 months and those with failure after 24 months or between BCG-naive patients and those with failure after 12 and 24 months. The number of previous BCG courses did not significantly affect the retreatment response to BCG plus IFN-\(\alpha\) on a multivariate analysis of patients with failure after 12 months.

These data suggest that patients with an initial CR and a late relapse are the ones most likely to benefit from additional courses of BCG. In contrast, patients who have undergone two BCG cycles and recurred within 12 months should be treated with cystectomy or alternate intravesical therapy.

**Patients relapsing with T1 disease after BCG therapy are at high risk of progression.** Herr reported a progression rate of 82% among 17 patients who had clinical stage T1 bladder UC at the three-month evaluation after induction BCG therapy. The median time to progression was 8.5 months [22,23]. The aggressive nature of T1 bladder UC at the three-month evaluation has been confirmed by others [24,25].

It seems reasonable, based on the current literature, to define **BCG-refractory UC** or **BCG failure** as any situation associated with a high progression rate. This includes:

1. **Persistent CIS** after two consecutive BCG courses (non-responders);
2. **Recurrent CIS** within less than six months of achieving a complete response after one or two courses of BCG;
3. **Recurrent CIS** while on maintenance therapy;
4. **Relapse with T1 disease**.

In addition to BCG-refractory UC, BCG failure includes [26,27]:

1. **BCG-resistant UC** – persistence or recurrence of UC three months after an induction cycle;
2. **BCG-relapsing UC** – recurrence of UC after achieving disease-free status by six months;
3. **BCG-intolerant UC** – recurrence of UC after the administration of a less than adequate course of BCG due to either the occurrence of a serious adverse event or symptomatic intolerance requiring the discontinuation of BCG therapy.

Shirakawa et al. assessed the prognostic significance of BCG failure classification in a retrospective study on 173 patients with NMIBC UC who underwent BCG induction therapy between 1987 and 2009 [28]. Forty-two patients were BCG-refractory, 3 were BCG-resistant, 106 were BCG-relapsing, and 22 were found to be BCG-intolerant. The median follow-up period from initial BCG failure was 4.7 years. Stage progression during follow-up occurred in 24 patients. Pathological Grade 3 at BCG failure \((p = 0.014\); risk ratio 2.84) and the BCG-refractory state \((p < 0.001\); risk ratio 4.68) were significant independent factors for prediction of stage progression on multivariate analysis. The ten-year PFS rates were 53.2%, 91.1%, and 93.8% in the BCG-refractory, BCG-relapsing, and BCG-intolerant groups, respectively. The stage progression rate was higher in the BCG-refractory than in the BCG-relapsing \((p < 0.001)\) and BCG-intolerant \((p = 0.007)\) groups. Similarly, the ten-year CSS rate in the BCG-refractory group was significantly worse than that observed in the other BCG failure groups \((p < 0.001)\). Patients in the BCG-refractory group had worse outcomes compared to the other BCG failure groups.

Studies on BCG for NMIBC used inconsistent methods for reporting their results. Most studies have included...
all patients who received one or more courses of BCG [29–32]. Investigators have often combined patients with persistent disease (non-responders) and patients with recurrent CIS after an initial response [8,10]. A few studies have combined patients who were non-responders to BCG and patients who could not complete BCG therapy because of toxicity (BCG intolerant) [10,29]. Furthermore, most studies have combined all patients with papillary tumors with and without CIS. Finally, most studies have not indicated the disease-free interval after the last BCG course. These inconsistencies have led to comparisons of outcome in a very heterogeneous population.

**Treatment of BCG-refractory CIS**

Patients whose bladder cancer progresses after failure of intravesical therapy have been shown to fare worse than patients presenting with de novo muscle-invasive tumor. Van der Heijden et al. reported a 37% three-year cancer-specific survival (CSS) rate for the progressive group vs. 65% in the de novo group [33]. Radical cystectomy is the gold standard in patients with BCG-refractory UC. However, patients, sometimes reluctant to undergo major surgery, are willing to explore alternatives. Furthermore, a subset of patients with severe comorbidities may not be fit for cystectomy. Several alternative approaches have been proposed.

**Intravesical valrubicin**

Valrubicin is an analog of adriamycin (N-trifluoroacetyl-ladriamycin-14-valerate [AD32]), an anthracycline antibiotic with a mechanism of action different from the parent compound. Valrubicin inhibits nucleoside incorporation into DNA and RNA, leading to chromosomal damage [34]. In a phase I study of 32 patients with NMIBC, 13 patients achieved a CR with valrubicin treatment [35]. The drug produced only minor systemic side effects and the serum levels of unmetabolized valrubicin and its two primary metabolites were very low. However, 29 patients (91%) had mild to severe irritable symptoms, which persisted for several days after each instillation.

The efficacy of valrubicin was demonstrated in a phase II study of 90 patients with CIS after the failure of multiple courses of intravesical therapy, including at least one course of BCG [32]. Patients received 800 mg of valrubicin weekly for six weeks. Nineteen patients (21%) had a CR, defined as no evidence of recurrence for at least six months from the initiation of therapy, and 7 of these 19 had a durable response, with a median follow-up of 30 months. Forty-four patients underwent a radical cystectomy (6 of whom had stage pT3 disease at cystectomy), and 4 patients died of bladder cancer during the 30-month follow-up. Most patients (90%) experienced mild to moderate local bladder symptoms during treatment, including urinary frequency in 66%, urinary urgency in 63%, and dysuria in 60%. In 1997, valrubicin was approved by the Food and Drug Administration (FDA) for the treatment of BCG-refractory CIS in patients who refuse cystectomy.

**Intravesical gemcitabine**

Gemcitabine (2’-deoxy-2’,2’-difluorocytidine monohydrochloride [β-isomer]; Gemzar, Eli Lilly and Co., Indianapolis, IN) is a deoxycytidine analog with a broad spectrum of anti-tumor activity. It was first approved in the United States for the treatment of pancreatic cancer [36,37] but has since been found to be effective in many other tumor types, including non-small-cell lung cancer, bladder cancer, soft-tissue sarcoma, metastatic breast cancer, and ovarian cancer. Gemcitabine has a molecular weight of 299.66, and, after intracellular activation, its active metabolite is incorporated into DNA, resulting in inhibition of further DNA synthesis. Gemcitabine may also inhibit ribonucleotide reductase and cytidine deaminase as part of its cytotoxic activity [24]. Gemcitabine is highly effective (overall response rates ranging from 22.5% to 28%) and well tolerated as both first- and second-line, single-agent therapy for the treatment of metastatic UC [38–40].

Dalbagni et al. reported a phase I study of intravesical gemcitabine twice a week for three weeks, followed by a second cycle after a week of rest, in a heavily pre-treated population with BCG-refractory NMIBC [29]. This study demonstrated that intravesical gemcitabine was well tolerated with minimal bladder irritation and acceptable myelosuppression. Serum levels of gemcitabine were undetectable at concentrations of 5 mg/mL, 10 mg/mL, and 15 mg/mL. However, serum gemcitabine was detected at a concentration of 20 mg/mL. CR, as defined by a negative post-treatment cystoscopy, including a biopsy of the urothelium and a negative cytology, was achieved in 7 of 18 patients (39%). This was followed by a phase II study of patients with BCG-refractory UC to
determine the efficacy of gemcitabine as an intravesical agent. Twenty-eight patients completed therapy, and 16 achieved a CR [41]. Sternberg et al. reported their experience with intravesical gemcitabine for NMIBC for BCG-refractory disease in 37 patients, BCG-recurrent disease in 20, BCG-resistant disease in 5, and BCG-intolerant disease in 5 [42]. Median follow-up was 3.3 years in progression-free patients and 3.6 years in disease-free patients. Irrespective of the type of BCG failure, approximately 80% of patients remained free of progression for five years and had a five-year CSS of 85%. Progression-free survival (PFS), CSS, and recurrence-free survival (RFS) were similar in patients with refractory disease and those with other types of BCG failure (\(p = 0.9, 0.7, \) and 0.2, respectively). Patients with refractory disease had lower (58% vs. 71%) five-year OS compared to patients with another type of BCG failure but this was not statistically significant (log rank test \( p = 0.096 \)). After gemcitabine treatment, CR was observed in 27 patients, partial response in 19, and no response in 20. PFS, CSS, and OS did not differ significantly between patients with and without a CR (\(p = 0.3, 0.3, \) and 0.8, respectively). Cystectomy was subsequently performed in 18 patients with recurrence after gemcitabine and 2 patients who experienced adverse events leading to premature discontinuation of gemcitabine. Those with a CR had a longer time to cystectomy (20.9 vs. 5.3 months) and no muscle-invasive bladder cancer at cystectomy. Twenty-eight patients in whom a cystectomy could not be performed received additional intravesical gemcitabine (5), BCG with or without interferon (13), or intravesical mitomycin (3). Some patients received more than one agent, and for 9 patients no further treatment was documented in their medical record. The most common treatment-related adverse events were fatigue and urinary symptoms in 24 and 25 patients, respectively. This study supported the use of gemcitabine for BCG failure in patients who refuse radical cystectomy or who are unfit for major surgery.

Laufer et al. reported a phase I study of weekly intravesical gemcitabine in 15 patients who had received intravesical therapy previously [43]. Serum gemcitabine levels were undetectable at concentrations of 5 mg/mL, 10 mg/mL, 15 mg/mL, and 20 mg/mL, while low concentrations were present in all patients receiving 40 mg/mL. However, the metabolite dFdU (2’-difluorodeoxyuridine) was detectable in plasma of patients receiving gemcitabine at concentrations of 15 mg/mL or higher, implying minimal absorption of gemcitabine at lower doses. The authors concluded that intravesical gemcitabine is well tolerated, with minimal toxicity. Furthermore, no evidence of recurrence at 12 weeks was noted in 9 of 13 evaluable patients.

A multi-institutional phase II study within the SWOG (Southwest Oncology Group) cooperative group evaluated the potential role of gemcitabine induction plus maintenance therapy in patients with NMIBC (high-risk in 89% of patients) and recurrence after two prior courses of BCG [44]. At the initial three-month evaluation, 47% of 47 evaluable patients were free of disease, confirming gemcitabine activity in high-risk NMIBC. However, at one year, 28% of the 47 patients were free of recurrence (all except 2 from the high-risk group), and at two years the recurrence-free rate was 21%.

Addeo et al. performed a randomized phase III trial to compare the efficacy and toxicity of gemcitabine with mitomycin administered intravesically in patients with a recurrent NMIBC after BCG failure [45]. BCG-intolerant patients were included in the study. Patients were treated with a six-week course of gemcitabine or a four-week course of mitomycin. At a median follow-up of 36 months for each arm, 72% of patients in the gemcitabine arm and 61% in the mitomycin arm remained recurrence-free. The total incidence of adverse events was greater in the mitomycin arm (38.8% vs. 72.2%; \(p = 0.021\)). Gemcitabine had a better efficacy and lower toxicity than mitomycin, however, the type of BCG failure could not be assessed since data on number of prior induction or maintenance BCG cycles were not provided.

All reports published thus far confirm the low systemic absorption of gemcitabine, the good tolerability with minimal local and systemic toxicity, and, more importantly, the efficacy of gemcitabine as an intravesical agent, even in heavily pre-treated patients [46,47]. This agent warrants continued investigation in a larger cohort of patients.

**Taxanes**

Docetaxel is a semi-synthetic analog of paclitaxel and a clinically well-established anti-mitotic agent. It binds reversibly to microtubules, thus stabilizing the microtubules by inhibiting depolymerization from calcium ions and ultimately disrupting the normal microtubular dynamics. Rangel et al. showed the in vitro activity and urine stability of taxol and taxotere in bladder cancer [48]. Both paclitaxel and docetaxel were shown to maximally inhibit the clonal growth of human bladder cell lines within one hour of drug incubation. The most
active agent in the panel of tumor lines was docetaxel. Paclitaxel and docetaxel were found to be stable in human urine for four hours over a pH range of 5 to 7. At least 85% of both drugs were present during this period of drug incubation.

Intravesical docetaxel is a promising agent with significant efficacy and durability for BCG-refractory bladder cancer, as shown by Barlow et al., who reported their cumulative experience with intravesical docetaxel in 54 patients with recurrent NMIBC after BCG failure who received salvage intravesical docetaxel between 2003 and 2012 [49]. The study included 18 patients treated during the original phase I trial [50]. During induction therapy, each patient who experienced recurrence or progression after at least one (average two to three) complete six-week course of BCG with (26 patients) or without (28 patients) IFN-α, received six weekly instillations of intravesical docetaxel. After the phase I trial, patients with a CR to induction treatment were offered single-dose monthly maintenance treatments for a total of up to 12 months of docetaxel therapy. Recurrence was defined as positive biopsy or urine cytology. Median follow-up was 39.1 months. After induction therapy, the CR rate was 59% (32 of 54 patients), including 18 patients who received additional monthly maintenance treatments. The median time to recurrence in initial responders treated with versus without docetaxel maintenance was 39.3 vs. 19.0 months. One and three-year recurrence-free survival rates for the entire cohort were 40% and 25%, respectively. Five-year OS and CSS rates were 71% and 85%, respectively. The RFS was similar in patients treated with induction course only and patients who received induction and maintenance therapy, although a trend towards increased RFS was observed after 12 months of follow-up in patients who received maintenance treatments. The authors suggested that the duration of RFS might be lengthened by the addition of maintenance treatments.

Paclitaxel, another taxane with a similar mechanism of action to docetaxel, has been studied for the treatment of bladder UC after pre-clinical studies showed a favorable partitioning of paclitaxel across the urothelium [51]. Bassi et al. reported the results of a phase I, open-label, single-institution study of paclitaxel–hyaluronic acid (ONCOFID-P-B) for intravesical therapy of BCG-refractory CIS of the bladder [52]. Paclitaxel was conjugated with hyaluronic acid to make the active ingredient water soluble. The solution was administered for six consecutive weeks in 16 patients. Each dose level (150 mg, 300 mg, 450 mg, 600 mg, and 750 mg – maximum deliverable dose) was given to a minimum of three eligible patients. All five dose levels were completed and no dose-limiting toxicities occurred. Adverse events included cystitis in 2 patients, and overactive bladder, fever, hypotension, atrioventricular block, sinus bradycardia, and anomaly of T wave on electrocardiogram in 1 patient each. The authors judged four of these adverse events to be unrelated and four unlikely to be related to treatment. Serious events included worsening atrial fibrillation and cardiocirculatory failure in 1 patient treated with a dose of 150 mg, who recovered completely and was withdrawn from the study (relationship with the study drug deemed not evaluable), and delayed gross hematuria (deemed not related to the study drug) after bladder biopsies performed 40 days after completion of the last treatment in 1 patient who received a dose of 300 mg. The authors recommended a six-week course using a weekly dose of 600 mg. Although 9 patients (60%) were disease-free at a mean follow-up of 12.2 months, further investigations in controlled clinical trials are needed to validate these promising preliminary results.

McKernan and colleagues conducted a phase I trial of intravesical nanoparticle albumin-bound paclitaxel (Abraxane, ABI-007) for the treatment of BCG-refractory NMIBC [53]. A total of 18 patients who either declined radical cystectomy or were not fit for surgery after the failure of one or more courses of intravesical BCG, Mitomycin C, IFN or any combination thereof were enrolled in the study. Six weekly instillations of Abraxane were administered with a modified Fibonacci dose escalation model used until the maximum deliverable dose of 500 mg was achieved. One patient showed detectable systemic absorption (16 ng/mL) at the 450 mg dose. Grade 1 local toxicities were observed in 10 patients (56%), including dysuria in 5 patients, hematuria in 3, urinary retention in 2, and urinary frequency in 2. At six weeks after the last instillation of Abraxane, the response rate was 28% (5 of 18 patients). Based on these safety data, the authors initiated a phase II study that is currently ongoing.
Intravesical BCG and Interferon-Alpha

Interferons are glycoproteins that mediate host immune responses such as the stimulation of phagocytes, cytokine release, enhanced natural killer cell activity, and activation of T and B lymphocytes. Intravesical α-2B interferon (IFN) has demonstrated activity in patients with NMIBC [54,55]. Among patients with CIS enrolled in a randomized trial, 2 of 9 who had failed earlier intravesical therapy had a CR to IFN-α-2B [9].

Other studies showed that the combination of BCG and IFN-α is a reasonable treatment option for patients with BCG failure. A phase I study of low-dose BCG with different doses of IFN-α-2B demonstrated that this combination is well tolerated [56]. O’Donnell et al. reported the efficacy of intravesical BCG plus IFN-α-2B in a cohort of patients who had received one or more induction courses of BCG [30]. Of 40 patients enrolled, 63% and 53% were disease-free at 12 and 24 months, respectively. The response for patients in whom a single course of BCG failed was similar to the response of those in whom multiple courses failed. There was a trend towards worse outcomes in patients with an early relapse after the induction course of BCG. From the same group, Joudi et al. reported the final results from a national multi-center phase II trial of combination BCG plus IFN-α-2B for reducing recurrence of superficial bladder cancer [57]. An identical dose of 50 million units of IFN-α-2B was given to BCG-naïve patients, although BCG was given at a reduced dose in BCG-failure patients and in the standard dose to BCG-naïve patients. Three series of three-week reduced (maintenance) dose BCG plus IFN-α-2B treatments were given to all relapse-free patients at 3, 9, and 15 months after completing induction. Of 1007 evaluable patients, 59% of the BCG-naïve and 45% of the BCG-failure patients, respectively, remained disease-free at a median follow-up of 24 months. Statistically significant risk factors for recurrence included stage T1, tumor size greater than 5 cm, multiple prior BCG failures, and tumor multifocality. In a subset of 231 patients with CIS alone or associated with Ta and/or T1 disease, factors associated with a poor response to BCG plus IFN-α therapy were prior tumor stage; immediate BCG failure and two or more prior BCG failures; and a BCG failure pattern (i.e., more than one failure and in less than one year) [58].

Punnen et al. reported a durable response to low-dose BCG plus IFN-α in 6 of 12 patients with NMIBC who received one or more courses of BCG [59]. Lam et al. treated 32 patients with NMIBC, including patients whose disease recurred after BCG. After a median follow-up of 22 months, 66% were disease-free [60]. Karakiewicz et al. treated 13 BCG-failure patients with an induction course of BCG plus IFN-α followed by maintenance therapy in 5 patients [61]. At a median follow-up of 12 months, the recurrence rate was 38%. RFS at 24 months was 66%, with maintenance therapy having no impact on RFS.

Photodynamic therapy

Photodynamic therapy (PDT) exerts its therapeutic effect through the accumulation of cytotoxic photosensitizing compounds which are activated when exposed to specific wavelengths of light (typically in the red region of the visible spectrum). The goal of PDT is to produce localized cellular damage (which ultimately leads to selective death of neoplastic cells and tumor regression) while limiting the damage to surrounding healthy tissues. PDT, which is approved for the treatment of cancers of the lung, digestive tract, and genitourinary tract, can be used in combination with radiotherapy and chemotherapy [62]. In urology, PDT has been used to treat bladder, prostate, and penile cancers [63].

Several investigators have reported the efficacy of PDT in managing NMIBC. This approach has also been tested in patients with BCG-refractory tumors. Nseyo et al. assessed the long-term role of PDT in the management of NMIBC in 58 patients with Ta, T1, and refractory CIS who had failed at least one course of standard intravesical therapy or had a contraindication to intravesical chemo- or immunotherapy [64]. Patients received a single PDT treatment with 2.0 or 1.5 mg/kg of Photofrin activated by 10–60 Joules/cm² red laser light (630 nm). At the three-month evaluation, CR rates for residual resistant papillary UC or refractory CIS were 84% and 75%, respectively. Ninety percent of patients treated prophylactically had not had recurrences. At a median follow-up of 50 months, 59% (34/58) of the responders were alive, with a disease-free rate of 91% (31/34).

Lee and co-workers evaluated the efficacy and safety of PDT using Radachlorin in 34 patients with recurrent, high-grade NMIBC refractory, or who were intolerant to BCG or who refused radical cystectomy [65]. Radachlorin (0.5 to 0.6 mg/kg) was injected intravenously two to three hours before photodynamic therapy. After completion of the TURBT, irradiation with a 662-nm laser light was performed using a diffuser placed in the bladder via a 22 French cystoscope for 16 to 30 minutes. Median follow-up was 28 months. The recurrence-free rate was 90.9% at
12 months, 64.4% at 24 months, and 60.1% at 30 months. Tumor size, presence of CIS, number of prior BCG courses, number of TURBTs, and multifocality had no impact on the efficacy of PDT on Kaplan–Meier analysis ($p > 0.05$). No severe adverse events were reported.

PDT after the oral administration of 5-aminolevulinic acid was performed in 24 patients with recurrent BCG-refractory NMIBC. At a median follow-up of 36 months, 3 of 5 patients with CIS and 4 of 19 with papillary TCC were free of disease [66]. A disease-free status was achieved with a repeat treatment in 3 patients. Cystectomy was performed in 3 patients. Tumor progression was observed in 4 patients (17%). Of note, hemodynamic instability occurred immediately after the oral administration of 5-aminolevulinic acid, including hypotension in 19 and tachycardia in 10 patients with prior history of severe cardiovascular disease.

**Other alternative therapies**

Other alternative therapies have been investigated, including oral bropirimine, an immunostimulant which has produced remission in patients with CIS after prior intravesical therapy [10]. CR was detected in 30% of the evaluable patients who were BCG-resistant. Progression to muscle-invasive or metastatic disease was documented in 6% of the patients [10].

A phase I study of the immunotoxin VB4-845 (Oportuzumab Monatox) targeting the epithelial cell adhesion molecule (EpCAM) given to 64 patients with Ta or T1 UC or CIS, either refractory to or intolerant of intravesical BCG showed good tolerance and minimal toxicity, with an overall CR of 39% [67]. Subsequently, a phase II study was conducted by the same group on 46 patients who received one induction cycle of 6 (cohort 1) or 12 (cohort 2) weekly intravesical Oportuzumab Monatox instillations of 30 mg, followed by up to three maintenance cycles every three months [68]. At the three-month evaluation, CR rates were 41% (9 of 22 patients) in cohort 1 and 39% (9 of 23 patients) in cohort 2. The median time to recurrence in patients who achieved a CR was 274 days in cohort 1 and 408 days in cohort 2. Overall, 7 patients (16%) remained disease-free.

![Figure 9.1](image-url) Management of BCG-refractory bladder cancer.
Conclusion

A management strategy for BCG-refractory non-muscle-invasive cancer is suggested in Figure 9.1. Radical cystectomy remains the standard of care for patients with BCG-refractory CIS. Salvage therapy for patients who refuse cystectomy is still under investigation. New, promising strategies and agents warrant further investigation.

Useful web links

2 http://www.uroweb.org/guidelines/online-guidelines/?no_cache=1 – European Association of Urology’s guidelines on the management of non-muscle-invasive UC of the bladder.

References

What to do when bacillus Calmette-Guérin fails


CHAPTER 10
Selection and perioperative management of patients undergoing radical cystectomy and urinary reconstruction

Robert S. Svatek¹ and Alon Z. Weizer²
¹ Department of Urology, University of Texas Health Sciences Center, San Antonio, TX, USA
² Department of Urology, University of Michigan, Ann Arbor, MI, USA

KEY POINTS

- The most common complications following radical cystectomy include infection (wound infection or pyelonephritis) and bowel-related problems (delayed return of function and post-operative paralytic ileus).
- Contraindications to continent urinary diversions include significant renal impairment (creatinine > 2 mg/dL), hepatic dysfunction, inflammatory bowel disease, and inability or unwillingness to empty reservoir.
- Neoadjuvant chemotherapy is associated with a 5–7% absolute improvement in survival.
- Relative contraindication to cisplatin-based chemotherapy is poor renal function (GFR less than 40–50).
- Assessment of cardiovascular risk for patients undergoing radical cystectomy includes attention to cardiac risk factors, functional capacity, and identification of active cardiac conditions warranting evaluation and treatment.
- Prealbumin and retinol-binding protein may provide a better approximation of nutritional status than serum albumin in geriatric patients.
- Pre-operative preparation for cystectomy should include ostomy teaching (when appropriate), nutritional assessment, and discussion with an anesthesiologist regarding the use of anticoagulation, antiplatelet therapy, epidural anesthesia, and fluid/hemodynamic management.
- Care pathways should be informed by existing evidence-based practices and should avoid the use of mechanical bowel preparation and nasogastric decompression; they should also utilize early mobility and diet to reduce the length of stay.
- Frequent communication and early post-discharge visits may reduce the risk of readmission by identifying potential complications earlier, which can be managed in the ambulatory setting.

Introduction

Despite major advances in surgery and cancer care generally, limited progress has been made over the past several decades toward improving oncologic outcomes for patients undergoing radical cystectomy. The suboptimal rate of durable disease control (recurrence rates of 50–60%) among contemporary cystectomy cohorts suggests that there are significant opportunities to improve proper patient selection for radical cystectomy. In the context of relative advances in treatment alternatives to cystectomy, namely combined chemo-radiation, the burden of responsibility for proper selection of patients to undergo radical cystectomy has heretofore never
been higher. Patient selection requires understanding of
the disease stage and natural history that is unique to
each patient as well as a thorough evaluation of the
patient’s functional status, comorbid conditions, and
personal preferences. Making matters more challenging
is the inherent high perioperative complication rate
associated with radical cystectomy, attributable to a
relatively lengthy operation with the potential for large
shifts in fluid volumes, advanced age, and comorbid
conditions of radical cystectomy patients. Following
careful selection of patients for radical cystectomy,
appropriate perioperative management is imperative to
ensure the best possible outcome so as not to delay
recovery or prevent receipt of proper additional therapy
as is often required.

Patient selection

Partial or radical cystectomy is the recommended
treatment of choice for local control for patients with
muscle-invasive or BCG-refractory non-muscle-invasive
bladder cancer. Alternatives include radiation or local
excision with “radical” TURBT. Selection of patients for
these treatment modalities is influenced by the extent
of their bladder cancer and the patient’s health and
treatment preferences. In addition, appropriate patient
selection is important for judicious use of additional
perioperative therapy such as chemotherapy or radiation
in addition to surgery.

Pre-operative evaluation of patients considered candi-
dates for cystectomy includes a complete and thorough
history and physical. Careful attention should be made
to the palpation of the abdomen and bladder – there
should be bimanual examination to determine the extent
of the bladder tumor, the involvement of the prostate
and seminal vesicles, and adjacent organs (rectum,
cervix, uterus, vagina). Close attention should be paid to
the patient’s overall nutritional and functional status.
A thorough exam of peripheral lymph nodes (cervical,
axillary, periumbilical, and inguinal) should be performed.
Preferred radiologic imaging includes a 2-view plain
chest X-ray and a CT urogram to evaluate the abdomen,
pelvis, and upper urinary tract. Laboratory evaluation
includes serum electrolytes, liver function tests, alkaline
phosphatase, and a complete blood count. The presence
of adenocarcinoma of the bladder should warrant
consideration of a primary colon tumor and colonoscopy
is warranted. This should also be considered in patients
undergoing a urinary diversion using colon.

The extent of bladder cancer will influence treatment
selection. Generally, radical cystectomy is not recom-
mended in the presence of metastatic disease due to the
morbidity associated with surgery, the potential delay in
systemic therapy, and the limited therapeutic benefit.
However, in selected cases of oligometastasis or substan-
tial response to systemic chemotherapy, local control
with radical cystectomy can render a durable recurrence-
free survival [1]. In addition, in some cases local surgery
may be warranted for symptomatic palliation in patients
with metastatic disease due to refractory pain, hema-
turia, or ureteral obstruction.

Partial cystectomy can be offered in cases where the
tumor is confined to an amenable location, such as the
bladder dome or a bladder diverticulum, and there is no
evidence of carcinoma in situ.

Functional assessment (or understanding frailty)

Assessing the functional status of the patient can
identify the ancillary tools needed to prepare a patient
for cystectomy. Historically in urology, functional
assessment has been limited to crude measures that rep-


sent the embodiment of a surgeon’s “gut” feeling
about whether a patient is capable of undergoing a cys-
tectomy. A good functional assessment would quantify
the risk of morbidity and mortality from the surgery to
aid the patient and surgeon in the decision to pursue
surgery. It would also help to identify areas in which
targeted interventions could be used to improve
functional status and optimize patients for surgery and
additional treatment.

At their heart, most functional assessments are aimed
at understanding patient frailty. While there are
numerous definitions, a frail patient is often considered
to be vulnerable because of reduced reserve and
decreased ability to withstand stress [2]. This could
result from medical comorbidities but also could be due
to limited social support or financial resources. It is
unlikely that any one individual test can accurately
serve as the ideal functional assessment, but a
combination may ultimately be better than the surgeon’s
intuition at aiding patients in the decision making and
recovering from surgery.

A number of surveys and clinician-based assessments
have been studied. However, the utility of these tools
Selection and management of radical cystectomy patients

Continues to be relatively understudied in the population of bladder cancer patients considered for radical cystectomy. In addition, many of these studies have chosen to focus on a variety of outcomes including 90-day mortality, complications, and overall/cancer-specific/progression-free survival. Most studies have been performed retrospectively, so that measures of comorbidity are estimated or abstracted from the medical record, leading to selection and information bias. However, they do provide insight into opportunities to evaluate a patient prior to surgery.

Age

The most commonly studied functional assessment in the literature is age. Age is an imperfect tool because while it takes into consideration the number of years a person has lived it does not consider how those years have impacted the individual. In addition, most of the studies have focused on survival with little attention focused on readmission, functional impairment, and long-term morbidity. Most studies demonstrate that elderly patients can undergo surgery safely and a previous study based on SEER/Medicare data suggested that there was a relative survival benefit of cystectomy versus other treatment options in patients older than 80 [3].

In addition to the bladder tumor burden, patient-related factors including age, comorbid diseases, and performance status contribute to selection of patients for radical cystectomy. Urothelial cell carcinoma is generally a cancer affecting older patients, with a peak incidence in the seventh decade of life. Thus, at least 50% of new cases of bladder cancer will occur in patients who are 65 years of age or older [4]. Perioperative mortality rates increase with advancing age and elderly patients are generally considered at higher risk of perioperative complications compared to younger patients. Also, age is highly correlated with multiple medical comorbidities. As a result, urologists have tended to utilize age as an important, if not principal, measure of comorbid illness in their consideration of treatment options. However, the true effect of age on perioperative morbidity and mortality is unknown due to the presence of coexisting comorbidities in elderly patients and because aggressive surgery is generally offered less frequently to elderly patients. However, when matched by comorbid conditions, elderly patients have no significant increase in perioperative mortality [5]. Thus, the use of age as a strict criterion to guide treatment decisions is not recommended. Indeed, several series have demonstrated acceptable outcomes for elderly patients including those over 75 years of age [6–8].

Comorbidity assessment tools

One of the most widely used tools for assessing perioperative comorbidity is the Charlson Index Score [9]. The Charlson Index Score was developed using clinical complication data from patients undergoing surgery to develop a proportional hazards regression model. The Score is calculated by assessing the presence and severity of comorbid conditions from among 19 common conditions. The severity of the disease is assessed and each condition is assigned a weight from 1 to 6. The Index Score is the sum of all the weighted scores from each condition. In patients with bladder cancer, no points are assigned for malignancy since this is the primary index disease. For example, a 65-year-old woman with moderate renal disease (GFR < 40) and a history of a myocardial infarction would receive a Charlson Index Score of 3.

Koppie and colleagues evaluated the use of the age-adjusted Charlson Comorbidity Index (ACCI) in a large cohort of patients undergoing cystectomy and found that higher scores were associated with worse overall survival but were not associated with disease-specific or progression-free survival [10]. Stimson et al. evaluated the prognostic significance of ACCI on 90-day readmission and found that it was an independent predictor of readmission along with gender, and suggested that it could be used to determine who may be a candidate for longer initial inpatient admission [11]. Utilizing the Nationwide Inpatient Sample database, Abdollah and colleagues developed a reference table that was associated with 70% accuracy for predicting post-operative mortality. This study found that age and CCI were the foremost determinants of post-operative mortality [12].

Novel means to incorporate comorbidity assessments with pathologic features have been developed. Recently, the SPARC (Survival Prediction After Radical Cystectomy) Score was developed to stratify survival outcomes for patients undergoing radical cystectomy based on traditional pathologic features (e.g. tumor stage, nodal status, lymphovascular invasion) in addition to patient-specific factors (e.g. CCI, performance status, active tobacco use) [13]. The development of SPARC reflects the emerging understanding of the importance of comorbid illness and functional status.
and the observation that methods that rely solely on clinical and pathologic features are consistently inadequate in predicting survival outcomes and guiding treatment decisions for cystectomy patients.

Additional comorbidity and performance indices used to evaluate cystectomy candidates include the American Society of Anesthesiologists (ASA) Score, the Adult Comorbidity Evaluation-27 (ACE-27), and the Eastern Cooperative Oncology Group (ECOG) Performance Status. The ASA Score is a physical status classification system [14, 15]. The ASA provides a crude assessment of patients’ physical conditions: ASA 1 – “healthy”, 2 – “mild systemic disease”, 3 – “severe systemic disease”, 4 – “Severe systemic disease that is a constant threat to life”, 5 – “a moribund person who is not expected to survive without the operation”, and 6 – “a declared brain-dead person whose organs are being removed for donor purposes”. The vast majority of patients will be classified with ASA categories of 2 or 3. The advantage of the ASA Score is its ease of calculation and its familiarity. The ACE-27 is a 27-item instrument that classifies comorbid conditions into three grades according to their severity. It has been validated in oncology patients, including patients with bladder cancer [16]. ACE-27 and CCI scores are associated with 90-day readmission rates and mortality following radical cystectomy [10, 11, 17–19]. The ECOG Performance Status is commonly employed in clinical trials to delineate eligibility criteria [20]. In one of the earliest papers to examine the impact of performance status on overall survival in elderly patients treated for invasive bladder cancer, Weizer et al. demonstrated that a Karnofsky Performance Score (KPS) of 80 or less was associated with worse overall survival [21]. Results of this study were substantiated by the group at UCLA who demonstrated that a similar KPS cutoff was independently associated with overall, cancer-specific, and progression-free survival in patients undergoing cystectomy for bladder cancer [22].

In a cohort of over 500 radical cystectomy patients, the prognostic significance of several comorbidity indices, including ASA, ACE-27, CCI, and the ECOG Performance Status was compared [23]. All indices were significantly associated with cancer-independent mortality and ASA significantly increased the predictive accuracy of a model that predicted cancer-independent mortality using routine clinical and pathologic parameters. In separate analysis, Mayr and colleagues [24] demonstrated that all four of these comorbidity indices can provide a useful estimate of perioperative mortality after considering standard clinical and pathologic features.

### Lab and imaging tests

Recently, a prospective study of patient frailty has aimed to study these as well as additional measures in the cystectomy population. In this study, patients aged 65 years or older undergoing cystectomy for curative intent undergo evaluation with self-reported measures, performance-based assessments, and morphometric assessments before and following the surgery at regularly scheduled intervals (Table 10.1). The primary objective of the study is to identify factors associated with impaired survival from radical cystectomy in elderly bladder cancer patients. Impairment-free survival is defined as the time from radical cystectomy to the identification of any of these events: Clavien complication of 3 or higher, loss of independent living status, Eastern Cooperative Oncology Group (ECOG)
Performance Status 3 or higher four weeks beyond surgery, poor global well-being, or death from any cause. This study has completed accrual of the 50 patients and is currently in follow-up to ascertain the primary endpoint at six months post-surgery.

Unique to this study is the evaluation of morphometric measures as predictors of impaired survival in the cystectomy population. Analytic morphomics evaluate other aspects of three-dimensional cross-sectional imaging that are not directly related to the patient’s pathology but may be indicators of the physiologic status of the patient. Examples of morphometric measures include evaluation of lean core muscle size, which may be indicative of sarcopenia or muscle wasting, which is frequent in elderly patients or those with cancer and other chronic diseases. Total psoas muscle area has been measured in a large surgical series where mortality increased by 45% for every 1000 mm² decrease in lean core muscle area. This measure was also correlated with an increased risk of surgical complications [25]. Other morphometric measures that can be obtained from pre-operative computed tomography scans are outlined in Table 10.2 and include body composition, bone health, arterial health, and solid organ health. Many of these factors have been correlated with surgical outcomes for a variety of disease processes.

We evaluated the impact of morphometric measures on outcomes in a cohort of 277 patients undergoing radical cystectomy at our institution. Total psoas area was associated with age and ASA Score. In a multivariate model, total psoas area was independently associated with overall survival ($p = 0.04$) (data not published).

**Physiologic assessment**

While the tools described above are useful for determining the functional status of the patient and provide semi-quantitative data to inform outcomes of patients undergoing radical cystectomy, they remain subject to bias predominantly because many of the studies were performed using retrospective cohorts. More recent efforts to assess the functional status of patients have focused on physiologic or quantitative parameters that are not influenced by physicians’ and patients’ desires to be treated or to avoid surgical intervention. These physiologic tests can be divided into two categories: performance-based measures and lab/imaging tests. While most of these tests are not currently used for medical decision making related to radical cystectomy, there are several studies that currently are evaluating these tools as part of clinical trials. It is likely that these parameters can be incorporated into pre-operative evaluation to aid in treatment decisions as well as helping to identify possible areas for physical improvement prior to surgery.

**Performance-based measures**

Performance-based measures have been used to assess the functional status of patients in a variety of disease settings. There is limited literature on the use of this type of testing in patients undergoing radical cystectomy. Mathur and colleagues evaluated a small cohort of patients ($n = 11$) undergoing radical cystectomy at their institution using a variety of tests aimed at understanding the catabolic process associated with radical cystectomy [26]. Each patient was tested the day before, 14 days, and 180 days following surgery. Patients were undergoing surgery for curative intent and the choice of diversion was at the discretion of the treating surgeon. No supportive nutrition was provided post-operatively until the return of bowel function. The median hospital stay was 15 days (range 9–42 days), with four major complications including urine leak ($n = 2$), wound dehiscence ($n = 1$), and pelvic hematoma ($n = 1$).

### Table 10.2 Morphometric measures associated with surgical outcomes.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Clinical relevance</th>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle health</td>
<td>Frailty</td>
<td>Psoas/Intracostal/paraspinal areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle density/fat content</td>
</tr>
<tr>
<td>Body composition</td>
<td>Truncal obesity/</td>
<td>Subcutaneous fat area</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome</td>
<td>Peritoneal fat area</td>
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<tr>
<td></td>
<td></td>
<td>Muscle/fat ratios</td>
</tr>
<tr>
<td>Bone health</td>
<td>Frailty/Osteoporosis</td>
<td>Spinal column bone density</td>
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<tr>
<td></td>
<td></td>
<td>Spinal column area</td>
</tr>
<tr>
<td>Arterial health</td>
<td>Atherosclerosis</td>
<td>Aortic/iliac calcification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arterial collateralization</td>
</tr>
<tr>
<td>Solid organ health</td>
<td>Liver function</td>
<td>Liver volume and perfusion</td>
</tr>
<tr>
<td></td>
<td>Renal function</td>
<td>Kidney volume and perfusion</td>
</tr>
</tbody>
</table>
Physiologic measures included body weight, total body nitrogen, total body fat, total body water, total body potassium, protein index, and resting energy expenditure. In addition, grip strength was measured with a handheld dynamometer. Finally, respiratory muscle strength was measured. In general, all measures saw a decline from baseline at day 14, which recovered or approached baseline measures on day 180. Because of the small sample size, there was no effort to correlate changes with outcomes including complications. Also, there was no evaluation of whether baseline measures predicted outcomes. However, the authors concluded, based on this and prior work demonstrating loss of muscle mass and baseline malnourishment, that there is a need for perioperative nutritional support.

A larger prospective study evaluated the use of functional measures in elderly patients undergoing major abdominal surgery to assess recovery [27]. This included a cohort of 372 patients older than 60 who were assessed pre-operatively and post-operatively at 1, 3, and 6 weeks as well as 3 and 6 months after surgery using self-reported (Activities of Daily Living (ADLs), instrumental ADLs (iADLs), Medical Outcomes Study Short Form-36 (SF-36), Physical and Mental Component Scales, Geriatric Depression Scale (GDS), and Folstein Mini-Mental State Exam (MMSE)) and performance-based measures (timed walk, functional reach, hand grip strength). Most of these patients underwent colorectal procedures with only one patient undergoing radical cystectomy and ileal conduit urinary diversion. The maximal decline on all of these measures was seen at one week, which was statistically significant. While most measures recovered, mean grip strength did not recover to baseline at six months.

In a multivariate analysis, only a serious complication and physical status (which included a combined score of the timed walk, functional reach, and grip strength) were predictive of recovery of ADLs. In a second multivariate analysis, serious complication, physical status, MMSE, GDS, and serum creatinine > 1.5 mg/dL were predictive of recovery of iADLs. In addition, serum albumin of < 3 mg/dL approached significance with an odds ratio of 0.11 (95% confidence interval: 0.01–1.22, p = 0.07). Most of these variables similarly predicted time to recover ADLs and iADLs. The authors’ conclusion is that certain factors such as major complications and depression are modifiable and interventions in future prospective studies should focus on these areas to improve functional recovery in the elderly [27].

Nutrition

It has been observed that malnourished patients have an increase in operative morbidity, operative mortality, and length of stay in intensive care following radical cystectomy [28]. This also contributes to nosocomial infection, poor wound healing, an increased length of hospital stay, multi-organ dysfunction, and mortality [29]. Nutritional deficiency in patients undergoing radical cystectomy, as measured by pre-operative weight loss, body mass index, and serum albumin, is a strong predictor of 90-day mortality and poor overall survival. In a cohort of 583 patients undergoing radical cystectomy for bladder cancer, the 90-day mortality rate was 16.5% in patients with nutritional deficiency and 5.1% in others (p < 0.01) [30]. In addition, serum albumin is used to assess nutritional deficiency and is a well-known risk factor for post-operative complications such as wound healing and infectious complications. Djaladat and colleagues observed that in radical cystectomy patients with a low albumin level, the 90-day complication rate was significantly higher than in patients with a normal albumin level (41.6% vs. 33.6%, p = 0.030). In addition, wound healing (p = 0.008) and gastrointestinal (p = 0.004) complications occurred significantly more often in the low albumin group than in the normal albumin group [31]. Albumin may also reflect the disease state, as a low pre-operative albumin level has been associated with increased overall and cancer-specific mortality risk [32].

Measurements of nutritional status

Given the influence of nutritional status on perioperative outcomes, a proper nutritional assessment should be performed during selection of patients for radical cystectomy. One of the most useful measures of malnutrition in adults is the body mass index (BMI), calculated as the weight (in kilograms) divided by the square of the patient’s height (in meters). Classification of malnutrition includes the following categories: Mild (BMI 17–18.5), Moderate (BMI 16–17), and Severe (BMI < 16) malnutrition.

However, because of the physiological changes that occur with aging [33], standard nutritional assessments may require special consideration in the elderly cystectomy population. For example, body weight increases in aging individuals until the fifth decade of life and will decline after the seventh decade. In addition, height decreases with advanced aging. Thus, additional parameters to include...
serum nutrition markers may be used to better determine patients’ pre-operative nutritional status. For example, serum albumin should be obtained prior to cystectomy, especially in patients where a concern for suboptimal nutritional status is present based on history or physical examination or in patients receiving neoadjuvant chemotherapy. Some studies suggest that albumin does not correlate with nutritional status in the elderly, whereas pre-albumin and retinol-binding protein are better maintained in the geriatric population [33].

Renal dysfunction
Renal dysfunction provides unique challenges during considerations for treatment of advanced bladder cancer. First, the ability to give adequate perioperative chemotherapy may be affected by renal dysfunction. Cisplatin is the most effective chemotherapy for bladder cancer and is commonly used in combination regimens: gemcitabine and cisplatin (Gem-Cis) or methotrexate, vinblastine, adriamycin, cisplatin (MVAC). The efficacy of cisplatin is dose dependent, but higher doses may be precluded due to the risk of nephrotoxicity. Cisplatin is toxic to the proximal tubules [34]. Although cisplatin analogs exist, namely carboplatin, comparable efficacy to cisplatin has not been established. Generally, a creatinine clearance of ≥ 60 mL/min is utilized to determine cisplatin eligibility [35]. However, in practical application and with renal protective measures including hydration, patients with a GFR between 50 and 60 may be able to undergo cisplatin treatment.

Renal impairment is not a contraindication to radical cystectomy but can influence the type of urinary diversion offered to patients. Patients undergoing urinary diversion with use of the ileum or colon can develop metabolic disturbances as a result of hyperchloremic metabolic acidosis. Because the intestinal diversion segment will reabsorb urinary solutes, the amount of intestine used and the length of time that urine is exposed to the intestine can result in metabolic side effects. Thus, continent urinary diversions utilizing segments of intestine length ≥ 60 cm result in substantially more solute reabsorption compared to a non-continenence conduit (length 15 cm). A GFR above 40 mL/min is generally required during consideration of a continent urinary diversion.

Additional renal function parameters used to determine the ability to offer a continent diversion include the following: ability to acidify urine, ability to concentrate the urine in response to dehydration, amount of protein loss in urine. “Patients whose serum creatinine is more than 2.0 ng/dL can be considered for continent diversion if they are able to (1) achieve a urine pH of 5.8 or less after an ammonium chloride load, (2) have a urine osmolality of ≥ 600 mOsm/kg in response to water deprivation, have a GFR ≥ 35 mL/min, and minimal urine protein” [36].

Cardiovascular disease
Cardiovascular complications following radical cystectomy can have devastating consequences and therefore cardiovascular risk assessment deserves special attention in the selection of patients for surgery. In some patients, a history of cardiac disease is known prior to the diagnosis of cancer. However, in many instances, patients with newly diagnosed bladder cancer have not been seen or evaluated by a physician for many years. Thus, signs or symptoms of cardiac disease states are often elucidated in the urologist’s office through a detailed history and physical examination and 12-lead resting electrocardiogram (ECG). Patients undergoing radical cystectomy appear to have an increased risk for cardiac complications because (1) risk factors contributing to bladder cancer (i.e. tobacco use and advanced age) are also risk factors for coronary artery disease; (2) the usual symptomatic presentation of ischemic heart disease in these patients is sometimes obscured by physical limitations as a result of advanced age; and (3) radical cystectomy can be associated with substantial fluctuations in fluid volume, blood pressure, heart rate, and filling pressure. If cardiac disease is known or discovered, the urologist must inquire as to the degree, severity, and stability of the condition as well as contributing comorbid disease states.

The American College of Cardiology/American Heart Association (ACC/AHA) 2007 guidelines [37] provide a useful algorithm for assessing cardiac risk prior to non-cardiac-related surgery. Patients undergoing radical cystectomy will experience an intermediate–high surgery-specific risk. In addition to the surgery-specific risk, three additional elements from a patient’s history and physical examination should be gathered, including (1) cardiac risk factors, (2) identifying active cardiac conditions, and (3) functional capacity. Cardiac risk factors include a history of the following:

1. Ischemic heart disease, defined as a history of myocardial infarction, a history of a positive treadmill test result, use of nitroglycerin, chronic stable angina, or an ECG with abnormal Q waves.
Congestive heart failure, defined as a history of heart failure, pulmonary edema, paroxysmal nocturnal dyspnea, peripheral edema, bilateral rales, S3, or a radiograph showing pulmonary vascular redistribution.

Cerebrovascular disease – history of transient ischemic attack or stroke.

Diabetes mellitus requiring insulin treatment.

Renal insufficiency – creatinine > 2 mg/dL.

In patients with three or more risk factors, a cardiovascular stress test is recommended if the results would change clinical management. In selecting patients for radical cystectomy, a positive stress test could indeed influence management, as alternatives to surgery in some patients, including radiation therapy, could be entertained. In patients with one to two clinical risk factors, recommendations for patients undergoing radical cystectomy would be either to proceed with surgery as planned with adequate heart rate control or consideration of non-invasive testing.

The presence of serious cardiac conditions such as unstable coronary syndromes, recent or past myocardial infarction, decompensated heart failure, severe valvular disease, or serious arrhythmias requires immediate attention and careful consideration before undertaking cystectomy. Functional capacity can be measured using metabolic equivalents and an index such as the Duke Activity Status Index [38]. Patients who are unable to climb a flight of stairs, walk up a hill, or do light work around the house have substantially increased cardiac risk with major surgery and should undergo cardiac consultation prior to selection for radical cystectomy.

Hepatic dysfunction

A thorough history and physical examination should be performed to identify the presence of or risk factors for hepatic dysfunction. Important points include prior family history of liver disease, jaundice, or jaundice following anesthesia, prior blood transfusions, tattoos, illicit drug use, and alcohol use. Physical examination findings indicative of hepatic dysfunction include jaundice, pruritis, increased abdominal girth (ascites), palmar erythema, spider telangiectasias, splenomegaly, testicular atrophy, and fatigue. Relative contraindications to radical cystectomy in patients with liver disease include the following: acute viral or alcoholic hepatitis, class C cirrhosis, fulminating hepatic failure, severe chronic hepatitis, severe coagulopathy, or severe extrahepatic complications such as acute renal failure, hypoxemia, or heart failure.

The use of bowel segments for urinary diversion following radical cystectomy may result in hyperammonemia in patients with hepatic dysfunction. The liver uses ammonia in the ornithine cycle to create urea, which is subsequently excreted via the kidneys. Urine ammonia is resorbed from urine by ileal and colonic bowel segments. Hepatic dysfunction can render the liver incapable of handling excess ammonia levels and patients can develop hyperammonemic encephalopathy or hepatic coma. Thus, a short ileal segment is preferred in the presence of liver dysfunction.

Prior surgery or radiation

Several other notable considerations are important for selecting patients for radical cystectomy. A history of multiple prior abdominal surgeries will influence the approach offered to include open versus a robotic approach (see Chapter 13: Laparoscopic/robotic radical cystectomy and urinary diversion: outcomes). Prior pelvic radiotherapy for prostate cancer or colon cancer may preclude the ability to give therapeutic levels of radiation to treat bladder cancer, thereby limiting local management to surgical options.

Selection of neoadjuvant chemotherapy

Neoadjuvant chemotherapy provides a 5–7% absolute improvement in five-year survival for patients undergoing radical cystectomy. Despite high-level evidence, assessment of current practice patterns for patients undergoing radical cystectomy indicates a substantial underutilization of neoadjuvant chemotherapy [39]. The reasons for this are multifactorial and likely include patient and physician-related factors.

Arguments supporting the use of adjuvant chemotherapy instead of neoadjuvant chemotherapy include avoiding delays in surgery due to chemotherapy, alleviation of patient anxiety, and enhanced chemotherapeutic effect against small-volume disease. However, the benefit of adjuvant chemotherapy, unlike neoadjuvant chemotherapy, has not been proven. While some centers recommend aggressive use of neoadjuvant chemotherapy for all patients, others recommend a risk-adapted selection of patients for neoadjuvant chemotherapy. The MD Anderson approach, for example, reconciles the modest survival advantage afforded with neoadjuvant chemotherapy with the potential toxicity
to offer neoadjuvant chemotherapy to patients at highest risk for disease recurrence and thus most likely to respond to or benefit from treatment. Highest risk patients under this paradigm include patients with extravesical extension or clinical ≥ T3 disease, variant tumor histology, the presence of hydronephrosis, and/or the presence of lymphovascular invasion [40].

Patients may be ineligible to receive neoadjuvant chemotherapy due to performance status or comorbid conditions such as renal dysfunction (see Renal dysfunction section above). Additional criteria characterizing patients who are “unfit” for cisplatin-based chemotherapy include the following: grade ≥ 2 hearing loss, grade ≥ 2 neuropathy, ECOG Performance Status of 2, and/or New York Heart Association Class III heart failure [35].

Selection of type of urinary diversion
The type of urinary diversion (ileal conduit, continent orthotopic reservoir, or continent catheterizable pouch) to be offered to patients depends on patients’ comorbid illness (see Renal dysfunction section above) and patients’ preferences. Following thorough examination and disease evaluation, patients should be informed of the available options and potential limitations and side effects of each diversion type. Patients who decide on an orthotopic continent diversion must be made aware of the fact that this will not be possible in cases such as urethral involvement or the inability of the intestine to reach the urethra (tight mesentery). In addition to the aforementioned metabolic consequence of continent urinary diversions, patients should be aware of the possibility of urinary incontinence, particularly nighttime incontinence due to the potential damage to the rhabdosphincter mechanism. In addition, patients should be aware of the possibility that intermittent catheterization may be needed to empty the reservoir.

Pre-operative preparation
Much of the above text has focused on patient selection and tools that may be used to assess and predict outcomes for patients undergoing radical cystectomy. In practice, once the decision is made to undergo radical cystectomy, there is a series of pre-operative evaluations that can be helpful in preparing patients for radical cystectomy. Key components of pre-operative preparation prior to radical cystectomy include anesthesia evaluation, nutritional assessment, ostomy/urinary diversion teaching, and medical clearance if indicated.

Anesthesia evaluation
Evaluation of the patient by the anesthesia team is important prior to radical cystectomy. Much of the evaluation is focused on the medical ability to undergo anesthesia, airway evaluation, and perioperative pain management. Details of anesthesia evaluation for patients undergoing radical cystectomy or other major abdominal surgical procedures are beyond the scope of this text. However, there are certain factors that require discussion between the anesthesia and surgical teams that can aid in the management of the patient during surgery.

The need to remain on antiplatelet therapy/venous thromboembolism prophylaxis
A particular issue that affects the surgeon, anesthesiologist, and patient is the need to remain on antiplatelet therapy throughout the radical cystectomy. Operating in the pelvis, especially in a patient with locally advanced disease, can lead to an increased risk of bleeding due to neovascularity and the need for extensive lymph node dissection in the internal iliac and pre-sacral regions. However, there is significant data to demonstrate that there is an increased risk of a cardiovascular event in patients with cardiac stenting who do not remain on aspirin during the perioperative period [41]. As such, we strongly recommend that patients remain on aspirin during the perioperative period. In our experience, this has not increased the risk of perioperative bleeding complications or the need for blood transfusions.

Use of epidural/spinal anesthesia
Perhaps the most common complication following radical cystectomy and urinary diversion is post-operative ileus (POI). Several factors have been proposed for the etiology of POI including the use of intra-operative and post-operative narcotics for pain management. In addition, many argue that the use of intravenous and
oral narcotics does not adequately manage the incisional pain, resulting in decreased mobility and further compounding the risk of ileus. While there are many other possibilities, the use of narcotics has driven investigation of regional anesthesia for intra-operative and post-operative pain management to reduce the risk of POI. Several studies have investigated combined general and regional anesthesia as well as regional anesthesia alone. Most of these series are small but show favorable results related to regional anesthesia. In one study, Friedrich-Freksa and colleagues [43] performed cystectomy and urinary diversion in 28 patients using a combined spinal and epidural anesthetic. They were able to perform all procedures safely and no patients experienced a complication of higher than Grade 1. Patients were discharged from the hospital over a range of 10–25 days and described their experience as positive.

While there are several other series that show favorable results with either spinal/epidural anesthesia alone or in combination with general anesthetic, it is highly likely that the outcomes are influenced by local practice patterns and unique patient populations. In addition, several newer approaches may decrease the need for regional anesthesia as part of anesthetic and pain management. In general, it is not possible to use regional anesthesia alone for robot-assisted surgery because of patient positioning in the steep Trendelenburg position. In addition, newer local blocks may allow better incisional pain control without the need for spinal or epidural access [44]. Finally, the use of alvimopam, which we will discuss later, has been shown to decrease the incidence of post-operative ileus, mitigating the need for specialized anesthetic approaches. However, spinal anesthesia alone may have benefit for a select few patients who are not candidates for general anesthesia.

**Hemodynamic management during the surgical procedure**

There has been greater emphasis placed on the hemodynamic management of patients during radical cystectomy in recent years. Perhaps the best evidence we have exploring the benefit of careful fluid management is a randomized trial performed by Wuethrich et al. from Switzerland [45]. In this single-center, double-blind randomized trial, 166 patients were randomized to either 1 mL/kg/hour during cystectomy and 3 mL/kg/hour until completion of surgery of a balanced Ringer’s solution along with preemptive norepinephrine infusion at an initial rate of 2 μg/kg/hr or 6 mL/kg/hour of a balanced Ringer’s solution throughout surgery. The primary endpoint was hospital complication rate, with secondary endpoints including length of stay and 90-day mortality. For both the primary and secondary endpoints, there was a clear advantage to the fluid-restricted group in terms of complications, length of stay, and, most notably, 90-day mortality, where there were no deaths in the fluid-restricted group and 4.8% of the non-fluid-restricted group died within 90 days. In a second report based on this randomized controlled trial, they demonstrated a decrease in blood loss as well as a need for blood transfusions [46].

While fluid restriction as an anesthetic approach has been reported in other studies, the power of this study is the high level of evidence behind the approach. However, across most studies reported in the literature, fluid restriction likely aids in decreased tissue edema, allowing for earlier bowel recovery. This must be balanced with the need for adequate tissue perfusion throughout radical cystectomy. It is likely that there is no “one size fits all” approach for anesthetic management during cystectomy. In addition to more high-quality studies such as the one from Switzerland, what is needed is the evaluation of the large amount of data collected during anesthesia and how they correlate with outcomes to provide guidelines for both physicians and anesthesiologists to manage patients in the operating room. This identifies potential opportunities to both improve anesthetic care and reduce variation that does not improve care [47].

**Perioperative nutrition**

The recognition that the nutritional status of a patient impacts the outcomes of radical cystectomy and urinary diversion is not a new one. Several studies support the fact that poor nutritional status portends a worse outcome. While it would make intuitive sense that improving nutritional status prior to surgery would therefore improve surgical outcomes, there is often not enough time to meaningfully impact this given the worse outcomes associated with a delay in radical cystectomy for bladder cancer [30]. In addition, there is no evidence to support either pre-operative or post-operative total parenteral nutrition improving outcomes in patients undergoing radical cystectomy [48]. Enhanced recovery protocols have focused on avoiding mechanical bowel preparation and prolonged periods
Selection and management of radical cystectomy patients

without food prior to surgery. This includes a normal breakfast the day before surgery followed by clear liquids and a clear carbohydrate drink up to two hours prior to surgery. In addition, most enhanced recovery or “fast-track” protocols utilize consultation with a dietician prior to surgery. While there are no data associated with improved outcomes with these approaches, we have found that consultation with a dietician does help the patient to understand the anticipated recovery process and likely weight loss associated with radical cystectomy. In addition, discussion of the recovery of bowel function and use of probiotic therapies may help avoid complications such as Clostridium difficile colitis, which has been associated with prolonged antibiotic regimens as well as with traditional bowel preparation [49].

**Ostomy preparation and care**

For those patients undergoing a cystectomy with an ileal conduit urinary diversion, pre-operative teaching can aid in the patient’s recovery. There is a wealth of educational material available both online and in printed form. A critical component of good pre-operative care as well as perioperative management is the inclusion of a nurse educated and certified in ostomy care. The ostomy nurse is involved in pre-operative teaching that centers around anatomic, physiologic, and lifestyle changes associated with a new ileal conduit urinary diversion. This includes explaining the pouching systems available, how they work, what is required of the patient in the management of the ostomy, and general information on the care of the stoma and troubleshooting of stoma and surrounding skin issues. In addition, the ostomy nurse marks the appropriate site for the ileal conduit prior to surgery based on patient wishes, the location of abdominal creases during sitting and standing, the location of the patient’s waistline, and functional/anatomic issues of the patient. Occasionally, it is necessary to mark an alternative site if the patient has had prior surgery and incisions that could compromise abdominal wall blood supply or the function of the stoma in that location.

Ostomy teaching and care continues in the perioperative period but also extends throughout the lifetime of the patient. In the immediate post-operative period, an ostomy nursing team is involved in initial evaluation of the stoma and placement of an ostomy appliance. Over the course of the hospital stay, the ostomy nurse teaches both the patient and their family member(s) troubleshooting and change of the appliance, how to avoid leaks, and how to attach a collection unit for night time so that the patient does not have to wake. At our institution, we have recently included ostomy change competency to the checklist for discharge from the hospital. Frustration with the ostomy can affect patient satisfaction but can also result in potential readmission by affecting functional status or by increasing the risk of urinary tract infections.

We routinely schedule a visit with the ostomy nursing team approximately six weeks following surgery. At that time point, most of the tissue edema is gone and patients can be fitted with a pre-cut ostomy that will aid in protecting surrounding skin and also reduce the complexity of appliance changes for the patient. During that visit, other issues such as stoma retraction, flush stoma, or surrounding skin changes can be assessed and changes to the ostomy supplies can be directed at addressing these issues. The need for access to a trained stoma provider is crucial for patient-centered care and quality of life, as the patient needs a resource to contact and be evaluated by throughout their lifetime.

** Continent urinary diversion**

Patients undergoing a cystectomy with continent urinary diversion require additional pre-operative teaching and care beyond those patients receiving an ileal conduit. The enterostomal nurse plays a very important role in patient education and preparation for surgery. Patient selection for continent urinary diversion has been discussed elsewhere in this chapter. All patients undergoing a continent urinary diversion using the colon should have a pre-operative colonoscopy to ensure that there is no evidence of cancerous or pre-cancerous lesions.

In our experience, it is imperative that the patients anticipating an ileal neobladder be taught to catheterize prior to the surgery. Failure to adequately demonstrate the ability to catheterize is a relative contraindication to orthotopic neobladder. In addition, patients must be counseled pre-operatively on the expected morbidity of neobladder, including the very real possibility of nocturnal incontinence and the up to 10–20% risk of urinary retention requiring dependence on intermittent self-catheterization. Additionally, patients must understand the frequency and need for post-operative catheter care, the frequency of intermittent self-catheterization following Foley catheter removal, and the presence/management of mucous. Finally, patients must be
counseled on the ideal neobladder capacity, the need to avoid over-distension, and the need for post-operative evaluation and training with physical therapy for pelvic floor rehabilitation. Also, patients need to be aware that they will need to wear an alert bracelet to inform other medical providers in case of a medical emergency, particularly for patients with continent cutaneous diversions.

Long-term consequences of neobladder should be discussed, including metabolic derangements, and the impact on sexual function, which is likely more important in this group of patients who are highly motivated to preserve functional outcomes. In general, we tend to utilize similar approaches to sexual function recovery as in the post-prostatectomy literature, although no definitive evidence exists to support this practice [50].

Patient-to-patient communication
Increasing attention to patient-centered care has led to the recognition that survivors and their family members can add tremendous value to the perioperative care of a patient undergoing cystectomy and urinary diversion. The primary advantage of a patient discussing the surgery and anticipated recovery is a deeper knowledge of the patient experience that we, as providers, do not have. There are also important aspects to the perioperative experience that providers do not have experience or knowledge of in order to discuss. There are several avenues by which patients can access these valuable resources. Many surgeons keep a list of patients willing to discuss their experience. The pitfall is that these will be the patients with the best experiences and that might skew the opinion of the patient undergoing cystectomy. In our experience, we have selected patients of different genders, ethnic backgrounds, and diversion type who are willing to discuss their care with other patients. It is best to choose patients that had a good experience but not necessarily a complication-free experience. Patient support groups represent an alternative to individual patient-to-survivor communication. Support groups provide a diversity of opinion as well as interaction with patients at various stages of their bladder cancer. For those patients who do not have access to a patient support group or one not specific to bladder cancer, online communities exist that have proved to be very supportive (www.bcan.org). We view some form of patient-to-patient interaction to be crucial in setting expectations prior to surgery.

Prehab
“Prehabilitation (prehab) is a series of physical and psychological assessments that establish a baseline function level, identify impairments and prescribe targeted interventions with the primary goal of preventing or reducing the severity of treatment-related impairments” [51]. This has been used in a variety of settings such as in preparation for elective intensive care unit admission or prior to certain orthopedic procedures [52]. It has been most extensively studied in the setting of lung cancer, where targeted pulmonary evaluation and intervention was shown to expand treatment options for patients with lung cancer and compromised pulmonary function. However, it has also been studied in colorectal, breast, prostate, and transplant surgery with promising results.

Prehab makes a great deal of sense in patients with bladder cancer undergoing cystectomy based on the prior discussion of nutritional and functional impairment we have described elsewhere in this chapter. Prehab can be performed while patients are undergoing neoadjuvant chemotherapy or during the four-week interval prior to surgery. At one of the authors’ institutions, we currently have a phase I/II study evaluating the use of a prehab program in patients undergoing cystectomy ≥ 60 years old who undergo evaluation by an exercise physiologist who then designs a targeted program within four weeks of surgery to improve functional capacity. The primary endpoint is reduction of 90-day readmission based on a historic control of 25%. Currently, we have 10 of 80 patients enrolled without adverse events related to the intervention. Prehab has the potential both to improve outcomes in patients undergoing surgery and to increase the possible treatment options in our most vulnerable patients.

Inpatient standardization and pathways (inpatient and beyond)
Care pathways make sense for all stakeholders (patient, physician, third-party payer, hospitals) because standardized care reduces waste based on individual variability that may not be based on best practices and potentially by reducing the length of hospital stay. Care pathways provide consistent expectations to the patient, nurses, physicians, and other providers as to the hospital course of a patient after surgery. Standardized processes
reduce error by decreasing variability and allow for the implementation of evidence-based care in real time. Chang and colleagues [53] were the first to report on inpatient care pathways in 2002 and demonstrated the ability to reduce the length of hospital admission.

There have been two more recent updates to care pathways in relation to radical cystectomy. Enhanced recovery programs (ERPs) have been reported since the 1990s for a variety of major surgical procedures. The underlying principle is similar to the care pathway but also includes standardizing pre-operative education, avoiding pre-operative fasting with carbohydrate loading two hours prior to surgery, standard anesthetic/analgesic algorithms, and early mobilization [49]. Many of the components of a “fast track” program have already been described in this text. While many studies related to the care of radical cystectomy patients have addressed components of these programs, there are few studies that have truly adopted the entire approach. The reported benefit of these ERPs is reduction in hospital stay, morbidity, and early return to normal activity. Pruthi and colleagues [54] reported outcomes of a fast-track recovery program in 362 patients undergoing radical cystectomy from 2001–2008. Their report included an evolution of their program showing the institution of new components based on best evidence from the published literature. Their program included no post-operative nasogastric tube, use of metoclopramide for gastrointestinal motility and reduction in nausea, adherence to the American Urological Association guidelines for antibiotic coverage, gum chewing, non-narcotic analgesia such as ketorolac, and early resumption of diet. This resulted in a reduction in hospital stay and complications without increased readmission to the hospital.

We have instituted a similar ERP at our institution and while there are potential benefits, we think that the evidence remains inconclusive regarding the true benefit. While most series are able to demonstrate a reduction in the length of hospital stay, there continues to be a reported readmission rate of 20–25%. The most common cause of readmission is dehydration and urinary tract infection. Readmission following cystectomy is associated with decreased overall survival [55] and the goal of a “fast-track” program should not only be early discharge but actually keeping patients out of the hospital.

A recent study has suggested that inpatient care pathways and ERPs should be coupled with checklist-driven criteria to determine discharge as well as extended early outpatient support to ensure that potential problems are addressed early and handled in a clinic or subacute setting rather than through the emergency room where the risk of intensive care unit utilization, imaging, procedures, and prolonged hospitalization with extended morbidity are increased. Jacobs et al., using SEER Medicare data, found that reductions in hospital stay for patients undergoing cystectomy resulted in increased use of post-acute care [56].

At our institution, we have initiated and are studying several interventions in the post-operative period focused on reducing readmission following surgery. Interventions are focused on patients at greatest risk such as elderly patients, little or no social support, long distance from our institution, and prolonged/complicated hospital course. This intervention includes a visit by the clinic nurse prior to discharge from the hospital to ensure the patient and family have access to contact information 24 hours a day and 7 days a week, an early call from a mid-level provider to assess functional and nutritional issues, an early post-operative visit from clinic and ostomy nurses as well as a dietician, routine utilization of a visiting nurse who reports to the treating team, and a low threshold for clinic visits to assess patients within the first six weeks after surgery. While we do not have data to support the benefit of this intervention currently, such interventions have been demonstrated to reduce hospitalizations in patients with congestive heart failure, for example. The cost of this must be balanced against the cost of readmission. Some payment models already exist for follow-up care after hospital discharge to support this model of care. In addition, future technologies such as automated phone calls and Web-based applications may decrease the cost of such interventions [57]. It is clear, however, that programs focused only on the inpatient setting fail to grasp the full spectrum of care required for these patients.

Other components of an extended care pathway include the appropriate utilization of discharge to skilled nursing facilities, increased education and involvement of family members, and other subacute levels of care that would allow for both transition out of the hospital to home and also a less intense setting of care to address certain complications without requiring acute inpatient care. These areas are understudied, especially in the radical cystectomy population, and further research is needed to drive these potential improvements so that benefit can be demonstrated to third-party payers that do not cover alternative mechanisms and models of care.
Conclusions and future state – what do we need to work on?

While it is clear that we have made improvements in patients undergoing cystectomy and urinary diversion, there is a great opportunity for improvement. Both patients and physicians caring for bladder cancer patients need better tools to assess frailty that can both identify the most vulnerable population and opportunities to intervene to improve outcomes prior to surgery. These tools must also allow us to identify which patients are at too high a risk for surgical intervention in a quantifiable way. In addition, further clinical research must be performed to improve every component of care for patients undergoing cystectomy from the time the decision is made for surgery to the time of return to normal activity. While individual groups implement and study pieces of the process, a quality collaboration could allow for real-time learning and implementation of best practices and identify outliers to either improve or shift patients to higher quality providers. Quality collaborations have been shown to improve outcomes, with perhaps the most well-known example being the one created for cardiovascular surgery in Massachusetts [58]. Although not addressed by this chapter, further study and better models of follow-up care and survivorship are needed to address longitudinal outcomes of patients undergoing radical cystectomy and urinary diversion. Acceptance of less than ideal surgical outcomes is no longer an option in this era where we have both the tools and technology to make a meaningful impact on the lives of our patients.

Useful web links

1 http://www.bcan.org
2 http://www.auanet.org/education/guidelines/bladder-cancer.cfm

References


CHAPTER 11
Radical cystectomy: Techniques and outcomes

Siamak Daneshmand1 and Seth P. Lerner2
1 USC Institute of Urology, USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA
2 Department of Urology, Baylor College of Medicine, Houston, TX, USA

KEY POINTS

- Radical cystectomy with a thorough pelvic lymph node dissection remains the gold standard therapy for high-grade muscle-invasive bladder cancer and high-grade non-invasive disease refractory to intravesical therapy.
- Clinical staging includes pelvic examination under anesthesia, transurethral resection of the bladder tumor, and biopsies of the prostatic urethra in men as well as contrast-enhanced cross-sectional imaging of the chest, abdomen, and pelvis. There is significant understaging despite stratification.
- Surgical technique along with surgeon and hospital experience is critical in optimizing clinical outcomes.
- Routine bowel preparations and nasogastric tubes are no longer used.
- Radical cystectomy still provides the best survival rate with the lowest chance of local recurrence (<15%) for high-grade invasive bladder cancer.
- Concomitant urethrectomy in the male is rarely performed since in the vast majority of cases a negative urethral margin can be achieved. Patients with a positive urethral margin on final pathology can be considered for secondary urethrectomy.
- Patients with no evidence of disease involving the anterior vaginal wall on bimanual examination can be considered for vaginal-sparing surgery, which can offer preservation of sexual function. In younger patients with lower stage disease, complete female organ preservation can be considered given the very low chance of involvement with urothelial carcinoma.
- Perioperative mortality rates are 1–3% at centers of excellence but can be twice as high in less-experienced hospitals. Perioperative complication rates remain high (up to 64% within 90 days of surgery).
- Evidence-based perioperative enhanced recovery pathways can help minimize morbidity and hasten recovery in patients undergoing cystectomy.

Introduction

In the United States, urothelial carcinoma of the bladder is the second most common malignancy of the genitourinary tract, and the second most common cause of death of all genitourinary tumors. An estimated 74,690 new cases of bladder cancer and 15,210 deaths from bladder cancer were expected in 2014 in the United States [1] Approximately 75% of patients with primary urothelial carcinoma of the bladder present with non-muscle-invasive tumors, while 20% to 40% will either present with or progress to high-grade, muscle-invasive disease. These cancers are highly lethal and without aggressive treatment, are the cause of death in the vast majority of patients within two years of diagnosis. Approximately 70% of patients present with localized disease, while 33% have regional spread and 5% have distant metastasis at the time of diagnosis [1] Radical cystectomy with or without neoadjuvant chemotherapy is still considered the standard of therapy for high-grade, muscle-invasive bladder cancer and high-grade non-muscle-invasive cancers deemed to be
at high risk for progression. In addition, radical cystectomy with a thorough, meticulous lymph node dissection provides accurate pathologic staging, and provides optimal outcomes in terms of survival and preventing local pelvic recurrence. Pelvic recurrence rates in patients undergoing an extended pelvic lymph node dissection range from 15–32% in large institutional series [2–4].

Over the past several decades, improvements in anesthesia, surgical technique, and perioperative management have led to a decrease in perioperative morbidity and mortality. Nevertheless, radical cystectomy with pelvic lymphadenectomy remains a formidable surgery with significant early and late complications. Mortality rates, however, have decreased significantly to 2–3% in contemporary series from centers of excellence [5]. In addition, radical cystectomy with a meticulous and thorough pelvic lymphadenectomy provides optimal local cancer control.

Bladder substitution with an orthotopic ileal neobladder in general has excellent functional outcomes in experienced centers and may allow some patients and surgeons to consider radical cystectomy earlier in the disease process when it has the best chance of cure. Currently, most men and women can safely undergo orthotopic lower urinary tract reconstruction to the native urethra following cystectomy [6, 7].

There have been significant refinements in the surgical technique of radical cystectomy over the past decade, particularly with respect to blood loss and preservation of the urethral rhabdosphincter and the neurovascular bundles without any compromise in oncologic principles of the operation. Given the complexity of the procedure and subsequent urinary diversion, the surgical technique of radical cystectomy with a thorough and meticulous pelvic and iliac lymphadenectomy is critical in minimizing local recurrence and positive surgical margins and to maximize cancer-specific survival. Positive surgical margins and/or tumor spill during surgery put the patients at exceedingly high risk for local recurrence and should be avoided at all costs. Local pelvic recurrence is a lethal event in the vast majority of patients, and salvage therapies are currently ineffective [2].

There has been significant debate regarding the ideal limits of pelvic lymphadenectomy throughout the decades. The role of an extended lymphadenectomy (LND) is thoroughly discussed in Chapter 15. All patients should undergo a bilateral pelvic lymphadenectomy to include at least the external, internal, and obturator lymph nodes. There are abundant retrospective data suggesting that an extended pelvic and iliac lymphadenectomy including bilateral pelvic, common iliac, prescatic (Fossa of Marcellus), and pre-sacral nodes increases the number of nodes identified by the pathologist and identifies more metastatic nodes in node-positive patients. Some surgeons further extend the proximal limit to include the para-caval and para-aortic nodes up to the inferior mesenteric artery. Two phase III trials are in progress that will determine if there is a benefit to an extended LND regarding progression-free and overall survival. This chapter will detail the pre-operative evaluation, surgical technique, and clinical results and outcomes of radical cystectomy.

Anatomy

The vascular anatomy of the urinary bladder is straightforward and uniformly consistent. The primary blood supply is derived from the anterior division of the hypogastric (internal iliac) artery through the superior and inferior vesical artery. When dissecting the ureters, preservation of the longitudinal blood supply is imperative. Dissection between the peritoneum overlying the sigmoid colon and the spermatic cord/infundibulo-pelvic ligaments and anterior to the iliac nodes maximally preserves the blood supply and peri-ureteral soft tissue, minimizing the risk of ischemia to the distal ureter and subsequent uretero-intestinal anastomotic stricture.

Colleselli et al. described the innervation of the urethral sphincteric mechanism in the female [8] Fibers from the pelvic nerve course along the lateral vaginal wall just posterior to the bladder to innervate the bladder neck, and fibers from the internal pudendal nerve travel underneath the endopelvic fascia to innervate the distal two-thirds of the urethra, the so-called rhabdoid sphincteric mechanism. Additional details are provided in Chapter 12.

Schlegel and Walsh extended their seminal observations regarding the neuroanatomic basis for erectile dysfunction after radical prostatectomy and described the relationship of the cavernous nerves to the bladder and seminal vesicles [9]. The neurovascular bundles
are contained within the fascia surrounding the inferior vesical artery and vein. In nerve-sparing cystoprostatectomy, it is important to preserve the hypogastric artery, dividing only the superior vesical artery proximally, in order to maintain the integrity of the internal pudendal artery and prevent vasculogenic impotence.

Radical cystectomy (RC) in the male includes complete removal of the bladder, surrounding perivesical fat, prostate, and seminal vesicles. The plane of the posterior dissection is between the posterior layer of Denonvillier’s fascia and the anterior rectal wall. The previously irradiated patient is at higher risk for rectal injury, as this surgical plane is frequently obliterated. Sharp dissection using the anterior longitudinal muscle fibers of the rectum as a guide is usually required. In the female, RC includes the infundibulopelvic ligament, ovary, fallopian tube bilaterally, uterus, cervix, and anterior vaginal wall in the case of invasive cancers involving the posterior bladder and/or trigone (see Chapter 12 for a more detailed description of RC in the female). A female organ-sparing approach is appropriate for patients who wish to retain reproductive function and/or to preserve vaginal anatomy for sexual function, as the involvement of these organs with invasive urothelial cancer is uncommon.

Lymph node drainage

The primary lymphatic drainage of the bladder is to the nodes in the true pelvis, which include the obturator, internal, and external iliac nodes. The secondary and tertiary lymphatic drainage is to the common iliac, paracaval and para-aortic nodes, respectively. The pre-sacral nodes also receive direct drainage from the trigone and posterior bladder wall and, although rare, nodal metastasis in this region may occur in the absence of disease distal to the CI bifurcation.

Lymph node metastases tend to track to the ipsilateral nodes associated with the invasive cancer. However, node metastases contralateral to the primary site of the tumor are common and thus mandate a bilateral node dissection [10]. Up to 12% of nodes found along the external iliac and distal common iliac vessels are located in the Fossa of Marcilles (also referred to as the pre-sciatic fossa), mandating dissection in this space in order to remove all of the potential node-bearing tissue.

Metastasis to common iliac and more proximal nodes in the absence of pelvic nodal metastasis is uncommon but can occur via the posterior lymphatic collecting ducts which may drain directly to the common iliac nodes [11, 12]. Leissner et al. reported that 6.9% of N+ patients had positive nodes in level II (CI and pre-sacral) and only distal nodal involvement [11]. Similar findings of 6% skip metastases were reported by Tarin et al. in a series of 591 patients [13]. Skip nodal metastases were also reported by Steven and Paulsen in a series of 336 patients undergoing extended node dissection [14], but these were not seen in the prospective series from Mansoura [15].

Small perivesical lymph nodes lie within the perivesical fascia and intercalate within the lymphatic ductal network, organized around the trigone, anterior and posterior bladder walls. These nodes may be the only site of node metastasis, have been associated with aggressive tumor biology, and have an independent association with worse overall and disease-specific survival [16].

Diagnosis and staging

Accurate assessment of clinical stage and grade starts with a carefully performed pelvic examination under anesthesia (EUA) transurethral resection of the bladder tumor (TURBT), site-directed bladder biopsies, and biopsies of the bladder neck (female) and prostatic urethra. Complete resection of an obviously invasive cancer is unnecessary when radical cystectomy is anticipated in order to avoid the risk of bladder perforation. Directed biopsies of the normal-appearing mucosa remote from the primary tumor establish the status of the remaining urothelium. Transurethral resection biopsies of the prostatic urethra are performed at 5 and 7 o’clock adjacent to the verumontanum to evaluate for the presence of diffuse CIS of the urethra and prostatic ducts [17]. This completes the staging of the tumor and establishes the suitability for continent diversion to the urethra.

The most common sites of visceral metastases are the lungs, liver, and bones, and clinical staging of a patient with muscle-invasive cancer is directed to these organs. Contrast-enhanced cross-sectional imaging with computed tomography or magnetic resonance imaging should be performed in all patients. A chest X-ray, liver
function tests, and serum alkaline phosphatase are obtained routinely and complete the imaging and laboratory evaluation. Alkaline phosphatase alone will identify only a small portion of asymptomatic patients with bone metastases [18]. Bone scintigraphy is not sufficiently sensitive or specific as a screening method for bone metastases [18] and is obtained in those patients with bone pain, an elevated alkaline phosphatase, or in patients with T4 or N+ disease by clinical staging. Magnetic resonance imaging (MRI) is more sensitive than bone scintigraphy for skeletal metastases but is limited to the axial skeleton and pelvis [19]. Computed tomography (CT) of the chest is obtained when the history and physical examination suggest pulmonary metastases or when patients have an abnormal chest X-ray.

Positron emission tomography combined with CT may identify patients with locally advanced bladder cancer and potentially change management [20]. Mertens et al. showed that FDG-PET doubled the rate of extravesical lesions compared to CT alone and that the time from first PET to death was shorter if the PET was positive for metastatic disease [21]. PET/CT may also be used to adjudicate abnormalities on CT that suggest metastatic disease and may obviate the need for biopsy confirmation [22]. False positives do occur however, and thus PET/CT is not considered a standard of care.

Despite a careful clinical staging strategy as outlined, staging errors are quite common. An international consortium reported results in 3166 patients and found 43% of patients upstaged to non-organ-confined disease [23]. A second report from the Netherlands Comprehensive Cancer Center Region evaluated 738 patients, of which 142 were considered organ-confined. Bimanual exam was accurate in 58% but 37% were understaged and 11% were overstaged [24].

The group from MD Anderson Cancer Center has proposed an algorithm for risk stratification and selection of patients for neoadjuvant chemotherapy using the following features to classify patients as high risk for understaging: hydronephrosis, lymphovascular invasion, three-dimensional mass on EUA, aberrant histology including micropapillary and neuroendocrine phenotypes, and clinical T4a. They found that patients in the high-risk group had an increased risk of overall and cancer-specific mortality compared to patients with cT2 and no high-risk features with similar results seen in an external cohort at the University of Southern California. Despite this apparent stratification in outcome, the understaging rate was significant at 49% [25].

### Indications and treatment

#### Accurate pathologic staging and local control

RC and bilateral PLND as monotherapy are indicated only in patients with anatomically resectable muscle-invasive bladder cancer and chronic kidney disease with eGFR and/or other comorbidities that limit the use of cisplatin-based neoadjuvant chemotherapy. A risk-adapted approach to the use of neoadjuvant chemotherapy is described above and remains to be validated prospectively. Integration of RC and neoadjuvant chemotherapy is discussed in detail in Chapter 25. The operation provides accurate pathologic staging of the primary tumor and involvement of adjacent organs and precise staging of the pelvic and iliac lymph nodes. Estimates of loco-regional failure (true pelvis and soft tissue distal to the aortic bifurcation) are 5–7% in patients free of node metastases and 15–20% in patients with locally advanced cancers (pT3,4 or node metastasis and ≥ 10 nodes identified by the pathologist in the PLND specimen) [26]. Published outcomes following attempts at controlling the regional lymphatics for bladder cancer date back to 1932 when the routine inclusion of a pelvic lymph node dissection at the time of radical cystectomy was initiated [27]. Prior to the incorporation of bilateral PLND with RC, loco-regional failure rates were as high as 50%, demonstrating the therapeutic benefit to an anatomic PLND. Jewett hypothesized that 25% to 30% of recurrences in pelvic lymph nodes were due to inadequate lymphadenectomy. Unfortunately, this concept remains elusive, as demonstrated in contemporary population-based registry databases, as up to 40% of patients had no nodes removed in an analysis reported in 2003 [28]. Despite modest improvements, the most current data reported in 2009 suggest that continued education is required to convince urologists of the benefit of bilateral PLND with RC [29]. RC is also indicated as primary therapy for some patients with non-muscle-invasive bladder cancer (NMIBC) when there is large-volume Ta disease that cannot be managed with transurethral resection, CIS that cannot be managed with intravesical BCG due to the volume of disease or intolerance of BCG, and for some patients with
high-grade T1 disease. RC is the standard of care for patients with high-grade NMIBC when BCG has failed the patient. This is discussed in detail in Chapters 8 and 9.

**Perioperative management**

Many patients undergoing cystectomy have significant comorbidities often related to long-term tobacco use. Pre-operative evaluation and optimization of cardiac and pulmonary function are crucial in reducing post-operative complications. Cardiac clearance is obtained for most patients with appropriate stress testing. Pulmonary function testing is not routinely performed unless a decision has to be made regarding the suitability of the patient for the surgery. Mechanical and antibiotic bowel preparations have been traditionally recommended in order to cleanse the bowel for urinary diversion, however this practice may lead to dehydration, the alteration of normal bowel flora, and electrolyte disturbances. Retrospective studies have shown that the elimination of bowel preparation prior to radical cystectomy shows no difference in perioperative outcomes, including gastrointestinal complications [30, 31]. In addition, a meta-analysis performed to investigate the effect of bowel preparation in reducing the incidence of post-operative complications in patients undergoing elective colorectal procedures showed no differences in the rates of mortality, reoperation, peritonitis, and wound infection [32].

Nasogastric (NG) decompression is also commonly used post-operatively following cystectomy in an attempt to decompress the stomach, prevent emesis and aspiration, and to minimize the risk of bowel anastomotic leak or dehiscence. However, data suggest that NG tube decompression is unnecessary and may, in fact, increase complication rates [33]. Donat et al. described an overnight-only NG tube (NGT) with use of metoclopramide, demonstrating the benefits of an early return of bowel function and reduced pulmonary complications [34]. In a study including 430 patients, Inman et al. demonstrated prolonged NGT decompression was associated with prolonged time to GI recovery. Omission of NGT in these patients was associated with a shorter time to return of flatus and a reduced length of stay [35]. Numerous other studies including general surgery cases in addition to radical cystectomy have shown that bowel resection can be safely performed without the use of post-operative NGT decompression [36, 37]. A meta-analysis involving 26 trials including nearly 4000 patients established the non-necessity of routine NGT decompression by demonstrating a higher incidence of pulmonary complications with no clinical benefits such as reduction in gastrointestinal complications or length of stay [38].

Fasting and adherence to a clear liquid diet prior to surgery has long been the dogmatic approach to a patient undergoing surgery requiring bowel resection. In response to fasting, however, insulin resistance can develop and, in fact, increase post-operative complications. Pre-operative carbohydrate loading has been shown to play an important role in decreasing hospital stay and in recovery after elective bowel surgery. Pre-operative administration of oral carbohydrate energy-containing fluids can help reduce insulin resistance and has been associated with a reduced length of stay following elective surgery [39].

Use of perioperative opioids for pain control is a significant contributor to post-operative ileus. Opioid receptors are distributed throughout the gastrointestinal tract, and most opiates have mu receptor activity that inhibits gastric motility and delays emptying [40]. Alvimopan is a mu-opioid receptor antagonist that has been shown in multiple randomized trials to accelerate the return of bowel function following bowel resection. Results from five multi-center, double-blind randomized placebo-controlled trials including 1877 patients, as well as a meta-analysis of three of the trials including a pooled modified intention-to-treat population of 1388 patients have documented the benefits of Alvimopan in reducing time to bowel recovery and hospital discharge in patients undergoing abdominal surgery [41]. A recent phase IV double-blind, placebo-controlled study involving the use of Alvimopan in patients undergoing radical cystectomy for bladder cancer confirmed the benefits by demonstrating quicker bowel recovery and shorter hospital stays compared with those who received the placebo. There were significantly fewer episodes of post-operative ileus in the Alvimopan group (8.4% vs 29.1%; \( p < 0.001 \)) with no increase in adverse effects [42].

Given the current available data we have adopted an evidence-based multimodal care pathway (commonly referred to as ERAS-enhanced recovery after surgery) aimed at providing optimal perioperative care for patients undergoing radical cystectomy. The goal of this protocol is to minimize perioperative gastrointestinal...
complications and reduce hospital stay while improving the perioperative experience. Given the evidence against the use of bowel preparation, and the potential for increasing complications, we have omitted all bowel preparation prior to surgery unless there is a pre-operative plan for using the colon for continent cutaneous diversion. A high-protein, high-carbohydrate liquid drink is recommended for a few days prior to surgery, without any recommendation for withholding intake the day prior to surgery, i.e. a regular diet is maintained up to the night prior to surgery. A pre-operative counseling session as well as educational classes aimed at detecting psychosocial barriers that may impede early recovery can help improve outcomes with this surgery. Standardized pre-operative educational classes may also provide a platform for improvement of patient compliance and understanding of the post-operative milestones required prior to discharge. Alvimopan is given in the pre-operative holding area 30–60 minutes prior to the operation. Subcutaneous heparin is given in the pre-operative holding area for thromboprophylaxis. Our enterostomal therapy nurse marks all patients for a stoma in cases of cutaneous incontinent diversion.

Intraoperatively, blood loss and bowel manipulation are kept to a minimum. Intraoperative fluid intake is maintained by warm lactated Ringer's solution with albumin boluses, if needed. Fluid intake is minimized while the ureters are clipped. Intravenous acetaminophen acetate and ketorolac are started intraoperatively if there are no contraindications, and opioid use is kept to a minimum. NGT (if used) is removed at the conclusion of surgery and the patient is then transferred to the ward on telemetry unless there is any indication for admission to ICU.

**Post-operative management**

Alvimopan is continued post-operatively and neostigmine is administered to facilitate bowel function recovery. Both of these medications are discontinued once the patient has a bowel movement. A magnesium-based lactulose or bisacodyl (suppository) is started on post-operative day (POD) one and continued daily until bowel movement. Prophylaxis for stress ulcer (proton pump inhibitor and H2 receptor blocker) and nausea and vomiting (ondansetron and/or metoclopramide) is administered regularly. Patients are encouraged to ambulate, starting on post-operative day one. Sips of liquids (including high-carbohydrate, high-protein fluids) are started early on the evening of surgery if tolerated. On POD 1, patients are started on a regular diet (tailored for post-operative surgical patients) provided the patient has no nausea, vomiting, or abdominal distention regardless of gas passage or bowel movement. If the patient is not tolerating oral food by POD 6 or 7 and there is no bowel activity, parenteral nutrition is considered.

**Pain management**

Ketorolac and oral acetaminophen acetate are used around the clock post-operatively for 48 hours with opioid medication given for breakthrough pain. Para incisional subfascial catheters (positioned between the rectus muscle and the posterior rectus sheath) with constant local anesthetic (0.2% Ropivacaine) release are also used for local pain control. Oral opioid pain medications are started on POD 1, and most patients transition to oral analgesics only by POD 3.

**Discharge and post-operative care**

Patients are considered ready for discharge when they have a bowel movement, adequate pain control with oral medications, adequate mobility, normal electrolytes, and adequate oral intake of at least one liter per day. In addition, prophylactic antibiotics are started and continued for three weeks or until catheter/stent removal, although there is a lack of strong evidence for its prolonged use. Patients who manifest early signs of hyperchloremic metabolic acidosis are started on oral sodium bicarbonate replacement. Patients are scheduled to return to clinic one week after discharge for the first post-operative visit and laboratory check. At Baylor, we obtain a gravity cystogram for patients with a neobladder and begin intermittent plugging of the Foley in order to achieve some passive expansion of the reservoir. In order to ensure adequate hydration during the early post-discharge period and to decrease readmission for dehydration and electrolyte abnormalities, we arrange for patients at USC to receive 1 liter of intravenous fluid therapy at home through a short peripherally inserted central line. All patients are
seen at three weeks post-operatively for removal of catheters, drains and stents and pouch training in cases of orthotopic diversion.

**Extent of lymph node dissection**

A brief overview is provided in this section and the reader is directed to Chapter 15, which reviews this topic in detail. There is strong consensus that every patient undergoing RC should have a bilateral PLND incorporating all of the potential node-bearing tissue in the true pelvis distal to the common iliac bifurcation. However, controversy regarding the proximal extent of the dissection necessary to obtain optimal pathologic staging of the lymph nodes and maximal tumor control persists. This is, in large part, due to the lack of level I evidence to guide urologists and variations in surgical education and experience.

Several multi-institutional studies have reported improved outcome in patients undergoing an extended lymph node dissection, as defined by the number of lymph nodes identified pathologically (reviewed in [43]). In a study of 447 patients, Leissner et al. found a 20% improvement in overall five-year survival [44]. Estimated five-year survival probabilities for patients with organ-confined UCB and ≥ 16 lymph nodes were 85% compared to 65% for patients with ≤ 15 lymph nodes resected. Control of local disease was also superior in patients having a more extensive, compared to a limited, nodal resection (17% recurrence compared to 27% recurrence) [44].

At Memorial Sloan-Kettering Cancer Center (MSKCC), the recent experience with radical cystectomy was reviewed to determine the relationship between the extent of lymphadenectomy and staging, disease control and prognosis [45]. A total of 322 patients with UCB treated by radical cystectomy were reviewed; 258 patients demonstrated no evidence of node involvement while 64 patients had regionally involved lymph nodes. Overall five-year survival was improved in patients with a greater number of lymph nodes examined regardless of the status of the nodes. For the node-negative group, five-year survivals of 80%, 60%, and 20% were observed for patients with greater than 8, 4 to 7, and 0 to 3 nodes, respectively examined following radical cystectomy. For patients with positive node disease, a 50% versus a 20% five-year survival was seen if greater than versus less than 11 nodes were examined [45]. Koppie and colleagues evaluated over 1000 consecutive patients from 11 different surgeons with different extents of dissection. They observed that the probability of survival continued to rise with increasing numbers of lymph nodes removed, up to a threshold of 23 nodes [46].

Poulsen et al. reported their group’s experience with 194 patients treated by either limited or extended lymph node dissection at the time of radical cystectomy [47]. These investigators found a significantly greater number of nodes were removed with the extended dissection (mean 25, range 9 to 67) compared to the limited dissection (mean 14, range 5 to 30). The extended dissection identified a larger percentage of patients with nodal metastases (improved staging). For patients where the primary UCB was confined to the bladder wall, positive nodes were identified in patients having the extended (12.5%) compared to the limited (8.9%) resection. The potential contribution of extended, compared to limited, dissection to improve cancer control was suggested by a recurrence-free survival at five years for the subgroups with tumors confined to the bladder wall (tumor stage pT2b or less) (85% versus 64%, \( p < 0.02 \)) and without evidence of lymph node metastasis (stage pT3a or less, pN0) (90% versus 71%, \( p < 0.02 \)). Similarly, local recurrence rates (2% versus 7%) and distant metastatic risk (10% versus 21%) were improved in patients undergoing an extended dissection compared to a limited dissection. These data were corroborated in a recent update of this series which highlighted the fact that one-third of patients had nodal metastasis proximal to the anatomical limits of a node dissection limited to the true pelvis only [14]. In summary, these data provide compelling evidence that an extended node dissection may provide a survival benefit for patients undergoing radical cystectomy for UCB. Nevertheless, the inherent aforementioned biases and lack of a control arm limits the conclusions drawn from these studies.

There are two randomized trials comparing extended (bilateral common iliac and pre-sacral) plus standard (external and internal iliac and obturator nodes) versus standard only. The first, conducted by the Association of Urogenital Oncology and the German Cancer Association, completed accrual and the second,
a National Cancer Institute-funded trial (SWOG 1011 NCT01224665) conducted in North America, is ongoing. The results of these two important trials will contribute substantially to our understanding of the appropriate anatomic limits of PLND in patients undergoing RC.

Technique: radical cystectomy with extended pelvic lymph node dissection

Radical cystectomy in the male patient includes removal of the bladder, the perivesical fat, the prostate, seminal vesicles, and pelvic lymph nodes. In the female, the term anterior pelvic exenteration is often used to include removal of the uterus, cervix, fallopian tubes, ovaries, and the anterior vaginal wall. A distal ureteral margin is usually sent for frozen section to ensure the absence of dysplasia or frank carcinoma, although its relation to outcome is controversial. Nerve-sparing techniques in the male are identical to those with prostate cancer surgery and include preservation of the neurovascular bundles just lateral to the prostatic capsule [48]. Some investigators have described prostate- or prostate-capsule-sparing techniques to improve erectile function and continence, however this must be tempered with the more than 50% chance of finding incidental involvement of the prostate with either urothelial carcinoma or adenocarcinoma [49, 50]. Urethrectomy is rarely performed concomitantly in the male since, in the vast majority of cases, a negative urethral margin can be achieved. Patients with a positive urethral margin on final pathology can be considered for secondary urethrectomy. In the female patient the reproductive organs are often removed, although risk of involvement in female patients who undergo anterior pelvic exenteration for urothelial carcinoma of the bladder is less than 10%, with the vagina the most commonly involved site [51]. Patients with lower stage disease and no evidence of disease involving the anterior vaginal wall on bimanual examination can be considered for vaginal-sparing techniques, which can offer the preservation of sexual function [52].

Patient positioning

The patient is placed supine with the iliac crest at the level of the fulcrum of the operating table (Figure 11.1). Female patients are placed in a frog leg or low lithotomy position to allow access to the vagina intraoperatively. The patient is hyperextended to allow better exposure to the pelvis, with care being taken to protect the arms and adequately pad all sensitive areas. The patient is placed in a reverse Trendelenburg position to level the abdominal wall parallel to the floor, which helps keep some of the small bowel contents within the abdominal cavity. Arterial and central lines are placed as necessary and an orogastric tube is placed, which is removed at the conclusion of the case. The patient is prepped per routine guidelines and in women the vagina is fully prepped. After draping, a Foley catheter is placed in the bladder and left to gravity drainage. A right-handed surgeon usually stands on the patient’s left-hand side of the operating table.

Incision and intra-abdominal exposure

Through an infraumbilical midline incision, the skin and the subcutaneous tissues are incised. The anterior rectus fascia is identified and incised and the rectus muscles are retracted laterally. The posterior rectus fascia and the peritoneum are entered and self-retaining retractors are placed. Manual palpation of the pelvis and retroperitoneum is performed to look for palpable

Figure 11.1 Patient positioning for cystectomy. Note that the iliac crest is located at the level of the fulcrum of the operating table. Source: Stein & Skinner, Br J Urol Int. 2004; 94: 197. Reproduced with permission from Wiley.
lymphadenopathy and to make sure the bladder is not fixed to the pelvic sidewalls. Next, the posterior peritoneum is incised, taking down the peritoneal attachments to the small bowel mesentery (Figure 11.2). The right colon is not mobilized unless a continent cutaneous reservoir using the colon is planned. It may be necessary to mobilize the mesentery of the terminal ilium off the retroperitoneum in order to allow maximal mobility for neobladder reconstruction. The rectosigmoid is mobilized along the avascular line of Toldt and its mesentery is elevated off the sacral promontory up to the level of the inferior mesenteric artery (IMA) in order to allow the left ureter to pass easily to the right side and to expose the lower retroperitoneum for the extended lymphadenectomy (Figure 11.3). The ureters are dissected into the deep pelvis where they are clipped and divided with the distal circumferential tip sent for frozen section analysis.

Next, we place a self-retaining retractor and pack the small bowel into the epigastrium using lap pads.

**Boundaries and techniques of pelvic lymphadenectomy**

A meticulous pelvic lymph node dissection is a critical part of the procedure. The extended pelvic lymph node dissection is initiated approximately 3 cm above the aortic bifurcation at the level of the IMA (superior limit of dissection). The dissection extends laterally over the aorta and vena cava to the genitofemoral nerve on either side, which represents the lateral limits of dissection. The para-aortic and para-caval nodal tissue is removed and the proximal tissue is clipped, with care being taken not to dissect too deeply in the interaortocaval area. Frequently, small anterior tributary veins originate from

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**Figure 11.2** The peritoneal attachments of the small-bowel mesentery (dotted line) are incised to expose the lower retroperitoneum and pelvis. The bowels are packed inside the abdomen. Source: Stein & Skinner, *Br J Urol Int*. 2004; 94: 197. Reproduced with permission from Wiley.

**Figure 11.3** The sigmoid mesentery is mobilized off the sacral promontory, common iliac vessels, and distal aorta up to the origin of the inferior mesenteric artery to allow exposure for an extended pelvic lymph node dissection. Source: Stein & Skinner, *Br J Urol Int*. 2004; 94: 197. Reproduced with permission from Wiley.
the vena cava just above the bifurcation, which should be clipped and divided. Hemoclips are generally used at the superior, inferior, and lateral limits of the dissection while the rest of the vessels are circumferentially skeletonized. In men, the spermatic cord is spared and retracted laterally while in women the infundibulopelvic ligament and ovarian vessels are ligated and divided in order to include the ovaries with the specimen.

Next, all fibroareolar and lymphatic tissue is peeled off the common iliac arteries, with the dissection extending out laterally to the genitofemoral nerve and then sweeping medially down over the sacral promontory into the hollow of the sacrum. The genitofemoral nerve is preserved although small branches that course more medially and that are intimately associated with the iliac arteries are excised. Care must be taken to avoid injury to the left common iliac vein, which courses directly posterior to the right common iliac artery. The sacral promontory is skeletonized and the pre-sacral nodes are removed. The left median sacral vein drains into the left common iliac vein and must be recognized and often clipped to avoid avulsion during removal of the pre-sacral nodes.

Once the proximal portion of the lymph node dissection is completed, a finger is passed under the peritoneum proximally over the external iliac artery and vein distally to the femoral canal. The opposite hand is used to connect with the proximal dissection from above and the peritoneum is divided medial to the spermatic cord while the vas deferens is clipped and divided. In female patients, the peritoneum is divided lateral to the infundibulopelvic ligament and the round ligament is clipped and divided in the same anatomic location as the vas deferens. The external iliac artery and vein are then circumferentially mobilized, freeing up all of the lymph-node-bearing tissue to join up with the proximal limits of dissection over the common iliac vessels. Care must be taken to recognize and ligate an accessory obturator vein, which originates from the inferomedial aspect of the external iliac vein in approximately 40% of patients. There is often a psoas branch arising from the lateral aspect of the proximal external iliac artery, which must be clipped and divided. The distal limits of the dissection are the circumflex iliac vein crossing anterior to the external iliac artery distally, the genitofemoral nerve laterally, and the lymph node of Cloquet situated on Cooper’s ligament medially. The lymph node of Cloquet (also known as the node of Rosenmüller) is removed and the iliac vessels are carefully retracted medially in order to clear the obturator fossa. This can be facilitated by passing a small gauze sponge lateral to the external iliac vessels and medial to the psoas muscle to aid in dissecting the obturator fossa, sweeping all fibroareolar and lymphatic tissue toward the bladder. Source: Stein & Skinner, Br J Urol Int. 2004; 94: 197. Reproduced with permission from Wiley.

Figure 11.4 Technique of passing a small gauze sponge lateral to the external iliac vessels and medial to the psoas muscle to aid in dissecting the obturator fossa, sweeping all fibroareolar and lymphatic tissue toward the bladder. Source: Stein & Skinner, Br J Urol Int. 2004; 94: 197. Reproduced with permission from Wiley.
vessels) is dissected and the lumbosacral branch of the sciatic nerve is identified (Figure 11.6a). The lymphatic tissue is sent as separate packets and includes the para-aortic, para-caval, the common iliacs, pre-sacral nodes, external iliacs, the pre-sciatic nodes (fossa of Marcilles), and the obturator/internal iliac nodes (Figure 11.6b).

The lateral and posterior bladder pedicles
After skeletonizing the proximal internal iliac artery and vein, the lateral vascular pedicle of the bladder is stretched, clipped, and divided down to the area of the endopelvic fascia. The left hand lifts the bladder anteriorly and caudally in order to align the lateral pedicle of the bladder, with identification of individual branches off the anterior branch of the internal iliac artery (Figure 11.7). The first branch to the bladder (the superior vesical artery) is clipped and divided and the rest of the branches of the lateral pedicle can be ligated using a tissue sealant device. The entire pedicle may also be ligated and divided with an appropriate vascular device. Care must be taken to medially retract the rectum using the left hand to avoid a rectal injury. The endopelvic fascia just lateral to the prostate may then be incised, which helps identify the distal limit of the lateral pedicle.

Once the lateral pedicles have been taken down, the bladder is retracted anteriorly and the pouch of Douglas is exposed, with the surgeon and assistant retracting the peritoneum using sponge gauze. The peritoneum in the area of the cul-de-sac is incised and the rectum is bluntly dissected off the posterior layer of the Denonvilliers’ fascia (Figure 11.8). This plane is developed all the way to the lateral pedicles of the prostate (Figure 11.9). The tissue is bluntly directed anterolaterally with the index finger in order to create a collar of tissue on either side of the bladder (Figure 11.10). If the rectum is adherent to the posterior bladder wall (such as in cases of prior pelvic surgery or pelvic radiation therapy), this dissection must be done sharply under direct vision to avoid blunt entry into the rectum. At this point the posterior pedicles are taken down using a tissue sealant device down to the prostatic apex. Clips or a vascular stapler may also be used. In men undergoing a nerve-sparing procedure, the neurovascular complex is released by incising the lateral prostatic fascia. Care is taken not to use cautery near the neurovascular bundles in order to avoid injury to the delicate nerve fibers. The posterior pedicle can be taken down just lateral to the seminal vesicles. The neurovascular bundles are released laterally at the apex.
of the prostate, and the rest of the pedicle is taken down with hemoclips in a retrograde manner to match up with the posterior dissection. Care must be taken to protect the rectum during the division of the posterior pedicle. If a rectotomy occurs and there is no gross contamination, a two-layered closure with absorbable suture followed by an omental interposition is recommended.

**Anterior apical dissection in the male patient**

The endopelvic fascia and the lateral prostatic fascia are incised anteriorly up to the puboprostatic ligaments, which are sharply incised enough to expose the apex of the prostate. The dorsal venous complex is ligated with a figure of 8 2-0 Vicryl suture and divided. The lateral pillars of the urethra are taken down gently and the urethra is incised at the apex of the prostate. In cases of orthotopic diversion, a series of 4–6 2-0 monocryl sutures are placed into the membranous urethra as the assistant provides traction on the prostate and the anterior suture should incorporate the fascia of the dorsal venous complex. The Foley catheter is then clamped proximally and distally and the catheter is divided between the clamps, followed by placement of two posterior urethral stitches with 2-0 Monocryl for a total of 6–8 urethral sutures. The remaining lateral pedicles of the prostate are then taken down with clips (in cases of nerve sparing) or a tissue sealant device. The apical urethral margin is then sent for frozen section analysis if pre-operative prostatic urethra biopsies have not been done or these biopsies showed CIS.
Posterior dissection in the female

When developing the posterior pedicles in women, the posterior vagina is incised at the apex just distal to the cervix and the cardinal ligaments are taken down. A lubricated sponge stick in the vagina directed cephalad allows precise identification of the apex of the vagina. The vaginal wall is then circumferentially incised and the cervix, along with the uterus, fallopian tubes, and ovaries (if present and being removed) are included in the specimen (Figure 11.11). The tissue sealant device is then used to divide the anterior vaginal wall, which is included in the specimen unless a vaginal-sparing technique is being performed. If the bladder tumor is not located posteriorly or at the trigone, then a female organ-sparing procedure may be performed by incising the peritoneum between the posterior bladder and uterus and then developing the plane between the anterior vaginal wall and the posterior bladder. It is critical to avoid entry into the bladder or end up with a positive margin during this maneuver, since there is no natural fascial plane between the two structures.

If there is copious fat lateral to the vagina, this is ligated first with the tissue sealant device. This aids with the precise identification of the lateral wall of the vagina and also significantly reduces blood loss. The dissection is carried just distal to the vesicourethral junction. Palpation of the Foley catheter balloon assists in identifying the bladder neck/urethral junction. In the case of orthotopic diversion, the plane between the anterior vaginal wall and the urethra is bluntly developed. The

Figure 11.9 Illustration of the formation of Denonvilliers’ fascia. Note that it is derived from a fusion of the anterior and posterior peritoneal reflections. Denonvilliers’ space lies behind the fascia. To properly enter this space and facilitate mobilization of the anterior rectal wall off Denonvilliers’ fascia, the incision in the cul-de-sac is made close to the peritoneal fusion on the anterior rectal wall side, and not on the bladder side. Source: Stein & Skinner, Br J Urol Int. 2004; 94: 197. Reproduced with permission from Wiley.

Figure 11.10 After the peritoneum of the cul-de-sac has been incised, the anterior rectal wall is swept off the posterior surface of Denonvilliers’ fascia. The tissue is bluntly directed anterolaterally with the index finger in order to create a collar of tissue on either side of the bladder. This effectively defines the posterior pedicle, which is taken down with a tissue sealant device or a vascular stapler. Source: Stein & Skinner, Br J Urol Int. 2004; 94: 197. Reproduced with permission from Wiley.
distal urethra is left intact along with the endopelvic fascia and the urethral support mechanism. The catheter can, at this point, be removed and the bladder neck clamped and divided. The vagina is usually reconstructed by a clam shell or side-to-side technique and pexed to the sacrum using a soft prolene mesh using permanent suture to prevent an enterocele. A well-vascularized omental pedicle graft is mobilized off the colon and secured on top of the reconstructed vagina to prevent fistulization. If a continent cutaneous diversion or ileal conduit is planned, the urethra can be removed en bloc by dividing the pubourethral ligaments and taking down the endopelvic fascia. The anterior vaginal wall is dissected further distally and incised around the urethral meatus. The vaginal cuff is closed as previously described. Alternatively, the urethra can be dissected transvaginally to meet up with the dissection from the pelvis. A more detailed description of techniques for female cystectomy is given in Chapter 12.

**Outcomes**

Patients with organ-confined, node-negative disease (≤ T2N0) have overall disease-specific survival in the 60–85% range over five years and ten years [53, 54]. Patients with extravesical disease have five-year disease-specific survival in the 50% range while patients with node-positive disease who have undergone a thorough lymph node dissection can still expect a 30% chance of long-term recurrence-free survival. Neoadjuvant cisplatin-based chemotherapy has been shown to increase survival and is discussed in depth in Chapter 25. Patients with significant disease following neoadjuvant cisplatin-based chemotherapy have very poor prognosis. Significant factors influencing outcome include soft tissue margins and lymph node involvement [55]. Local recurrence is not common (<15%) in large series from experienced centers. Perioperative mortality rates are 1–3% at large centers but can be twice that in community hospitals with less experience [5]. Perioperative complications, however, are far more frequent, particularly when prospectively annotated. In the prospective series from Memorial Sloan-Kettering Cancer Center, 64% of patients undergoing radical cystectomy experienced at least one perioperative complication within 90 days of surgery and 13% experienced a high-grade complication (Grade 3 or higher) [56].

In the series from Mansoura (Egypt), where more than half the cases (59%) are squamous cell carcinomas, the overall five-year survival is 48%. The outcome for salvage cystectomy is generally worse than that of primary cystectomy in non-irradiated patients, although robust data are not available. In select cases, surgery can offer a prolonged survival even in the presence of gross nodal disease. In a series of 84 patients from Memorial Sloan-Kettering, a ten-year survival rate of 24% was noted in this group [57].

In the updated experience from the University of Southern California (USC), 2039 patients with primary urothelial carcinoma of the bladder underwent radical cystectomy with intent to cure between 1971 and 2009. The cohort consisted of 1616 (79%) men with a median age of 67 years and a median follow-up of
12 years, during which 636 (31%) patients recurred and 1236 (61%) died. The five-year recurrence-free (RFS) and overall survival (OS) probabilities were 64% and 55%, respectively. From a staging perspective, 1149 (56%), 424 (21%), and 466 (23%) patients had organ-confined, extravesical and node-positive disease, respectively. The five-year RFS probabilities for these stages were 81%, 54%, and 32%, respectively \( p < 0.001 \). Corresponding five-year OS probabilities were 72%, 40%, and 28%, respectively \( p < 0.001 \).

Gender \( p = 0.005 \), stage, tumor upstaging (46% upstaged), surgical margin status (5% positive), lymphovascular invasion status (29% positive), and neoadjuvant (6% administered) and adjuvant (21% administered) chemotherapy \( p < 0.001 \) were associated with RFS. In this large cohort, recurrence data were available on 1817 patients. 81 (4.5% of all recurrences) patients had pelvic recurrence without distant metastasis, and 437 (24.1% of all recurrences) recurred at distant sites without/with pelvic recurrence at last follow-up. Only 3.8% of patients with pT2N0 disease experienced pelvic recurrence (without distant metastases) as opposed to 7.4% of those with pT3N0 and 9% of node-positive patients.

**Complications**

Radical cystectomy is associated with significant perioperative and long-term morbidity. The estimated 30-day mortality rate is 1.6–3%, with the most common causes being cardiovascular, thromboembolic events and infection [58]. Hospital readmissions range from 25–40% over the first 30 days, with the most common causes being dehydration, electrolyte disturbances, and infection. The overall complication rate has been reported in detail by Shabsigh et al. and Donat et al. in the large series from Memorial Sloan-Kettering with 2/3 of patients experiencing at least one complication, the majority being Grades 2–5 [56, 59]. Lawrentschuk et al. undertook a comprehensive review of the literature reporting complications associated with RC [60]. Surgeon and hospital volume are both associated with perioperative morbidity and mortality risk [61–63]. Enhanced Recovery After Surgery (ERAS) protocols (see above) are designed to reduce the risk of perioperative morbidity and to date have contributed to significant reductions in the length of stay but complication rates remain high [64].

**Conclusion**

Radical cystectomy with a thorough pelvic lymph node dissection remains a challenging operation with considerable morbidity. Surgical technique along with surgeon and hospital experience is critical in optimizing clinical outcomes. Radical cystectomy still provides the best survival rate with the lowest chance of local recurrence for high-grade invasive bladder cancer. Evidence-based perioperative enhanced recovery pathways can help minimize morbidity and hasten recovery in patients undergoing cystectomy.

**Useful web link**


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CHAPTER 12
Cystectomy in the female patient

Ryan Werntz, Georgios Gakis, Theresa Koppie, and Arnulf Stenzl

Department of Urology, University Hospital Tübingen, Tübingen, Germany

KEY POINTS

- Although the incidence of bladder cancer is higher in men, mortality is higher in women.
- Various factors contribute to differences in survival between men and women after radical cystectomy, including hormonal factors, predisposed differences in the metabolism of carcinogens, and anatomical differences in bladder architecture.
- In both men and women, the appropriate treatment for recurrent high-grade or muscle-invasive bladder cancer is radical cystectomy with pelvic lymphadenectomy.
- For the female patient, the treating surgeon must be prepared to (1) perform an anterior exenteration in the event of locally advanced disease, (2) be familiar with vaginal reconstruction and surgical management of the female urethra to prevent either post-operative incontinence or urinary retention associated with orthotopic urinary diversions, and (3) understand the impact of pelvic surgery on female sexual function.
- The choice of surgical intervention must be specific to female anatomy and optimize local cancer control as well as sexual and urinary function.

Introduction

According to the American Cancer Society, about 72,570 new cases of bladder cancer are diagnosed each year (54,610 in men, 17,960 in women) and 15,210 deaths from the disease occur per year (10,820 in men, 4390 in women) [1]. Men are at higher risk for developing bladder cancer than women, most likely because of higher rates of smoking and the higher likelihood of workplace exposure to environmental toxins (i.e., nitrogen) [2]. Although the incidence of bladder cancer is more than twice as high in men, a sharper increase in the incidence in women has been noted in recent years [1].

Although incidence is higher in men, mortality is higher in women, possibly due to delayed diagnosis [3]. Stage-specific investigations have shown that when stratified by disease stage, women have poorer outcomes than men [4]. A recent multi-center study of 2483 patients treated with radical cystectomy (RC) at tertiary referral centers reported that five-year cancer-specific survival was significantly lower in women compared with men (60% vs. 66%), and female sex contributed independently to lower cancer-specific survival after RC. These data underscore the significant impact that sex-related differences have on oncologic outcomes after RC.

Various factors contribute to differences in survival between men and women after RC, including hormonal factors [5], predisposed differences in the metabolism of carcinogens [6], and anatomical differences in bladder architecture (i.e., the thickness of the muscularis propria), which might facilitate tumor cell penetration.
into deeper layers [7]. In recent animal studies, after exposure to the bladder carcinogen N-butyl-N-(4-hydroxybutyl) nitrosamine, knockout mice lacking the androgen receptor were at significantly lower risk for developing bladder cancer than their wild-type counterparts. Another observational study found that, for postmenopausal women, early age at menopause (<45 years) compared with late age at menopause (>50 years) was associated with a significantly increased risk of bladder cancer [8].

Anterior exenteration and pelvic lymphadenectomy

RC with anterior pelvic exenteration and pelvic lymph node dissection (PLND) is the mainstay of treatment for muscle-invasive bladder cancer [7, 9]. While the diagnostic and therapeutic value of a standard PLND is beyond question, the anatomical extent remains controversial [7, 9]. (This is reviewed in detail in Chapter 15.)

According to current guidelines [7], a “standard” PLND for bladder cancer is defined as the removal of all lymphatic tissue surrounding the common iliac vessels cranially, to the genitofemoral nerve laterally, the circumflex iliac vein and node of Cloquet down to the lacunar ligament distally, and the hypogastric vessels along with the obturator fossa medially. By dissecting down to the lacunar ligament, lymph nodes receiving lymphatic drainage from the mid and distal third of the urethra can also be removed. Although an extensive resection of pre-sacral lymphatic tissue might be beneficial for staging purposes [10], it might destroy the sympathetic fibers of the hypogastric plexus. The impact of the common iliac dissection on these crossing sympathetic fibers remains to be elucidated. Figure 12.1 demonstrates the intraoperative anatomy of extended and superextended PLND templates at RC.

Surgical considerations in preoperative planning of orthotopic diversions in female patients

In both men and women, the appropriate treatment for recurrent high-grade or muscle-invasive bladder cancer is RC with bilateral pelvic lymphadenectomy [7, 9]. When considering RC in the female patient, the treating surgeon must be prepared to (1) perform an anterior exenteration in the event of locally advanced disease, (2) be familiar with vaginal reconstruction and surgical management of the female urethra to prevent either post-operative incontinence or urinary retention associated with orthotopic urinary diversions, and (3) understand the impact of pelvic surgery on female sexual function.

Age

Increased age used to be a contraindication for performing orthotopic urinary diversions in women because it was believed that reduced urethral length might impair post-operative continence and that the tumor might continuously infiltrate the urethra. Thanks to better understanding of the anatomy of the female urethra [11, 12], orthotopic urinary diversion has evolved to the diversion of choice for many female patients undergoing RC for muscle-invasive bladder cancer [13–16]. Figure 12.2 delineates the anatomy of an ileal neobladder made of 40-cm ileal length. Folding (according to Goodwin’s principle) the vertically implanted ureters into the reservoir (according to the Wallace technique) near the urethra enables easy instrumentation of the upper tract during follow-up. Although older patients may take longer to achieve daytime and night time continence,
diurnal continence rates are similar to those of younger patients [17]. Beside tumor characteristics, successful neobladder reconstruction in women depends on functional status of the lower urinary tract (i.e., preexisting incontinence, prior pelvic irradiation), medical comorbidities, renal function, and manual dexterity [18]. Biological age, rather than chronological age, should guide the choice of appropriate urinary diversion [17]. For an extremely functional and motivated octogenarian, an orthotopic neobladder may be an appropriate option. Conversely, for a 60-year-old woman with significant comorbidities and poor overall functional status, an ileal conduit may be the option that allows her to recover more expeditiously after surgery [18].

**Manual dexterity**

Manual dexterity is an important consideration in patients scheduled for orthotopic neobladders because the ability to perform self-catheterization per urethra may affect recovery, long-term health, and overall quality of life. In some series, routine clean intermittent catheterization rates in women after cystectomy are as high as 58% [19]. Clinicians must appropriately counsel their patients, and patients must be willing and able to perform clean, intermittent catheterization daily if retention occurs [18].

**Functional aspects of orthotopic neobladder reconstruction in female patients**

**Anatomy of the female urethra**

In female patients, the urethral length is approximately 3 to 4 cm, traversing from the bladder neck to the vaginal vestibule. The urothelium covers the proximal third of the urethra and gradually changes to non-keratinized squamous epithelium in the distal two-thirds. In the proximal urethra, small submucosal glands open into the urethra. In the distal urethra, the submucosal glands group together on either side of the urethra, thereby forming the Skene glands. The mucosal and submucosal tissue of the urethra are estrogen-dependent and aid in maintaining urethral closing pressure. Importantly, the submucosa contains vascular elements that contribute to resting urethral tone along the length of the female urethra. When engorged, these submucosal vessels cause coaptation of the urethra mucosa and contribute to a watertight seal [20] As women age, atrophy of the mucosa and submucosa may contribute to stress urinary incontinence. Along the proximal four-fifths of the urethra there are two layers of smooth muscle. The innermost layer is the longitudinal smooth muscle fibers. Contraction of this muscle may aid in opening the urethral lumen when micturition is initiated, however,
this theory has not been proven. Next, the inner circular smooth muscle lies superficial to the longitudinal layer. When this muscle contracts, the smooth muscle fibers contract concentrically, effectively constricting the urethral lumen, aiding in continence. At the bladder neck, superficial to the smooth muscle fibers, the urethra is supported by a U-shaped reflection of detrusor smooth muscle that constricts to close the urethral lumen [20]. Moving distally, beginning at the termination of the detrusor fibers and ending at the mid urethra, one finds the striated urethral sphincter. This muscle layer is composed of slow-twitch fibers that form an omega-shaped mechanism surrounding both the urethra and inner longitudinal and circular layer smooth muscles [20]. These slow-twitch fibers are well suited for providing a constant tone and are under volitional control, making this muscle very important for continence. The striated sphincter, with the circumferential fiber orientation, ends at the distal two-thirds of the urethra, but is continuous with the striated muscles of the urethrovaginal sphincter and compressor urethrae. These sphincters end in the distal three-fourths of the urethra [20]. The compressor urethra muscle fibers pass only anterior to the urethra and insert into the perineal membrane near the pubic ramus. When this muscle contracts, it compresses the urethra against the support behind the urethra (vagina), constricting the lumen. The striated urethrovaginal sphincter surrounds both the vagina and the urethra and aids only marginally in continence. This complex of striated muscle fibers will be referred to as the rhabdosphincter complex.

Continence
Continence has slightly different mechanisms in women than in men. In women, stress urinary continence occurs when bladder pressure is greater than urethral resistance. Women who have orthotopic bladder substitution remain affected by this relationship. It has long been known that women who undergo a distal urethrectomy for cancer, stricture, or diverticula maintain continence as long as the middle and proximal thirds of the urethra are preserved [21]. These anatomical and functional relationships become important when considering an orthotopic neobladder approach. Because the rhabdosphincter is present in the middle to lower urethra, the entire bladder neck can be resected in a woman without compromising eventual continence. These striated fibers intertwine proximally with smooth muscle fibers of the urethra. Careful dissection around the bladder neck is extremely important to preserve autonomic nerve function to the smooth muscle fibers along the proximal urethra. The autonomic fibers innervating the periurethral smooth muscle fibers contribute significantly to continence by maintaining tone and urethral resistance. These nerves emerge from the hypogastric plexus dorsolaterally to the rectum, deep to the ureters, laterally along the vagina, and finally near the bladder neck. Therefore, complete resection of the vagina and a margin below the bladder neck leads to complete resection of the autonomic nerves supplying the periurethral smooth muscle. By careful dissection along the lateral vaginal walls and bladder neck, a large portion of these nerves can be preserved, therefore preserving urethral tonicity.

Another important mechanism in female continence is the somatic innervation of the urethra originating from S2 to S4. These nerves course laterally and ultimately on the levator muscles deep to the endopelvic fascia. These nerves are intimately close to the bladder’s inferior vascular pedicle and proceed anteriorly across the vagina, making them very susceptible to injury during RC. Another reason to avoid dissection deep into the endopelvic fascia is to avoid resecting the suspensory facial attachments and ligaments of the urethra to the pelvic floor.

Urethral resistance is an important consideration when thinking about continence in a low-pressure system like an orthotopic neobladder. An overly long urethral stump can lead to poor emptying and urinary retention after orthotopic neobladder placement because of the increase in urethral resistance. Therefore, during RC, the bladder neck should be removed along with a portion of an adjacent segment of proximal urethra. However, no consensus has been reached regarding the length of urethra that should be taken.

Nerve sparing
The nerve-sparing approach for radical prostatectomy has become popular in selected patients [22]. However, it is not as frequently discussed with regard to female patients undergoing RC [17]. There are some cases where a nerve-sparing approach is not advised, especially in patients with cT4 disease along the posterior bladder wall that is possibly invading the vagina. In this scenario, the oncologic outcome must not be sacrificed, and a formal anterior pelvic exenteration is necessary along with the removal of the anterior vagina [23].
This will undoubtedly dissect the somatic nerves innervating the urethra. However, if a vaginal nerve-sparing approach is indicated, careful dissection along the lateral vaginal walls, bladder neck, and proximal urethra will leave both the nerve plexus and the sphincter mechanism intact [14, 16, 17]. Figure 12.3 demonstrates the anatomic course of autonomic nerves along the vagina in relation to the bladder, urethra, and rhabdosphincter.

**Sexual function**

When counseling patients about life after cystectomy, sexual function is often overlooked. Yet, three of the five most important symptoms that cause long-term post-operative distress are pain during intercourse, vaginal issues during sexual activity, and altered vaginal anatomy [24], which are particularly important in younger women diagnosed with bladder cancer. In a study reporting objective outcome data, 27 sexually active women that underwent cystectomy received a self-administered questionnaire (Female Sexual Function Index, FSFI). At a median follow-up of 24 months, the FSFI score significantly decreased, with the most frequent complaints being vaginal lubrication issues (41%), difficulty reaching orgasm (45%), decreased sexual desire (37%), and dyspareunia (22%) [25].

Many anatomists and physicians have looked into possible reasons for sexual dysfunction and found that in cadaveric dissections, neurovascular bundles course laterally on the vaginal walls and may be easily damaged during the removal of the bladder, urethra, and anterior vaginal wall [26, 27]. In addition, dissection of the urethra seems important to sexual sensation, because the clitoris may become devascularized during urethral dissection [28]. Bhatt et al. [29] tested how nerve-sparing affected post-operative sexual function, by prospectively assessing female sexual function in six patients who had undergone nerve-sparing and seven patients who had non-nerve-sparing procedures, and concluded that all domains of sexual function declined in patients who did not have nerve-sparing procedures [29]. Clearly, with appropriate patient selection, the correct operation can be offered to limit the negative impact on a woman’s quality of life after RC.

**Technique of anterior exenteration**

The limits of anterior pelvic exenteration are outlined in Figures 12.4 and 12.5. The techniques presented here are specific to female cystectomy and are crucial.
in order to optimize local cancer control as well as sexual and urinary function:

1 Position women undergoing RC in a supine position with their legs slightly abducted in a V-shape using a split-leg table or stirrups in low lithotomy. This allows for proper sterile preparation of the female genitalia as well as surgical access if necessary.

2 Next, insert an 18-F Foley catheter into the urethra during the initial prep and inflate with 10 to 15 cc of sterile water. The vagina can then be marked by placing a betadine-soaked towel or sponge stick, which helps the intraoperative identification of the vagina.

3 To gain extraperitoneal access to the bladder, make a Pfannenstiel or lower midline incision. Intraperitoneal access is obtained by dividing the median umbilical ligament. The peritoneum can then be incised in a reverse V-shaped incision along the common iliac arteries and carried laterally toward the white line of Toldt.

4 At this point, some surgeons prefer to perform the lymph node dissection first because it can aid in identifying the vesical and uterine arteries.

5 The ovaries can be removed by freeing them from the lateral attachments, ligation and dividing the infundibulopelvic ligament, and the uterus is typically removed en bloc with the bladder. Along the course of the hypogastric artery, the superior and inferior vesical, uterine, and lower ovarian arteries and veins are ligated and dissected.

6 If the surgeon is attempting a nerve-sparing procedure, he/she should take the vascular pedicle to the bladder as medially as possible because the autonomic nerve fibers from the hypogastric plexus course deep to the vascular pedicle. The ureters can then be mobilized and divided below the common iliac bifurcation and clipped. Clipping the ureters hydrodistends them, allowing for an easier uretero-enteric anastomosis.

7 At this time, the authors send the distal margins for frozen section to reduce the risk of positive margins at...
the uretero-enteric anastomosis, which has been associated with increased risk for upper tract recurrence [30].

8 Next, identify the pouch of Douglas and carefully incise the peritoneum overlying the anterior rectal wall.

9 The posterior vagina can then be dissected off the pre-rectal fat using blunt or sharp dissection to about 1 cm below the cervix, which can be palpated under the posterior vaginal wall. This dissection is carried down to the anterior urethra. To optimize vaginal length, position the vaginal sponge stick as superior as possible in the posterior cervical fornix, and open the posterior vagina, exposing the sponge stick.

**Vaginal-sparing approach**

If the primary tumor is low-volume and non-invasive, resection of a large portion of the vagina should be avoided because this may damage the pelvic plexus, which lies along the lateral aspects and innervates portions of the urethra. In this case, a finger should be placed in the anterior fornix for circumferential incision. The uterus and bladder can then be retracted anteriorly to expose the plane between the anterior vaginal wall and posterior bladder. The vagina is retracted cephalad, and the anterior vaginal wall is sharply dissected free of the posterior bladder wall, down to the urethra. Tubularized omentum can be mobilized and interposed between the anterior vagina and neobladder-urethral anastomosis. This helps to prevent the formation of a urethrovaginal fistula and urethral kinking due to posterior fall of the orthotopic reservoir [18].

**Partial vaginal sparing**

In the event of a posterior bladder tumor where deep invasion is a concern, the anterior wall can be taken with the bladder specimen. Once the posterior vagina is opened at the posterior cervical fornix, the lateral vaginal walls can be incised in the caudal direction, leaving the anterior vaginal wall attached to the posterior bladder. The preferred method of vaginal closure is transverse closure (clam-shell technique), rather than longitudinal, because this provides the widest opening with the fewest post-operative side effects (e.g., dyspareunia). However, this can result in vaginal shortening. If there is adequate vagina, longitudinal closure can be possible to maintain adequate vaginal length. Some techniques to increase vaginal support include mobilizing a piece of omentum from the left gastroepiploic artery and interposing it between the neobladder and vagina. If performing an orthotopic neobladder, it is prudent to spare the distal 1 to 2 cm of anterior vagina to separate the vaginal and urethral anastomotic suture lines, to prevent a urethro-vaginal fistula.

**Urethral dissection for orthotopic neobladder**

Nerves to the urethral striated rhabdosphincter branch from the pudendal nerve, which runs behind the levator muscle. Thus, efforts to maintain post-operative continence for women undergoing orthotopic neobladder must include avoiding dissection anterior to the urethra and careful dissection along the bladder neck. This can be achieved by leaving the endopelvic fascia intact. The proximal urethra cephalad to the endopelvic fascia should be dissected, exposing the bladder neck and a large clamp placed across the bladder neck to prevent tumor leakage. The urethra can then be taken sharply, and the catheter cut. The urethral margin should then be sent for frozen section histological analysis before starting with the urethro-ileal anastomosis [7]. An additional approach to determine whether or not an orthotopic diversion can be performed safely is to do pre-operative bladder neck biopsies at the time of TURBT. If the biopsies are negative, there is no need to perform an intraoperative frozen section. Figure 12.6 delineates the level of urethral dissection in relation to the bladder neck.

**Urethral dissection for cutaneous diversion**

If cutaneous diversion is planned, the endopelvic fascia is opened and the urethra is clamped over the Foley catheter to prevent tumor leakage. The urethral meatus can be incised circumferentially from an intra-abdominal or perineal approach.

**Risk of cancer recurrence in the urethra in women**

Traditionally, anterior exenteration consisted of a complete urethrectomy. Urethral recurrence has been recently reported to be lower in women than in men [7]. This lower incidence in women can be attributed to the fact that as women age, urothelial mucosa gradually get replaced by squamous cell
mucosa, where the area of demarcation between squamous and urothelial epithelium moves cranially. This does not occur in men. In the sixth and seventh decades of a woman’s life, the metaplastic squamous cell mucosa can cover the entire urethra, the bladder neck, and even parts of the trigone.

The risk of synchronous or secondary urethral tumor involvement was investigated in a series of 356 women undergoing RC over a 19-year period. Seven patients (2%) had urethral tumor at presentation [27]. Bladder neck involvement was the only factor significantly associated with urethral tumor involvement, and no association was reported between urethral involvement and carcinoma in situ, tumor volume, or multifocality.

Stein and colleagues sought to prospectively identify pathologic risk factors for urethral involvement in women undergoing cystectomy with orthotopic neobladder [31]. In their series, tumor involvement at the bladder neck was again the most significant risk factor for urethral involvement, although only half of patients with bladder neck involvement had a tumor-free urethra. It is notable that in all cases, intraoperative frozen sections of the proximal urethra correctly identified and correlated with the final pathologic diagnosis. Furthermore, a recent multi-center study of 456 women undergoing RC with ileal neobladder reported that the risk of urethral recurrence was significantly associated with a positive urethral margin but not with bladder neck tumor involvement [32]. Altogether, the current data suggest that women with bladder neck tumor involvement should not be a priori excluded from an orthotopic approach unless a carefully obtained full-thickness biopsy of the proximal urethra reveals evidence of malignancy [7].

Incontinence, residual urine, and urinary retention after orthotopic neobladder reconstruction

After orthotopic neobladder diversion, women may experience daytime and night time incontinence, residual urine, and urinary retention. Many variables affect urinary incontinence including age, prior pelvic surgery and irradiation, gender, and diversion technique. Observations across studies of post-operative continence from the time of neobladder reconstruction suggest gradual improvement of daytime continence over the course of one year. In addition, a high incidence and persistence of night time incontinence is observed in about 7% to 70% of patients (male and female), with an average of around 28% [33]. Night time incontinence occurs because of the lack of neurologic feedback, decreased volitional external sphincter pressure, and the absence of the sphincter–detrusor feedback loop. However, night time incontinence can improve as the
capacity and compliance of the neobladder increases, which may improve as late as 24 months after surgery [34]. Either conscious or unconscious sensations of urine in the membranous urethra contribute to increased or decreased tone in the external sphincter. This autonomic feedback loop can become damaged during the operation, contributing to urinary leakage [35]. In a recent series of 49 women who underwent RC with orthotopic neobladder, daytime incontinence, night time incontinence, and urinary retention were reported by 43%, 55%, and 31% of women, respectively [36]. A neobladder-vaginal fistula developed in three women (6%). The severity of daytime incontinence correlated significantly with only pre-operative incontinence, and the severity of night time incontinence was associated with patient age.

The reported rates for urinary retention after orthotopic neobladder placement in female patients vary considerably between 2% and 58% [19, 37–39]. In the authors’ experience, issues with urinary retention present more often when patients experience a urinary tract infection, especially in the setting of new onset stress or overflow incontinence. When counseling patients about the risk of developing urinary retention, however, it is important to note that it often develops late. When patients present during follow-up with the aforementioned urinary incontinence issues, evaluation and management should be delayed by six months to one year, or until the neobladder has increased in functional capacity. Figure 12.7 outlines schematically possible reasons for residual urine or urinary retention in female orthotopic bladder substitution.

**Follow-up of women with ileal neobladder placement**

Because of the low risk of urethral recurrence after cystectomy, the exact method of follow-up for an asymptomatic patient with an orthotopic neobladder remains under debate [40]. All symptomatic patients with urethral bleeding, pain, or mass should be evaluated promptly. Follow-up regimens described in the current literature derive mainly from different high-volume centers and are based on urinary cytology, urethral washings, urethroscopy, and different imaging modalities [40–42]. Regarding the frequency of follow-up, some authors suggest routine use of urinary cytology, urethral washings, and urethroscopy on a quarterly basis for the first two years and semiannually thereafter [41], whereas others conduct only clinical follow-up [43]. It seems reasonable, therefore, to tailor surveillance regimens to the patient’s individual risk factors for urethral recurrence. Urinary cytology is an easy and non-invasive diagnostic tool to detect malignant cells, but its sensitivity
Cystectomy in the female patient

is considerably reduced in patients after ileal neobladder placement [44]. Urethroscopy is certainly the method of choice for the histological diagnosis of urethral recurrence, but the use of urethroscopy on a regular basis has not shown a significant survival benefit [7, 40–42, 45]. A method utilized by the authors is to perform a urethral swab and voided cytology on these patients annually.

Most major complications after cystectomy with orthotopic diversion are associated with the neobladder itself (15% to 20%) [46]. These include abscess formation, pyelonephritis, ureterointestinal stricture, and urinary leakage, which may lead to prolonged ileus [47]. In these cases, prompt evaluation and immediate treatment is necessary, since a delay in treatment may lead to increased mortality, often observed between 30 and 90 days post RC [48]. Severe urinary incontinence during both day and night should prompt a workup for neobladder-vaginal fistula, including a vaginal exam, pouchoscopy, and/or a methylene blue test while vaginal packing or a tampon is in place.

Over the long term, renal deterioration after orthotopic neobladder reconstruction has many causes. Urological causes include the transmission of either high-pressure or infected urine into the kidneys due to ureterointestinal stenosis, stone formation, or increased postvoid residual urine. For the treating urologist, the key issue is to provide a surveillance protocol for the patient, aiming at achieving a capacity of 400 to 500 mL residual-free voiding of sterile urine and eliminating any outlet or upper tract obstruction. Urinary tract infection should prompt physicians to exclude the presence of residual urine volume and correct for metabolic acidosis by bicarbonate substitution and electrolyte imbalances. Untreated chronic metabolic acidosis may also decrease bone mineral density and lead to skeletal-related events [49]. Furthermore, vitamin B12 supplementation may become necessary in the long term and should be checked from the second to third post-operative year on [47].

Besides urological conditions, a post-operative decline in renal function may also be attributed to poorly regulated diabetes and arterial hypertension or drug-associated side effects. Therefore, the treating urologist needs to be aware of all medical conditions that may lead to long-term renal deterioration and treat them as thoroughly as possible. A proposed ten-year functional follow-up scheme is outlined in Table 12.1.

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Source: Gakis, 2012 [50]. Adapted with permission from Thieme.
Useful web links


References

Cystectomy in the female patient


The first laparoscopic cystectomy was described by Parra et al. in 1992 [1]. It was initially performed for benign disease and then expanded to the management of bladder cancer, but was technically very challenging and did not gain widespread popularity. The da Vinci robotic system was approved by the FDA and initially was used in urology for radical prostatectomy in 2001 (Intuitive Surgical, Sunnyvale, CA, USA). Menon et al. developed the robot-assisted radical cystectomy (RARC) technique in 2002, and it gained a steady but slow acceptance in the urological community [2]. Since robot-assisted radical prostatectomy has been shown to reduce blood loss and provide faster recovery time while upholding excellent oncological and functional outcomes, RARC was developed with the hope of providing the same advantages [3].

We are presenting a comprehensive discussion of the outcomes in minimally invasive radical cystectomy that have been reported to date. We will discuss the operative, perioperative, oncologic, and functional outcomes of robotic and laparoscopic radical cystectomy and urinary diversion. The radical cystectomy series included in our discussion are from centers with the longest and largest experience.

While we are evaluating the best data available in the robotic and laparoscopic literature, we are also aware that we are still in the adolescence of minimally invasive bladder surgery. We need to acknowledge that many of

KEY POINTS

- Most RARC series demonstrate operative times that appear to be similar to the open surgical series, and estimated blood loss and transfusion rates appear lower than in the RARC series.
- Limited data do not allow us to draw conclusions on the return of bowel function and pain medication requirements.
- The length of stay with RARC appears to be at least comparable to open radical cystectomy (ORC).
- The most common complications reported with RARC are infectious, gastrointestinal, hematologic, and genitourinary.
- Urinary tract infection is the most common infectious complication and ileus is the most common gastrointestinal complication.
- The oncologic outcomes, such as positive surgical margin rates and lymph node yield, of RARC are comparable to the open series.
- Continence rates in patients with continent cutaneous and orthotopic urinary diversion reported in RARC appear comparable to ORC.
- No conclusions can be drawn about the long-term efficacy of RARC until five-year survival data become available, but the current data suggest that the long-term survival in patients undergoing RARC is likely to be comparable to ORC.
the largest series are still subject to selection bias, involve relatively small sample sizes, and include only intermediate-term outcomes. In addition, the majority of RARC procedures are performed at tertiary care centers, which may result in an under-reporting of complications, since some patients may present to community hospitals with complications. Most importantly, the lack of long-term follow-up prohibits us from drawing any final conclusions regarding oncologic and functional outcomes.

Robot-assisted radical cystectomy is a technically challenging operation. Pruthi et al. determined that after the 20th case there is no further improvement in operative time or estimated blood loss (EBL) [4]. The complication rates were similar and there was no compromise on oncologic outcomes, including lymph node yield and margins, at the beginning and the end of the learning curve. Hayn et al. showed that 20 cases were required to achieve lower operative times, but it took 30 cases to increase lymph node yield to 20 and to reduce positive surgical margin (PSM) to < 5% [5]. Therefore, 30 patients was a preferable, but not the sole, criterion for inclusion in our discussion.

### Operative outcomes

Operative and perioperative outcomes for minimally invasive radical cystectomy are the most readily comparable variables we can evaluate when relating the minimally invasive to open surgical techniques. We need to ensure a fair comparison of the two approaches in order to draw any conclusions about the safety and efficacy of minimally invasive cystectomy.

When evaluating pre-operative parameters, the patients undergoing RARC and ORC appear comparable. In the series reviewed, the median age of the patients undergoing RARC was 69–74 years old, body mass index (BMI) was 26–28, and 41–79% of patients had an American Society of Anesthesiologists (ASA) Score equal to or greater than 3 [6–13]. The median age of patients in the ORC series was 66–70 years old, their BMI was 26–27, and 43–86% had an ASA Score of 3 or greater [14–19] (Table 13.1).

The laparoscopic radical cystectomy (LRC) data appear different. The laparoscopic groups had lower BMI and

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<td>70</td>
<td>– / 60</td>
<td>– / 27</td>
<td>16</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Azzouni et al. 2013</td>
<td>100</td>
<td>71 /–</td>
<td>29 /–</td>
<td>52</td>
<td>–</td>
<td>–</td>
<td>57</td>
</tr>
<tr>
<td><strong>Laparoscopic radical cystectomy</strong></td>
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</tr>
<tr>
<td>Haber et al. 2008</td>
<td>37</td>
<td>– / 66</td>
<td>– / 26</td>
<td>24</td>
<td>8</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Springer et al. 2013</td>
<td>37</td>
<td>67 /–</td>
<td>28 /–</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Cathelineau et al. 2005</td>
<td>84</td>
<td>61 /–</td>
<td>– /–</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>Huang et al. 2010</td>
<td>171</td>
<td>63 /–</td>
<td>21 /–</td>
<td>34</td>
<td>–</td>
<td>–</td>
<td>22</td>
</tr>
</tbody>
</table>

N = number of patients; – = not recorded
lower ASA Scores, so it is hard to draw parallels with ORC. This may be a reflection of the early experience where healthier patients were selected to undergo this approach, which was thereafter replaced by the more rapidly adaptable robotic technique. The median age of patients undergoing laparoscopic cystectomy was 61–67 years, BMI was 21–28, and 0–34% had an ASA Score of 3 or greater [20–23] (Table 13.1).

On further comparison, 34–55% of RARC patients had prior abdominal or pelvic surgery, which is similar to the 40–57% in the ORC group [6–9, 11–13, 15]. However, only 20–38% of the LRC group had prior abdominal or pelvic surgery, which again makes this group a healthier and less surgically challenging population [20–23] (Table 13.1).

As for neoadjuvant chemotherapy, 8–46% of patients in the RARC series, 0–36% of patients in the ORC series, and 0–8% of patients in the LRC series received it [6–10, 12, 13, 15, 16, 19–21, 23–25]. This potentially makes the RARC group the more challenging group to operate on due to surgical difficulties and the increased chance of potential complications associated with neoadjuvant chemotherapy. On the other hand, the chemotherapy may shrink the size of the tumor, making the operation more feasible (Table 13.1).

Most RARC series demonstrate operative times that appear to be similar to the open surgical series, and EBL and transfusion rates appear lower than in open series. The length of surgery in major RARC series ranged from a median of 258–432 minutes, compared to 258–426 minutes in major open series [4, 6, 9, 13, 15, 16, 26, 27] (Table 13.2). Median EBL in RARC was 250–400 mL, and 600–1000 mL in the open series [6, 7, 9, 13, 15, 16, 18, 26, 27]. Two to 44% of RARC patients received a blood transfusion, as opposed to 29–66% of ORC patients [6–8, 10, 12, 13, 15, 16, 18, 27] (Table 13.2).

When comparing ORC and RARC within a single institution, operative times were longer for RARC even though both groups underwent a comparable percentage of ileal conduits and continent diversions [8, 11, 12, 14, 17, 28]. At this point in the evolution of RARC, it is accepted that outside of high‐volume centers, operative times would be expected to be longer than open times. As more surgeons become adept at robotic surgery, we expect that operative times will decrease and be at least comparable to open surgical times.

Table 13.2 Intraoperative characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Length of surgery (min) (median / mean)</th>
<th>EBL (ml) (median / mean)</th>
<th>Transfusion %</th>
<th>Ileal conduit %</th>
<th>Neobladder %</th>
<th>Continent cutaneous diversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic radical cystectomy and extracorporeal urinary diversion</td>
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<td></td>
<td></td>
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<tr>
<td>Yuh et al. 2012</td>
<td>196</td>
<td>432 / –</td>
<td>400 / –</td>
<td>44</td>
<td>32</td>
<td>44</td>
<td>24</td>
</tr>
<tr>
<td>Kaufman et al. 2010</td>
<td>85</td>
<td>360 / –</td>
<td>400 / –</td>
<td>–</td>
<td>71</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Hayn et al. 2011</td>
<td>156</td>
<td>378 / –</td>
<td>400 / –</td>
<td>16</td>
<td>93</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pruthi et al. 2010</td>
<td>100</td>
<td>258 / –</td>
<td>250 / –</td>
<td>–</td>
<td>61</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Ng et al. 2009</td>
<td>83</td>
<td>– / 375</td>
<td>– / 460</td>
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<td>57</td>
<td>31</td>
<td>12</td>
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<tr>
<td>Kader et al. 2013</td>
<td>103</td>
<td>– / 451</td>
<td>– / 423</td>
<td>15</td>
<td>97</td>
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<td>0</td>
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<tr>
<td>Styin et al. 2012</td>
<td>50</td>
<td>– / 454.9</td>
<td>– / 350</td>
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<td>72</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Khan et al. 2011</td>
<td>50</td>
<td>– / 361</td>
<td>– / 340</td>
<td>4</td>
<td>90</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Smith et al. 2012</td>
<td>227</td>
<td>– / 327</td>
<td>– / 256</td>
<td>–</td>
<td>74</td>
<td>26</td>
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<tr>
<td>Robotic radical cystectomy and intracorporeal urinary diversion</td>
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<tr>
<td>Tyritzis et al. 2013</td>
<td>70</td>
<td>420 / –</td>
<td>500 / –</td>
<td>–</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Azzouni et al. 2013</td>
<td>100</td>
<td>352 / –</td>
<td>300 / –</td>
<td>10</td>
<td>100</td>
<td>0</td>
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<tr>
<td>Laparoscopic radical cystectomy</td>
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<tr>
<td>Haber et al. 2008</td>
<td>37</td>
<td>– / 498</td>
<td>– / 608</td>
<td>13</td>
<td>49</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>Springer et al. 2013</td>
<td>37</td>
<td>330 / –</td>
<td>410 / –</td>
<td>5</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Cathelineau et al. 2005</td>
<td>84</td>
<td>280 / –</td>
<td>550 / –</td>
<td>5</td>
<td>39</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>Huang et al. 2010</td>
<td>171</td>
<td>325 / –</td>
<td>270 / –</td>
<td>17</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>
It is important to note in the series reported what form of urinary reconstruction was utilized and how it was constructed (intracorporeal versus extracorporeal). Thirty-two to 97% of RARC patients underwent ileal conduit diversion, 3–44% neobladder, and 0–25% had continent cutaneous diversions [6–13, 25, 26]. In the open series, 25–65% of patients underwent ileal conduit diversion, 28–48% neobladder, and 1–35% continent cutaneous diversions [15, 16, 18, 19, 27]. Though it looks like more RARC patients underwent ileal conduits, when comparing single-institution RARC and ORC experiences, the rates of ileal conduit versus continent diversions were similar [8, 11, 12, 14, 17, 28]. This appears to be more consistent with surgeon preference than a true selection bias.

Patients undergoing continent diversions had longer operative times. When comparing types of diversions, ileal conduit length of surgery was 300–360 minutes, neobladder was 444–486 minutes, and continent cutaneous diversion was 438–480 minutes [10, 13, 17]. In the ORC series, the length of surgery for ileal conduit diversion was 246–348 minutes, and 266–432 for neobladder. These times are shorter compared to RARC, but the overall operative times were similar [15, 27].

In laparoscopic cohorts, length of surgery was 280–330 minutes, EBL was 270–550 mL, 5–17% received blood transfusions, 0–49% underwent ileal conduit diversion, and 51–100% neobladder [20–23]. Again, this was a healthier cohort of patients with what appears to be a strong selection bias, so these cannot be compared with large open series.

**Post-operative outcomes**

We combined results of RARC with extracorporeal and intracorporeal urinary diversions since complications and outcomes appear to be similar.

There is an opinion that, as with many laparoscopic surgeries, the RARC patients might have a faster return of bowel function. A few small studies reported the return of bowel function marked by flatus to be 2–4 days, as compared to an ORC cohort within the same institution of 3–5 days [17,26,28]. However, it is difficult to draw any major conclusions as these studies had very small sample sizes. Since the diversions were performed extracorporeally, involving the same amount of bowel manipulation as compared to ORC series, the return of bowel function would not be expected to be significantly different. Pruthi et al. retrospectively compared 30 patients undergoing RARC with extracorporeal and intracorporeal urinary diversion and noted no difference in the return of bowel function between the two groups [29].

It has been suggested that the minimally invasive cystectomy patients have less post-operative pain medication requirements. Nix et al. performed a prospective study of 41 patients randomized into RARC and ORC groups, which showed that the RARC cohort had a lower intravenous narcotic pain medicine requirement, but larger studies are necessary to confirm this finding [28].

The median length of stay (LOS) was similar for both RARC and ORC groups, ranging from 5–9 days for RARC patients, and 6–9 days for ORC patients [6–8, 11, 13–16, 18, 27] (Table 13.3). A few single-institution studies noted that the LOS for the RARC group was statistically significantly shorter than for the ORC group [8, 11, 17].

**Complications**

The short-term perioperative outcomes are reported as complications occurring in less than 30–90 days postoperatively. Complications are another variable that can be compared easily to open series. Most complications are presented using the Clavien–Dindo classification, which aids in standardization of the complications reported in the surgical literature [30].

As far as the large open series go, the most common complications reported are gastrointestinal (GI) and infectious, followed by wound-related, genitourinary (GU), and cardiac, and the least common are pulmonary, hematologic, thromboembolic, neurological, and surgical complications [15, 31].

The most common complications reported in the robotic series were infectious, GI, and hematologic, followed by GU, vascular, metabolic, and cardiac. Respiratory, thromboembolic, and neurologic complications were rare [7, 8, 11–13, 17, 26, 28]. Urinary tract infection was the most common infectious complication. Ileus was the most common GI complication, followed by small bowel obstruction. Rates of ileus and small bowel obstruction appear to be similar in extracorporeal and intracorporeal urinary diversions [32–34].

A large focus of concern for extracorporeal urinary diversion in the setting of RARC is uretero-enteric anastomotic stricture. Performing the uretero-enteric anastomoses at the level of the skin through a small
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Incision is thought to lead to more strictures, due to using more distal ureter and not getting to see the natural orientation of the ureter that one would see through a larger incision. However, on review of the literature, the ureteral stricture rate is not significantly different between robotic and open series (7–8% versus 2–13%, respectively) [10, 13, 16, 35–38].

One of the most dreaded complications in pelvic surgery is thromboembolic events. In both ORC and RARC series, thromboembolic events, including deep venous thrombosis (DVT) and pulmonary embolism (PE), were rare. The DVT and PE rates were comparable, with 3–5% and 1% respectively for the RARC groups, and 3–5% and 1–3% for the ORC group [6, 11, 15, 16, 26–28].

In the RARC series, the overall 30-day complication rates were reported as 30–66%, with 7–28% major complications (Clavien Grade 3 or greater), and 90–day overall complication rates were 26–80%, with 10–35% major complications [6–8, 10–14, 25, 26]. The ORC groups had overall 30-day complication rates of 35–45%, with 5–7% major complications, and the 90-day rate was 28–64%, with 13–40% major complications [15, 16, 18, 19, 27] (Table 13.3). The mortality rate was 0–6% for RARC patients, and 0–3% for ORC patients, which is comparable between the two groups [6–8, 11, 13, 15, 16, 18, 19, 27].

When examining small retrospective series of RARC, the 30-day major complication rate was higher when compared to ORC patients. However, the two RARC groups with the highest complication rates also reported complication rates in their ORC groups within the same institution, and the overall and major complication rates were similar between the groups [12,14]. The RARC series with higher complication rates had more patients with ASA Scores of 3 or greater and performed more continent diversions. The technical complexity of the procedure, the use of the colon or a longer segment of the ileum, and the metabolic sequelae of holding of urine in the intestinal pouch for hours at a time, are all factors that may contribute to a higher complication rate in series where more continent urinary diversions are performed [13].

According to Yuh et al., the ileal conduit patients had the least number of overall and major complications when compared to the patients undergoing IP and neobladder. Overall complication rates were 73%, 92%, and 78% for ileal conduit, Indiana pouch, and neobladder, respectively, with a major complication rate of 27%, 31%, and 42%, respectively. These findings were demonstrated even though the ileal conduit patients were older and had higher ASA Scores [13].

### Table 13.3 Post–operative characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>LOS (days) (median / mean)</th>
<th>Re-admission %</th>
<th>% 30 Day complications (overall / major)</th>
<th>% 90 Day complications (overall / major)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Robotic radical cystectomy and extracorporeal urinary diversion</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yuh et al. 2012</td>
<td>196</td>
<td>9 / –</td>
<td>–</td>
<td>60 / 20</td>
<td>80 / 35</td>
</tr>
<tr>
<td>Richards et al. 2010</td>
<td>35</td>
<td>7 / –</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ng et al. 2009</td>
<td>83</td>
<td>6 / –</td>
<td>–</td>
<td>–</td>
<td>48 / 17</td>
</tr>
<tr>
<td>Kader et al. 2013</td>
<td>103</td>
<td>6 / –</td>
<td>17</td>
<td>–</td>
<td>36 / 10</td>
</tr>
<tr>
<td>Hayn et al. 2011</td>
<td>156</td>
<td>8 / –</td>
<td>21</td>
<td>–</td>
<td>52 / 17</td>
</tr>
<tr>
<td>Styn et al. 2012</td>
<td>50</td>
<td>– / 10</td>
<td>28</td>
<td>66 / 28</td>
<td>–</td>
</tr>
<tr>
<td>Pruthi et al. 2010</td>
<td>100</td>
<td>– / 5</td>
<td>11</td>
<td>36 / 8</td>
<td>–</td>
</tr>
<tr>
<td>Khan et al. 2011</td>
<td>50</td>
<td>– / 10</td>
<td>18</td>
<td>–</td>
<td>34 / 10</td>
</tr>
<tr>
<td>Johar et al. 2013</td>
<td>939</td>
<td>8 / –</td>
<td>20</td>
<td>–</td>
<td>48 / 19</td>
</tr>
<tr>
<td>Smith et al. 2012</td>
<td>227</td>
<td>– / 6</td>
<td>–</td>
<td>30 / 7</td>
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</tr>
<tr>
<td><strong>Robotic radical cystectomy and intracorporeal urinary diversion</strong></td>
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<tr>
<td>Tyrizis et al. 2013</td>
<td>70</td>
<td>–</td>
<td>–</td>
<td>48 / 31</td>
<td>59 / 37</td>
</tr>
<tr>
<td>Azzouni et al. 2013</td>
<td>100</td>
<td>9 / –</td>
<td>20</td>
<td>63 / 13</td>
<td>81 / 15</td>
</tr>
<tr>
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<tr>
<td>Haber et al. 2008</td>
<td>37</td>
<td>– / _</td>
<td>–</td>
<td>46 / 16</td>
<td>19 / 3</td>
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<tr>
<td>Cathelineau et al. 2005</td>
<td>84</td>
<td>12 / –</td>
<td>–</td>
<td>18 / –</td>
<td>–</td>
</tr>
<tr>
<td>Huang et al. 2010</td>
<td>171</td>
<td>– / –</td>
<td>–</td>
<td>23 / 5</td>
<td>15 / 8</td>
</tr>
</tbody>
</table>
In a discussion of radical cystectomy complications, readmission rate is an important outcome to measure, and this was similar for both groups. Readmission rates in RARC series were 11–28% [6–8, 10, 12, 26], as compared to 18–26% in ORC series [15, 27].

The discussion cannot be complete without mentioning the LRC. Many centers adopted robotic techniques and stopped performing LRC, however it might still be employed in centers where the cost of the Da Vinci system is prohibitive. The data are not robust, so the utility of this information is limited. The several small retrospective series report their overall 30-day complication rates as being 18–46%, with 0–16% major complications [20–22].

**Oncologic outcomes**

The most important determinant as to the efficacy of RARC is oncological outcomes. First and foremost, we must be performing an equal (if not better) cancer operation. A discussion of oncological outcomes in the context of radical cystectomy requires a review of positive surgical margin rates, lymph node yield, and disease-specific and overall survival.

Controversy exists regarding the extent to which pelvic lymph node dissection (PLND) should be performed. Generally speaking, the current standard is a complete bilateral extended PLND when performing radical cystectomy for muscle-invasive bladder cancer. Herr et al. studied radical cystectomy and lymph node counts at Memorial Sloan-Kettering Cancer Center. They noted that the longer-surviving lymph node positive patients were those with nine or more total nodes harvested [39]. In addition, they found that the number of lymph nodes harvested also predicted survival in node-negative patients. The group subsequently recommended that at least 10–14 lymph nodes be removed, as this confers a survival advantage [40]. Leissner et al. found an improved disease-free and disease-specific survival at five years if 16 or more lymph nodes were removed [41].

Recent RARC series are presented in Table 13.4. The median lymph node yield is 16–28 nodes [9, 11, 13]. Twelve to 29% of patients had positive lymph nodes. These numbers are well within the recommended standards.

Poulsen et al. established that not only the number of lymph nodes but also the extent of the lymph node dissection was important. They concluded that the lymph node dissection carried out to the aortic bifurcation

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>T3 + T4 %</th>
<th>PSM %</th>
<th>Lymph node yield (median / mean)</th>
<th>Lymph node +/- %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Robotic radical cystectomy and extracorporeal urinary diversion</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Yuh et al. 2012</td>
<td>196</td>
<td>36</td>
<td>4</td>
<td>28 / –</td>
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<td>Ng et al. 2009</td>
<td>83</td>
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<td>7</td>
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<td>Kauffman et al. 2010</td>
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<tr>
<td>Guru et al. 2007</td>
<td>58</td>
<td>50</td>
<td>10</td>
<td>– / 20</td>
<td>29</td>
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<tr>
<td>Kader et al. 2013</td>
<td>103</td>
<td>42</td>
<td>12</td>
<td>– / 18</td>
<td>30</td>
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<tr>
<td>Khan et al. 2011</td>
<td>50</td>
<td>28</td>
<td>2</td>
<td>– / 17</td>
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<tr>
<td>Johar et al. 2013</td>
<td>939</td>
<td>41</td>
<td>9</td>
<td>– / 18</td>
<td>26</td>
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<tr>
<td>Smith et al. 2012</td>
<td>227</td>
<td>15</td>
<td>2</td>
<td>– / 18</td>
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<tr>
<td><strong>Robotic radical cystectomy and intracorporeal urinary diversion</strong></td>
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<tr>
<td>Tyritzis et al. 2013</td>
<td>70</td>
<td>15</td>
<td>2</td>
<td>–/21</td>
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</tr>
<tr>
<td>Azzouni et al. 2013</td>
<td>100</td>
<td>–</td>
<td>4</td>
<td>24/–</td>
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<td><strong>Laparoscopic radical cystectomy</strong></td>
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<tr>
<td>Haber et al. 2008</td>
<td>37</td>
<td>38</td>
<td>5</td>
<td>14 / –</td>
<td>17</td>
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<td>Springer et al. 2013</td>
<td>37</td>
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<td>3</td>
<td>– / 18</td>
<td>19</td>
</tr>
<tr>
<td>Huang et al. 2010</td>
<td>171</td>
<td>34</td>
<td>0</td>
<td>– / 16</td>
<td>22</td>
</tr>
</tbody>
</table>
resulted in a higher node-positive rate and improved survival in pathologic T3aN0 patients, though these data are derived from a retrospective series of patients [42]. At this point, there is no standardized pelvic lymph node dissection template. However, many centers are adopting extended pelvic node dissection techniques as a result of these findings. Yuh et al. report the inferior mesenteric artery as the superior cranial limit of the lymph node dissection routinely performed, showing that the RARC technique does not compromise the extent of pelvic lymph node dissection [13]. Soft tissue margins are equally important in achieving the best oncological outcomes. Dotan et al. showed a 4% positive surgical margin rate in ORC series, and found that a positive surgical margin in the perivesical soft tissue was an independent indicator of the disease progression and of disease-specific mortality [43]. Herr et al. determined that positive surgical margins (PSM) increase the risk of local recurrence and decrease five-year survival [40]. Herr et al. further determined that the acceptable PSM is < 10% of all cases, and < 15% for bulky (T3–4) tumor [44].

The RARC studies reviewed reported positive margin rates of 2–12% despite the finding that 15–50% of patients had extravesical (T3/T4) disease [7–11, 13, 25, 45]. The studies with lowest PSM rates had the least amount of patients with extravesical disease. The PSM in ORC studies were 4–9%, with 45–46% of patients with T3/T4 disease [40, 43, 46]. It should be noted that the RARC group with the highest PSM rate of 12% also reported an open surgical margin rate of 11% at that same institution, and all of the PSM occurred in T4 tumors [8]. The above data demonstrate that RARC can achieve a PSM that is comparable to the ORC standards.

Unfortunately, there are no five-year survival data yet for RARC. The mean follow-up for RARC groups was 21–52 months. Table 13.5 represents overall survival, cancer-specific and cancer-free survival for these various ranges [9,26,47–50]. Khan et al. reported on 14 patients with a median follow-up of 84 months, with overall survival (OS) of 64%, cancer-specific survival (CSS) of 75%, and cancer-free survival (CFS) of 50% [47]. Yuh et al. reported three-year OS of 61%, CFS of 76%, and CSS of 83% [50]. ORC series report 59–60% OS at five years, and 37–43% at ten years, with CFS as 62–68% at five years and 50–66% at ten years [3,19]. No conclusions can be drawn about the long-term efficacy of RARC until five-year survival data become available, but the current data suggest that the long-term survival in patients undergoing RARC is likely to be comparable to ORC.
The data are sparse regarding functional outcome in RARC. In addition, there are inherent difficulties in comparing functional outcomes due to the high variability in the definition of continence and potency.

Whelan et al. performed analysis on all male RARC patients undergoing extracorporeal Studer neobladder and found that the daytime continence rates were 78% and night time 61% at 12 months, with the median patient age of 65 years [51]. The daytime continence was slightly lower and night time continence similar when compared to the ORC series where daytime continence rates were 85–95% and night time 60–93%, with the median patient age of 61 years, of which 75–100% were male patients [52–54]. However, a more recent report by Ahmadi et al. reported male daytime continence rates as 60% and night time 45%, which are lower than the other ORC series if the incontinence is defined as no pad use [55].

With regard to continent cutaneous urinary diversion, Torrey et al. reported a 97% daytime and night time continence rate for patients undergoing RARC with extracorporeal Indiana pouch diversion, which is comparable to ORC rates of 96–100% daytime, and 73–100% night time continence [54, 56–58].

About 10% of urinary diversions are performed intracorporeally. Intracorporeal diversion is time consuming and technically challenging. Jonsson et al. report daytime continence rates of 97% for intracorporeal neobladder and 83% night time at 12 months of follow-up, with the median patient age of 62 years [59]. Tyriritzis et al. reported a daytime continence rate of 70% at 12 months with an average patient age of 60 years [34]. As the robotic radical cystectomy technique matures, it will be exciting to see if minimally invasive cystectomy may be able to improve the functional outcomes established in open surgery.

Potency recovery after RARC is difficult to report because there are very few published data. Haberman et al. reported on 29 patients undergoing bilateral cavernosal nerve-sparing RARC. Forty-five percent of patients remained potent with or without the use of phosphodiesterase 5 inhibitors, and an additional 21% were potent with intracavernosal injections [60]. Potency rates were 47–71% in the ORC series [61, 62].

The future of minimally invasive radical cystectomy looks promising. We acknowledge that the body of literature regarding RARC is not yet mature. However, in all aspects, operative, post-operative, oncological, and functional outcomes, RARC appears at least comparable to ORC. The early evidence suggests advantages with RARC with regard to blood loss and transfusion rates. Ultimately, the hope is that with increasing experience and advances in robotic surgical techniques, RARC may be able to improve on all aspects of radical cystectomy that we consider acceptable today. While oncological outcomes are not likely to be greatly improved by surgical approach, we do believe that some of the most important advantages lie in the realm of surgical precision and nerve-sparing, which may ultimately result in higher potency rates and improved continence for patients undergoing an orthotopic urinary diversion.

References


Open radical cystectomy (ORC) has been the time-tested gold standard for the treatment of muscle-invasive bladder cancer. However, since the turn of the millennium, we have seen a technology paradigm shift toward robotic surgery. In 2003, Menon et al. published their procedure for robot-assisted radical cystectomy (RARC), ushering in an era of robotic surgery for bladder cancer [1]. Since then, the literature on robotic radical cystectomy has flourished. Nevertheless, before we can wholeheartedly adopt RARC, we must critically appraise the literature, and, in particular, clinical trials. In this chapter we will rigorously review the current and forthcoming clinical trial literature on RARC. Specifically, we will evaluate oncologic outcomes, lymph node dissection, urinary diversion, complications, and outcomes in specific populations.

A Medline database search for “robotic radical cystectomy” shows only six publications in the year 2005. There were 30 publications in 2010 and 53 in 2012. This shows the exponential growth in interest and publications regarding robotic cystectomy. The vast majority of these articles are from academic settings and most are from the United States and Europe. However, as we are approaching a decade of minimally invasive radical cystectomy, a rigorous assessment of its benefits and drawbacks will determine whether this technology continues to flourish and spread, or whether it will be confined to a selective niche.
Although robotic assisted radical cystectomy is a relatively new approach, it is important to remember that robotic technology is not making its debut in urology. Largely, the data from robotic cystectomy series come from surgeons who already have experience with robotic surgery, including robotic prostatectomy and pelvic lymph node dissection. As such, many of the technique-related issues and technological difficulties have largely been addressed through early series on robotic prostatectomy.

**Oncologic outcomes**

The oncologic success in surgery is ideally defined by long-term data on cancer recurrence and cancer-specific survival in a large group of patients. However, these data are cumbersome to gather, in part due to the nature of research, the average age of bladder cancer patients, the disease process, the relative infancy of robotic surgery, and a host of other factors. Hence, we are left with a collection of retrospective studies from which we must infer oncologic efficacy. Many studies lack sufficient follow-up to determine accurate cancer-specific survival or cancer recurrence rates. Given this, many studies analyze surgical quality factors as a surrogate for oncologic success, including surgical margin status and lymph node yield. In addition, it is important to note that the oncologic success for patients with invasive bladder cancer is determined entirely by the extirpative portion of the surgery. Certainly, the reconstructive phase can affect survival, complications, and cost, but these are distinct from oncologic outcomes and will be discussed in later sections.

The gold standard for muscle-invasive bladder cancer is open radical cystectomy. There is an abundance of research on ORC, and this has defined our current standards of oncologic efficacy. Table 14.1 lists some of the largest studies with the long-term oncologic data for ORC patients. The data indicate that patients undergoing ORC can expect five-year overall survival of 60%, recurrence-free survival of 58–70%, and cancer-specific survival of 56–71% [2–6]. Hautmann et al. presented their data on 1100 patients who underwent ORC without adjuvant or neoadjuvant therapy from 1986–2009 [2]. In that series, the ten-year OS rate was 44.3%. The RFS and CSS rates at ten years were 65.5% and 66.8%. The similarities in five-year and ten-year cancer-specific survival indicate that most recurrences for bladder cancer come within five years, and this seems to be a reasonable benchmark to define long-term efficacy. Taking a closer look at the data, we can see that the pathologic stage of disease has a marked impact on cancer outcomes as well.

RARC is a relatively new technique and, accordingly, long-term data are scarce. Nevertheless, there are increasingly more studies available and relevant long- and medium-term follow-up is being reported.

In a contemporary series, Xylinas et al. reported on 175 consecutive patients undergoing RARC between

<table>
<thead>
<tr>
<th>Patients (n =)</th>
<th>Median follow-up (months)</th>
<th>Five-year OS</th>
<th>Overall five-year RFS</th>
<th>Five-year CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hautmann et al. [2]</td>
<td>1100</td>
<td>38</td>
<td>58%</td>
<td>70%</td>
</tr>
<tr>
<td>Stein et al. [3]</td>
<td>1054</td>
<td>122</td>
<td>60%</td>
<td>68%</td>
</tr>
<tr>
<td>Ghoneim et al. [4]</td>
<td>2090</td>
<td>66</td>
<td>n/a</td>
<td>65.8</td>
</tr>
<tr>
<td>Shariat et al. [5]</td>
<td>888</td>
<td>39</td>
<td>n/a</td>
<td>46.1</td>
</tr>
<tr>
<td>Madersbacher et al. [6]</td>
<td>507</td>
<td>45</td>
<td>59%</td>
<td>76</td>
</tr>
</tbody>
</table>

**Table 14.1** Open radical cystectomy series with long-term follow-up.
2004 and 2011 [7]. Pathologic analysis indicated 15% with pT2 disease, 25% with pT3 disease, and 10% with pT4 disease. Four patients were converted to open surgery, of which three had pT4 disease. With a median follow-up of 37 months, three-year cancer-specific survival was 68% and recurrence-free survival was 63%. Five-year cancer-specific survival was 66% and recurrence-free survival was unchanged at 63%. With reasonable mid-term follow-up, these outcomes are consistent with outcomes for open radical cystectomy.

In the 2011 Genitourinary Cancer Symposium, Mmeje et al. reported on 139 patients who underwent RARC with nearly three years of follow-up [8]. The patient cohort included 27% with pT3/4 disease and 29% with node positivity. At a mean of 35.9 months of follow-up, 39 patients had recurred, 27 died of bladder cancer, and 5 died of other causes. This translates to recurrence-free survival of 80%, cancer-specific survival of 71%, and overall survival of 68%.

Despite the dearth of publications on long-term follow-up for RARC, these data compare favorably to large series of ORC patients. However, until further RARC data reach maturity, we can only assess surgical quality variables including surgical margin status and lymph node yield.

**Surgical margin status**

Surgical margin status is an important marker for surgical quality in radical cystectomy, in part because the results are immediately available and pathologically defined. A positive surgical margin (PSM) refers to tumor associated with the index cancer at the inked surgical margin of the cystectomy specimen. Many studies have assessed the impact of a positive surgical margin on oncologic outcomes for bladder cancer. A positive surgical margin confers a significantly increased risk of both local recurrence and distant metastasis [9]. In a large study involving 1589 patients who underwent open radical cystectomy at MSKCC, the authors found a PSM in 4.2% of patients. Patients with a PSM were significantly more likely to develop local recurrence (21% versus 6%) and metastatic disease (84% versus 32%) at five years compared to patients without a positive surgical margin [9]. No patients with organ-confined disease had a positive surgical margin in this study compared to 9% margin positivity in patients with extravesical disease. Furthermore, the authors found a higher PSM rate in women, and in those patients with positive lymph nodes, vascular invasion, and higher pathologic stage. Patients with a PSM had a bleak median survival of 1.8 years. These data demonstrate that PSM is a strong predictor of subsequent cancer recurrence and death, and suggest that PSM could be used as a surrogate marker for oncologic efficacy.

It is critical that RARC meets the standard of care for PSM in open radical cystectomy. Although many standards have been reported, Herr et al. suggested widely cited oncologic standards for radical cystectomy in 2004, concluding that the overall PSM rate should be less than 10%. For patients with advanced disease (pT3, pT4), the PSM rate should be less than 15%, and in the salvage setting, no more than 20% [10].

How does RARC compare to ORC in this regard? The University of North Carolina has one of the largest single-center series of RARC. They published their data on 100 consecutive patients who underwent RARC and demonstrated 0% positive margins, including one-third of patients who had non-organ-confined disease [11]. The International Robotic Cystectomy Consortium (IRCC) compiles data from 15 centers in the United States and Europe, creating the largest database of robotic cystectomy procedures. They evaluated 513 patients who underwent RARC and found a PSM in 35 patients (6.8%) [12]. Table 14.2 lists the largest studies looking at PSM rate in recent RARC series. These data included 887 patients and demonstrated an overall PSM rate of 6.54%, well within the standards for ORC. In addition, 29–56% of these patients harbored extravesical disease, suggesting a comparable disease distribution to ORC [11–15].

**Lymph node dissection**

Pelvic lymph node dissection for bladder cancer provides staging and diagnostic information as well as a potential therapeutic benefit. In 2004, Herr et al. suggested standards for lymph node dissection, recommending that 70–80% of patients should undergo at least a standard pelvic lymph node dissection and at least 10–14 nodes should be identified by the pathologist [10]. Subsequently, there has been much debate regarding the extent of pelvic lymph node dissection.
For ORC, Leissner et al. found a significant correlation between improved survival and increased lymph node yield in 447 patients. Patients with > 15 nodes removed experienced increased five-year recurrence-free survival (65% vs 51%), less loco-regional metastasis (17% vs 27%), and less distant metastasis (17% vs 10.5%) [16]. Their results showed increased cancer-specific survival in patients with > 15 nodes removed, regardless of tumor stage or lymph node positivity. In a 14-year retrospective review involving 1121 patients, Koppie et al. found a statistically significant relationship between overall survival and number of lymph nodes retrieved. They found that the probability of survival continued to rise with increased nodal counts, even up to 24 nodes, without any evidence of plateau. Although the median node count in their study was nine, they advocate extended node dissection and conclude that there is no minimum threshold for lymph nodes removed at radical cystectomy to optimize outcomes [17].

Although the limits of pelvic lymphadenectomy have been debated, it is suggested by some groups that an extended pelvic lymphadenectomy (above the iliac bifurcation) can improve staging and survival [16, 18, 19].

A phase III surgical trial is currently underway comparing standard and extended PLND. Sponsored by the Southwest Oncology Group, the study has an accrual goal of 620 patients, with projected completion of accrual in 2015. Objectives include assessment of disease-free progression, overall survival, and complications following the procedure [20]. A second phase III trial conducted by the Association of Urogenital Oncology and the German Cancer Association has completed accrual but no data have been reported to date.

As we await these critical data, we must evaluate the quality of lymphadenectomy in RARC. It has been unequivocally demonstrated that an adequate lymph node dissection can be performed robotically. Table 14.3 lists five large studies involving over 800 patients who underwent a robotic pelvic lymphadenectomy at the time of RARC. For these collective studies, the average lymph node yield was 18, notably above the recommended 15 nodes in open extended pelvic lymphadenectomy series mentioned above [11, 13–15, 21]. Whether or not 18 nodes is sufficient to find metastatic deposits is a matter of debate. Capitanio et al. performed a ROC analysis of number of nodes removed with the likelihood of finding lymph node metastasis in 731 patients. 23.8% of patients had lymph node metastasis and a median of 18.7 nodes was removed. They concluded that removing 15 nodes corresponded to a 50% chance of finding a positive node, whereas removing 25 nodes corresponded to a 75% chance. They suggested 25 nodes may be the lowest threshold for a lymphadenectomy [22].

### Table 14.2 Robot-assisted radical cystectomy series with surgical margin status.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects (n =)</th>
<th>Follow-up</th>
<th>Organ-confined disease (%)</th>
<th>Extravesical disease (%)</th>
<th>PSM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruthi et al.</td>
<td>100</td>
<td>n/a</td>
<td>337 (65.7)</td>
<td>176 (34.3)</td>
<td>35 (6.8)</td>
</tr>
<tr>
<td>Kader et al.</td>
<td>103</td>
<td>n/a</td>
<td>60 (58)</td>
<td>43 (42)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Kang et al.</td>
<td>104</td>
<td>12</td>
<td>73 (70.1)</td>
<td>31 (29.9)</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>Pruthi et al.</td>
<td>100</td>
<td>21.2</td>
<td>67 (67)</td>
<td>33 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Guru et al.</td>
<td>67</td>
<td>n/a</td>
<td>29 (43.3)</td>
<td>38 (56.7)</td>
<td>6 (8.9)</td>
</tr>
</tbody>
</table>

### Table 14.3 Robot-assisted radical cystectomy with lymph node dissections.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects (n =)</th>
<th>Lymph node yield (range)</th>
<th>Patients with positive LNs n (%)</th>
<th>Patients undergoing extended LND n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruthi et al.</td>
<td>100</td>
<td>19 (18–40)</td>
<td>20 (20)</td>
<td>n/a</td>
</tr>
<tr>
<td>Guru et al.</td>
<td>67</td>
<td>18 (6–43)</td>
<td>n/a</td>
<td>67 (100)</td>
</tr>
<tr>
<td>Kang et al.</td>
<td>104</td>
<td>18 (5–61)</td>
<td>10 (9.6)</td>
<td>33 (31.7)</td>
</tr>
<tr>
<td>Hellenthal et al.</td>
<td>437</td>
<td>17 (0–68)</td>
<td>80 (18)</td>
<td>n/a</td>
</tr>
<tr>
<td>Kader et al.</td>
<td>103</td>
<td>17 (2–52)</td>
<td>30 (31)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
It is believed that the quality of the lymph node dissection is more important than lymph node yield for bladder cancer. Davis et al. assessed the quality of robotic lymph node dissection by performing a second-look open PLND via a mini-laparotomy in 11 patients immediately after robotic PLND. The robotic technique yielded an average of 43 lymph nodes (range 19–63) while the open second look yielded only an additional average 4 lymph nodes (range 0–8) [23]. In 80% of these patients, no additional lymph nodes were found despite open dissection. Although limited by small sample size and lack of blinding, this study suggests that robotic lymph node dissection can be performed with completeness comparable to open surgery in expert hands.

In addition, extended PLND can be performed safely in a robotic fashion. At the University of Southern California, Desai et al. have described their experience with robotic extended PLND including 10 patients who underwent dissection to the inferior mesenteric artery. In the entire cohort, they harvested a median of 31 nodes and did not require any conversion to open surgery. This node count, however, is less than one half that reported by the same pathologists with ORC at USC. The median operative time was 400 minutes and estimated blood loss was 500 mL [24]. These data suggest that robotic super-extended PLND is feasible and can be performed safely in expert hands, although with longer operative times. Future studies will determine if extended lymphadenectomy will continue to thrive and whether operative duration will decrease with further experience. The question remains, however, whether a more extensive lymphadenectomy provides any benefit regarding overall or disease-specific survival.

Complications

Radical cystectomy is a lengthy and complex operation with high morbidity, even in experienced centers [25]. Shabsigh et al. reported up to 64% complications within 90 days after surgery, using standardized reporting [26]. Complications can lead to mortality, prolonged hospital stays, worsened quality of life, and significantly increased cost, representing a burden to patients and society. Many factors play a role in the morbidity, including pre-operative variables such as age, BMI, comorbidities, and nutritional status. Post-operative complications are common and diverse, including ileus, infection, cardiac complications, and thromboembolism. Many of these complications are not directly related to surgical approach and are therefore beyond the scope of this chapter. In fact, many complications are related to the reconstructive rather than the extirpative process. Since the majority of RARC data still include extracorporeal urinary diversion, complications specific to the cystectomy portion may be hard to tease out. Instead, we will focus on selective surgical factors and pre-operative variables that may play a role in predicting post-operative complications.

Ng et al. examined complication rates between robotic and open cystectomy in a non-randomized, prospective cohort study of 187 consecutive patients at Cornell. They found the robotic cohort had fewer total complications (41% versus 59%) as well as fewer major complications (10% versus 30%) at 30 days. Specifically, they found decreased pulmonary complications (0% versus 8.7%), decreased cardiac complications (12.4% versus 10.9%), and increased GI complications (30.9% versus 22.4%) in the robotic group [27].

Kader et al. compared 90-day complication rates between 100 patients who underwent ORC and 100 who underwent RARC at Wake Forest University. They found significantly decreased overall complications (35% vs 57%) and major complications (10% vs 22%) in the robotic group. Operative variables showed decreased EBL (423 mL vs 986 mL) and shorter hospital stay (7.8 vs 12.2 days) in the robotic group. However, patients in the open group had shorter operative times (393 vs 451 minutes) and were more likely to undergo neobladder formation (13% vs 3%), although utilization was low in both groups [13].

For the IRCC, Johar et al. reported 90-day complications in 939 patients who underwent RARC at multiple institutions. 68% of their patients underwent ileal conduit diversion while 32% had a continent diversion. At 90 days, 48% of patients had experienced a complication, of which 29% had Clavien Grades 1–2 and 19% Grades 3–5. The five most common groups of complications were GI (27%), infectious (23%), genitourinary (17%), hematologic (10%), and cardiovascular (5%). They also performed a variable analysis and found significantly increased complications in patients of advanced age, increased BMI, and those who received neoadjuvant chemotherapy in both univariate and multivariate analyses. Also, those patients requiring blood transfusion were more likely to
experience a major complication in both univariate and multivariate analysis [28].

**Elderly patients**

Bladder cancer primarily affects older adults, and therefore there is a predominance of elderly patients undergoing major bladder cancer surgery. Hence, it is particularly important to ascertain how well older patients fare after major bladder cancer surgery.

In 2012, Richards *et al.* compared outcomes at a single center in patients over 75 years old who underwent robotic and open radical cystectomy. They identified 20 patients in each group and performed a retrospective analysis of the data. Both cohorts were matched for comorbidities and each group had 80% of patients classified as ASA 3. They found the open group had shorter operative times (370 vs 461 minutes), but the robotic group had a lower EBL (275 vs 600 mL), shorter hospital stay (7 versus 14 days), and fewer major complications (10% vs 35% of Clavien 3 or higher) [29].

In a comparative evaluation of open versus robotic cystectomy, Knox *et al.* performed a sub-analysis looking at patients over 70 years old. At 30 days, patients over 70 years old were less likely to experience a complication after robotic compared to open surgery (17% vs 58%). They even found that elderly patients undergoing RARC had fewer complications than younger patients undergoing ORC (17% vs 59%) [30]. In concert, these studies suggest that RARC is at least as safe in the elderly population. Additional studies are warranted to validate the safety of robotics in this subgroup.

**Intracorporeal diversion**

Most of the patients in published RARC series underwent extracorporeal urinary diversion. In fact, only 3% of robotic bladder cancer surgeries in the US involve intracorporeal diversion [31]. Some factors that hinder intracorporeal diversion are the limited space to expose the bowel, port placement, and time efficiency. The putative benefits include improved bowel convalescence, less incisional morbidity, and shorter hospital stays.

Tyrizitis presented data on 70 patients who underwent total intracorporeal neobladder creation at the Karolinska University Hospital in Sweden, representing the largest series on intracorporeal neobladder creation. Median follow-up was 30 months, median operative time 400 minutes, and median EBL 500 mL. Four percent of patients required conversion to open surgery.

In the short term (<30 days), there were 17% minor complications and 31.4% major complications, while at 90 days the total complication rate was 58.5% (21.4% minor and 37.1% major) [32]. Although direct comparison was not performed, the operative time, EBL, and complications appeared satisfactory for a new technique on a complex surgery.

Goh *et al.* examined their series of intracorporeal ileal conduits and neobladders, including a total of 15 patients (7 with ileal conduit and 8 with neobladders). Average operative time was 7.5 hours for either reconstruction. The average time to regular diet was six days in the ileal conduit group and five days in the neobladder group, and the length of hospital stay was nine and eight days, respectively. 73% of patients had short-term complications (<30 days), with the vast majority (67%) having low-grade complications. Only 2 patients experienced complications between 30 and 90 days [33].

Currently, intracorporeal diversion is performed at select centers with highly experienced surgeons. However, if the safety and feasibility of this procedure persist as the literature matures, there will likely be further acceptance and growth of these techniques. The early data do not, however, suggest any benefit with respect to perioperative morbidity at the cost of potentially longer operations with associated increased cost.

**Randomized studies**

In the current era, randomized clinical trials remain the gold standard for comparison of surgical techniques. However, these studies are difficult to accomplish, as they require sufficient time for enrollment and follow-up and meticulous design and analysis. There are two completed randomized prospective trials thus far in the urologic literature comparing robotic to open radical cystectomy. First, Nix *et al.* performed a randomized controlled trial comparing 21 patients who underwent RARC with 20 patients who underwent ORC at the University of North Carolina. When evaluating perioperative variables, they reported decreased EBL (258 mL vs 575 mL), longer operative time (4.2 vs 3.5 hours), and more rapid return of bowel function in the robotic group. They also found fewer complications in the robotic group (33% versus 50%), however this did not reach statistical significance. For pathologic variables, they reported 0 PSMs in both
groups and similar lymph node yield (19 for RARC versus 18 for ORC) [34].

At the University of Texas Health Science Center in San Antonio, Parekh et al. performed a pilot randomized controlled trial comparing RARC to ORC in 40 patients. They found less EBL (400 mL vs 800 mL) in the robotic group. Pathologic outcomes were similar, with 5% positive margin rates in each group and no significant difference in nodal counts (11 vs 23) [35].

In Europe, Dr. Dasgupta and his group presented interim data from the CORAL trial, a randomized, three-arm, controlled trial comparing open, laparoscopic, and robotic radical cystectomy. Interim data were presented at the European Association of Urology Annual Meeting in 2013. Of 59 patients (20 ORC, 20 RARC, 19 LRC) treated at a single center, no significant differences in pathologic variables (e.g. PSM, lymph node yield) were found among any of the three groups. However, they did show that the robotic group had significantly decreased EBL (350 mL vs 650 mL), faster time to eating solid foods (4 vs 7.5 days), and longer operative times (367 vs 277 minutes) compared to the open group. No significant differences were seen in complications, Clavien grade, or mortality among any of the groups [36].

There are two ongoing large randomized trials in the US. MSKCC performed a study to evaluate differences in complications at 90 days between ORC and RARC, with goal accrual of 210 patients (clinicaltrial.gov identifier: NCT01076387). They presented an interim analysis on 116 patients at the AUA in 2013. They found no significant differences in overall complications (61% for robotic vs 62% for open). Sub-analysis of major complications (Clavien Grades 3–5) showed 24% in the robotic group and 22% in the open group. Significant differences were noted for OR time (454 vs 328 minutes) and EBL (518 mL vs 679 mL) in the robotic and open groups, respectively. Positive margin rates (3% RARC versus 5% ORC) and nodal counts (30 RARC vs 25 ORC) were equivalent. Since the study had met its objective with no significant difference noted for complications, the trial was closed for further accrual [37].

The second large trial is a multi-center, randomized controlled study with the goal of comparing oncologic efficacy between ORC and RARC (clinicaltrials.gov identifier NCT01157676). In particular, the study was designed to assess two-year progression-free survival. Fifteen major academic centers around the US are involved in this trial, with a goal accrual of 320 patients. As of August 2013, 286 patients have been randomized. Primary completion is projected in August of 2016 [38].

Thus far, data from randomized trials demonstrate that perioperative and pathologic outcomes for RARC are comparable to ORC. Pending the completion of the multi-center trial in the US and the CORAL trial in Europe, we should have sufficient data to understand whether RARC safety and oncologic efficacy is similar to that of the gold standard ORC.

**Conclusions**

The literature on RARC is increasing rapidly. Minimally invasive approaches to radical cystectomy are complex operations with a high bar for surgical quality metrics established for open cystectomy. After a decade of scrutiny, the collective literature renders a favorable verdict on the future of robotic cystectomy with respect to mastery of the technical aspects in expert hands. Most trials show equivalent pathologic outcomes, similar complication rates, improved blood loss, faster convalescence, and longer operative times with robotic surgery. Long-term survival outcomes from randomized trials are not available. With each passing year, surgeons are pushing the envelope and successfully tackling more complex and challenging aspects of the surgery. Although the vast majority of data presented is retrospective and therefore subject to bias, limited data from randomized controlled trials are very encouraging. Completion of these trials in the next few years should help us understand the proper place for robotic assisted laparoscopic radical cystectomy in contemporary urologic practice.

**Useful web links**


**References**

20 A Phase III Surgical Trial to Evaluate the Benefit of a Standard Versus an Extended Pelvic Lymphadenectomy Performed at Time of Radical Cystectomy for Muscle Invasive Urothelial Cancer. NCT01224665 http://clinicaltrials.gov/show/NCT01224665


CHAPTER 15
Role of extended lymphadenectomy

Eugene K. Cha¹, George N. Thalmann², and Bernard H. Bochner¹
¹ Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
² Department of Urology, University of Bern, Bern, Switzerland

KEY POINTS

• Radical cystectomy with bilateral pelvic lymphadenectomy provides accurate staging and optimal local and regional control for invasive bladder cancer.
• No consensus exists regarding the optimal extent of lymphadenectomy or the magnitude of therapeutic benefit conferred by lymphadenectomy.
• Some retrospective studies have reported associations between extended lymphadenectomy and improved clinical outcomes.
• There are two ongoing prospective clinical trials designed to define the relationship between the extent of lymphadenectomy and disease progression and survival.
• Future advances in our understanding of the appropriate extent of lymphadenectomy will require well-designed prospective clinical trials that directly compare varying extents of surgery with their ability to provide local and distant disease control as well as disease-specific survival.

The role of extended lymphadenectomy

For patients with muscle-invasive or high-risk non-muscle-invasive bladder cancer, radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) provides accurate staging and optimal local and regional control [1, 2]. The pathologic tumor (pT) stage and lymph node (LN) status are the strongest prognostic factors in patients undergoing RC for bladder cancer [1–4]. Although the importance of PLND in the management of invasive bladder cancer is generally accepted, no consensus exists regarding the optimal extent of PLND or the magnitude of therapeutic benefit conferred. While many retrospective studies have reported an association between the extent of PLND and clinical outcomes, there are no reports from prospective randomized trials to address this issue in regards to cancer-specific and overall survival.

Lymphatic drainage of the bladder – historical and anatomic considerations

Multiple anatomic studies have provided detailed descriptions of the lymphatic drainage of the urinary bladder. Colston and Leadbetter performed an autopsy study on 98 bladder cancer cases in 1936 [5]. They described pelvic or retroperitoneal metastases in 25% of the cases and postulated that lymphadenectomy might cure early loco-regional disease. In 1956, Whitmore and
Marshall published their experience of 100 consecutive bladder cancer patients treated with RC and a regional PLND [6]. In 32 patients with LN-positive disease, only 22% were alive at one year. Three LN-positive patients (9%) survived two years and only one (3%) was alive at three years. While these data represented an improvement in outcomes for LN-positive patients, the poor rate of survival in patients with regionally advanced disease led many to question whether RC was indicated in the presence of positive regional LNs.

Leadbetter and Cooper presented the surgical boundaries and approach for an extended PLND, in which the common iliac LNs were identified as the secondary echelon of metastases, intermediating between the pelvic and aortocaval LNs [7]. They proposed a thorough PLND at the time of RC that included the internal iliac, external iliac, pre-sacral, and common iliac lymphatics. Subsequently, Skinner championed the benefits of a thorough PLND at the time of RC and reported on its therapeutic benefits [8].

Studies have suggested that the primary lymphatic drainage for the urinary bladder includes the internal iliac, external iliac, obturator, and pre-sacral LNs; secondary drainage then progresses to the common iliac LNs and then into the para-aortic, interaortocaval, and paracaval LNs [9–11]. Abol-Enein described the location of LN metastases in 200 patients who underwent RC and extended lymphadenectomy up to the level of the IMA [9]. Of the patients, 48 (24%) had positive LNs. The authors found that extrapelvic nodal metastasis was always associated with involvement of the obturator and/or internal iliac LNs, suggesting that there were no cases in which the primary drainage sites were skipped.

In contrast, other studies have described multiple instances in which the primary drainage sites are skipped. Leissner et al., who reported on a prospective multicenter study of 290 patients who underwent RC with extended PLND [10], were not able to conclusively identify a primary drainage site. In 81 of 290 patients (27.9%) with positive LNs, there were a total of 599 LN metastases whose locations were mapped. Involved LNs above the bifurcation of the common iliac vessels comprised 35% of all positive LNs. A total of 20 patients (6.9%) demonstrated involvement of the common iliac LNs without evidence of disease within the more distal nodal regions (obturator, internal iliac, external iliac). In the 29 patients with a single LN metastasis, 10% were located above the bifurcation of the common iliac vessels.

Similarly, Vazina et al. analyzed 176 consecutive patients who underwent RC and extended PLND up to the aortic bifurcation [11]. They identified 43 patients (24.4%) with LN metastases. Of the patients with pT3 or pT4 disease, 16% had LN metastases outside the boundaries of a standard PLND (involvement of the common iliac LNs and at or above the aortic bifurcation). A skip lesion was identified in one patient who had positive LNs above the common iliac bifurcation without evidence of involvement of the more distal nodal basins. Likewise, in a study of 591 patients who underwent RC with mapping PLND, Tarin et al. identified 7 of 114 LN-positive patients (6%) with skip lesions (involved LNs only above the common iliac bifurcation) [12].

A recent single-photon emission computed tomography/computed tomography (SPECT/CT) lymphatic drainage study was performed to identify the primary lymphatic drainage of the bladder [13]. In this clinical trial, a radionuclide tracer was injected into the bladder wall and SPECT/CT was utilized in conjunction with intraoperative gamma probe verification. The study demonstrated that 19% of the primary lymphatic drainage sites are located proximal to the bifurcation of the common iliac vessels. In addition, the researchers found that the primary lymphatic drainage sites were sometimes found contralateral to the site of injection in the bladder.

Contralateral LN involvement in bladder cancer is not uncommon; it has also been demonstrated and evaluated in other studies. Leissner et al. reported on 119 patients whose bladder tumors could be strictly localized to one side of the bladder [10]. They found a significant rate of contralateral LN involvement, with the risk of contralateral LN metastases only slightly lower than for the ipsilateral side. Furthermore, in the 13 patients with unilateral tumors and a solitary LN metastasis, 3/13 (23%) of the solitary positive LNs were located on the contralateral side.

Taken together, these studies suggest that a standard PLND including only the internal iliac, external iliac, and obturator LNs may understage a proportion of patients undergoing RC.

**Prognostic importance of lymph node status**

Pathologic tumor (pT) stage and LN status are the strongest prognostic factors in bladder cancer patients undergoing RC and PLND [1, 3, 4]. Approximately
25% to 33% of bladder cancer patients undergoing RC and PLND found to have LN-positive disease will remain disease-free following surgery [1, 3, 10, 14, 15]. Madersbacher et al. reported a five-year recurrence-free survival rate of 33% for 124 LN-positive patients following RC and PLND [2]. Stein et al. reported the five- and ten-year recurrence-free survival to be 35% and 34%, respectively, for a series of 244 patients with LN-positive bladder cancer following RC and an extended PLND including all LNs from the aortic bifurcation to the inguinal ligament [16]. The Memorial Sloan-Kettering Cancer Center experience with 193 LN-positive bladder cancer patients undergoing RC and PLND (proximal limit at the bifurcation of the common iliac vessels) reported a 31% cancer-specific survival and 25% overall survival at five years [17]. Similarly, in a large multi-center study of bladder cancer patients undergoing RC and PLND that included 1550 LN-positive patients, approximately one-third were free of disease at five years [3].

Subgroups of LN-positive bladder cancer patients with a lower burden of disease and significantly better prognosis can be identified by considering the number of positive LNs, the size of the involved LNs, or the presence of extracapsular LN extension. Vieweg et al. reported the five-year cancer-specific survival of 193 LN-positive patients that underwent RC and PLND as 44%, 27%, and 0% for N1, N2, and N3 patients (1987 TNM system), respectively [17]. The median survival for these groups was 3.1, 1.9, and 0.9 years, respectively (p = 0.0006). The number of positive LNs has been identified as an independent prognostic factor following RC and PLND. Lerner et al. reported that patients with < 6 involved LNs had a significantly improved five-year survival compared to patients with ≥ 6 positive LNs [18]. An update of this series found that eight or fewer LNs was an optimized cutoff, as patients with ≤ 8 positive LNs demonstrated a 41% five-year recurrence-free survival and 37% five-year overall survival, as compared with 10% and 4%, respectively, in patients with > 8 positive LNs [16].

Additional measurements of the burden of regional disease, such as the size of LN metastases and the presence of extracapsular LN extension by tumor, have also been reported to be prognostically important. Mills et al. reported that patients with positive LNs > 0.5 cm or the presence of extracapsular extension within involved LNs had worse survival [14]. Multivariable analysis including the number of positive LNs, the size of involved LNs, and the presence of extranodal extension demonstrated that only the presence of extranodal extension remained an independent predictor of clinical outcomes. Fleischmann et al. evaluated extranodal extension in a cohort of 124 patients treated with RC and PLND found to be LN-positive and reported that it was an independent predictor of worse recurrence-free survival [19]. Fajkovic et al. demonstrated that extranodal extension was an independent predictor of worse recurrence-free survival and cancer-specific survival in a cohort of 748 LN-positive patients treated with RC and PLND, of whom 375 (50.1%) had extranodal extension [20].

In addition to nodal parameters, pT stage can be used to stratify LN-positive patients into prognostic subgroups. Lerner et al. demonstrated an increased risk of progression and death with advanced pT stage in the aforementioned study of 132 LN-positive patients (both p < 0.001) [18]. Vieweg et al. similarly found that LN-positive patients with non-organ-confined (pT category) disease (n = 149) experienced worse disease-specific survival than LN-positive patients with organ-confined disease (n = 44, p < 0.001) [17]. In the study by Fajkovic et al., advanced pT stage was significantly associated with disease recurrence and cancer-specific mortality in multivariable analyses [20].

**Extent of lymphadenectomy**

While the importance of the staging information provided by PLND is well accepted, the anatomic boundaries of the dissections required for adequate and optimal staging remain to be clarified. A lack of prospectively validated studies regarding this topic has led to ongoing controversy regarding the necessary extent of dissection [21]. A number of studies have examined the location of LN metastases based upon different anatomic templates of dissection.

Wishnow et al. studied the rate of involvement of the pelvic LNs within the common iliac chain and more distally within the obturator, internal iliac and external iliac LNs in bladder cancer patients undergoing RC [22]. In a series of 130 patients with clinically negative LNs at the time of RC, 88% of whom had common iliac LNs resected, 14% were identified to have LN metastasis. Seventeen of the 18 LN-positive patients had only one
or two positive LNs. None of the 17 patients with one or two microscopically involved LNs had involvement of the common iliac or lateral external iliac LNs. Based on these findings, the authors advocated limiting the proximal limit of the PLND to the bifurcation of the common iliac vessels for patients with no gross evidence of nodal involvement at RC.

A multi-center, prospective trial in which all patients underwent an extended lymphadenectomy (proximal limit of dissection at or above the bifurcation of the aorta) provided additional information on the distribution of positive pelvic LNs [10]. Of the 290 patients in this study, 81 (28%) had tumor involvement in 599 pelvic LNs. Involved LNs proximal to the bifurcation of the common iliac vessels comprised 35% of all positive LNs. Twenty patients (6.9%) had common iliac LN involvement without evidence of disease in the more distal nodal regions (obturator, internal iliac, or external iliac). Furthermore, in the 29 patients with only a single LN metastasis, 10% had the solitary positive LN proximal to the bifurcation of the common iliac vessels, providing support for extending the dissection to at least include the common iliac chain.

More recently at Memorial Sloan-Kettering Cancer Center, a series of 591 patients undergoing RC with extended mapping PLND identified 114 patients (19%) with LN involvement [12]. In the LN-positive group, 42 patients (37%) had involvement of the common iliac LNs (pN3), so these patients would have been understaged had a standard PLND been performed. Even more dramatically, seven of these patients (17% of pN3 patients, 6% of the LN-positive group) had no positive LNs within the true pelvis, so they would have been classified as LN-negative had they undergone a standard PLND. These data provide strong support for the need to extend the PLND to include the common iliac LNs in order to maximize the accuracy of nodal staging.

**Outcomes based on the extent of lymphadenectomy**

A number of studies have reported or suggested an association between a greater extent of lymphadenectomy and improved clinical outcomes. Investigators have generally compared number of LNs removed or different anatomic templates of lymphadenectomy.

**Number of lymph nodes removed**

The number of LNs removed has been widely used as a surrogate for the extent of lymphadenectomy and has been shown to be an important prognostic factor in bladder cancer patients undergoing RC and PLND [10, 23–25]. However, the number of LNs analyzed and reported depends not only on the quality, extent, and thoroughness of PLND, but also the packaging of specimens and pathologic processing [26–30]. While the benefit of PLND in terms of oncologic outcomes was initially reported in LN-positive patients [8], its value in LN-negative patients has also been suggested [31].

Leissner et al. studied 447 patients who underwent RC and PLND and reported an association between the number of LNs removed and clinical outcomes [32]. A threshold value of 16 LNs removed was used because the correlation between the total number of LNs removed and the percentage of patients with positive LNs was strongest at this cutoff. The authors found significant differences in recurrence-free survival and cancer-specific survival between patients with ≥ 16 LNs removed and patients with < 16 LNs removed.

Herr et al. analyzed data on 322 patients with muscle-invasive bladder cancer who underwent RC and PLND [23]. The authors evaluated the associations between the number of LNs removed with local recurrence-free and overall survival. In both LN-negative and LN-positive cases, improved overall survival was associated with a greater number of LNs removed. Herr and colleagues concluded that at least nine LNs should be removed by urologists and examined by pathologists to accurately define LN status.

May et al. reported on 1291 LN-negative patients who underwent RC and PLND and found that a higher number of LNs removed was associated with improved cancer-specific survival [31]. Similarly to Leissner and colleagues, the authors defined an LN threshold of 16 and showed that patients with < 16 and ≥ 16 LNs removed had five-year cancer-specific survival estimates of 72% and 83%, respectively \( (p = 0.01) \). Other groups have also performed studies to attempt to arrive at an optimal or minimal number of LNs to be removed [33–35].

The concern that patient selection may bias who receives a more extended PLND at RC led Koppie et al. to control for a variety of factors in their analyses to minimize the effects of surgical selection [25]. These authors found that older patients with a greater number of comorbidities were less likely to undergo more
extensive PLNDs. However, when correcting for age and comorbidity, the reported LN number was still associated with cancer-specific outcomes. The authors demonstrated that the probability of overall survival continued to increase with a greater number of LNs removed.

**Anatomic limits of dissection**

Given the limitations and biases of studies examining the number of LNs removed, some researchers have analyzed data regarding the impact of anatomically defined extended PLND on outcome in bladder cancer patients. Poulsen et al. compared two consecutive series of patients who underwent extended PLND up to the aortic bifurcation with those who underwent standard PLND [36]. The authors found that extended PLND was associated with improved five-year probabilities for pelvic and distant recurrence-free survival in patients with ≤ pT3a disease.

A prospective single-center, non-randomized study was performed by Abol-Enein et al. to evaluate the effect of a defined extended lymphadenectomy on recurrence-free survival [37]. Specimens from individual anatomic regions were packaged separately. An intraoperative decision to perform an extended PLND was based upon the status of the liver, body mass index, and performance status. The authors found that an anatomically defined extended lymphadenectomy up to the level of the inferior mesenteric artery (IMA), compared with a standard PLND (endopelvic region composed of obturator, internal iliac, and external iliac LNs), was associated with an improved recurrence-free survival for LN-positive patients independent of other clinicopathologic factors.

While no prospective randomized data are currently available comparing a standard PLND (bilateral external and internal iliac and obturator nodes) to more extensive PLND, comparative data from institutions performing varying extents of PLND do exist. Dhar et al. reported a comparative study evaluating disease-specific outcomes in 336 patients from one institution who underwent RC with a more limited PLND (boundaries included the pelvic sidewall between the genitofemoral and obturator nerves, and bifurcation of the iliac vessels to the circumflex iliac vein) to 322 patients from another institution who underwent a more extensive PLND (cerebral extent extended to the crossing of the ureters with the common iliac vessels and removal of all tissue along the lateral and medial portion of the internal iliac vessels) at RC [38]. Patients who underwent a more extensive PLND were more likely to be LN-positive (improved staging) and demonstrated improved recurrence-free survival. Five-year disease-free survival for LN-positive patients undergoing an extended PLND was 35% versus only 7% in patients that received a limited PLND. Furthermore, patients treated with a more extensive PLND were less likely to experience isolated local recurrence (4% extended vs. 38% limited); this difference persisted when analyzing by pathologic subgroups (1% extended vs. 19% limited in pT2N0 cases and 7% extended vs. 60% limited in pT3N0 cases).

A study by Zehnder et al. also compared outcomes at two separate institutions based upon different templates of PLND: 405 patients underwent extended PLND (mid-upper third of common iliac) and 554 patients underwent super-extended lymphadenectomy (up to the IMA) [39]. Patients who underwent super-extended lymphadenectomy had a higher number of LNs removed, a higher number of positive LNs, and a higher rate of LN metastasis (35% vs. 28%, p = 0.02) compared to those who underwent extended PLND. Despite these differences, the two groups had equal recurrence rates and similar five-year recurrence-free survival when stratified by pathological tumor stage or LN status.

Tarin et al. specifically addressed the outcomes of patients undergoing an extended PLND at RC based on location of the positive LNs [12]. In 591 patients, 19% were identified with positive LNs, including 7% with common iliac involvement (N3). Recurrence-free survival at five years was 38%, 35%, and 25% for N1, N2, and N3 positive patients, respectively. These differences were not statistically different and support the recent TNM modification to LN staging in bladder cancer [40].

**Lymph node density**

A concept that incorporates both the burden of disease and the extent of PLND is that of LN density [16, 41–43]. LN density is defined by the ratio of positive LNs to the total number of LNs removed [41, 42]. Some studies evaluating LN density have demonstrated its prognostic value; however, others have not shown that LN density adds additional prognostic information over that obtained by LN status alone or the number of positive LNs and the number of total LNs removed alone.

Herr retrospectively analyzed LN density as a prognostic factor and found that patients with an LN density
> 20% after RC and PLND had a worse prognosis compared with patients with an LN density < 20% [41]. Stein et al. analyzed LN density in their patients who underwent an extended PLND up to the aortic bifurcation and confirmed the prognostically relevant threshold of 20% [16].

As a follow-up to these studies, there have been a number of subsequent reports with a wide variation in the number of LNs removed, analyzing different threshold values of LN density [43–45]. Kassouf et al. reported the superiority of LN density compared with TNM nodal status in predicting cancer-specific survival after RC [43]. Wiesner et al. demonstrated that LN density was an independent predictor of cancer-specific survival in a multivariable analysis [45]. May et al. reported that LN density, but not TNM nodal status, was an independent predictor of cancer-specific survival in 477 LN-positive bladder cancer patients. In contrast, Tarin et al. showed no added prognostic value of LN density over LN status alone in a series of 591 patients who underwent RC with extended PLND [12]. Additional multi-center series have not noted added prognostic benefit to LN density over standard LN status (positive vs. negative) [3].

Ongoing randomized studies evaluating the extent of lymphadenectomy

The aforementioned studies have provided some insights into how the extent of PLND affects the accuracy of staging and may have an effect on clinical outcomes. However, there exists no high-level evidence to define the relationship between the extent of lymphadenectomy and disease progression, disease-specific survival, and overall survival. To that end, there are two ongoing clinical trials designed to address this question.

The Association of Urogenital Oncology and the German Cancer Association have completed accrual to a phase III trial comparing extended PLND (up to the IMA) with conventional PLND (obturator, internal iliac, and external iliac LNs). The primary endpoint is progression-free survival; the study has 90% power to detect a 15% difference at five years. Analyses are currently ongoing.

The trial being performed by the Southwest Oncology Group (SWOG) 1011 is similarly designed but utilizes different assumptions and power calculations. The SWOG study has 85% power to detect a 28% reduction in the hazard rate of progression or death with extended PLND compared with conventional PLND. The trial has a target accrual of 620 patients.

These two important clinical trials should help to characterize the magnitude of clinical benefit that may be conferred by an extended PLND at RC and will provide additional data to help define appropriate standards of care. Given the previously reported rates of N3 involvement in the overall group of muscle-invasive bladder cancer patients, careful evaluation of the frequency of common iliac LN involvement in these studies will determine if they were adequately statistically powered to reach their primary endpoints.

Conclusions

Anatomic and clinical studies of patients with bladder cancer have provided insights into the natural pathways of disease progression. Decades of experience with radical surgery for the management of muscle-invasive bladder cancer clearly illustrate the role that surgical quality may play in patient outcomes. Future advances in our understanding of the appropriate extent of lymphadenectomy will require well-designed prospective clinical trials that directly compare varying extents of surgery with their ability to provide local and distant disease control as well as disease-specific survival. These will allow for clear benchmarks and surgical standards that can then be broadly applied to clinical practice.

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Role of extended lymphadenectomy

CHAPTER 16

Management of the urethra in the cystectomy patient

Kamal S. Pohar1 and Norm D. Smith2

1 Department of Urology, Ohio State University, Wexner Medical Center, Columbus, OH, USA
2 Section of Urology, The University of Chicago Medicine, Chicago, IL, USA

KEY POINTS

- Contemporary studies report that the risk of developing a cancer of the retained urethra after radical cystectomy is low (ranging from 1–15%) and generally occurs within two years of surgery. Urethral cancer is likely secondary to urothelial field change and a metachronous tumor.
- The risk factors that best predict for urethral cancer after radical cystectomy include prostatic (men) or bladder neck (women) involvement by urothelial carcinoma, tumor multifocality, or a cutaneous urinary diversion.
- A pre-operative transurethral prostatic urethral biopsy is not as sensitive as an intraoperative frozen section of the distal urethral margin for predicting the likelihood of a urethral cancer. This is especially relevant in patients considering orthotopic urinary diversion.
- Intraoperative evidence of carcinoma on frozen section of the distal urethral margin is a contraindication to orthotopic bladder substitution.
- Most bladder cancer guidelines suggest the urethra should be monitored for life following radical cystectomy. Monitoring relies on urethral cytology, either a voided (orthotopic substitution) or washed specimen or routine urethroscopy, at defined intervals. A washed specimen has the highest sensitivity.
- Urethral cancers after radical cystectomy may be uncommon but carry a poor prognosis when at an invasive stage at diagnosis. A complete urethrectomy is the treatment of choice for most urethral cancers.

Introduction

Urothelial carcinoma can be a multifocal disease involving any portion of the urinary tract, including the urethra. Today it is uncommon to perform a simultaneous urethrectomy at the time of radical cystectomy unless there is a concurrent diagnosis of tumor in the urethra. This is different from the approach to the urethra in the past when prophylactic urethrectomy was recommended even in the absence of identifiable tumor. The change in management was influenced by several factors including greater enthusiasm for orthotopic urinary diversion and several reports describing a relatively low risk of developing a urethral tumor in most patients following radical cystectomy [1,2]. Furthermore, a recent analysis of the Surveillance Epidemiology and End-Results (SEER) database evaluated the timing of urethrectomy as a possible predictor for improved survival among men who underwent radical cystoprostatectomy for bladder cancer. No significant independent survival benefit was identified when comparing concurrent or salvage urethrectomy [3]. Nonetheless, in selected patients, concurrent urethrectomy remains appropriate at the time of radical cystectomy. Management of the urethra in the cystectomy patient will be reviewed in detail in this chapter.
Incidence of urethral cancer following radical cystectomy

Several theories have been proposed to explain how urethral cancers arise following radical cystectomy. Historically it was suggested that occult synchronous disease of the proximal urethra was present at the time of radical cystectomy, supporting the rationale for en bloc urethrectomy. However, studies evaluating synchronous disease suggest that when en bloc prophylactic urethrectomy was performed, urethral tumor was rarely identified [2]. Therefore it is more widely accepted that tumors of the urethra develop in a metachronous manner as a result of urothelial field change or tumor spillage and implantation during radical cystectomy. Another possibility is that of a true recurrence or contiguous invasion from a positive urethral margin at radical cystectomy.

Irrespective of the cause of metachronous urethral cancers, contemporary studies report that the risk after radical cystectomy is low (ranging from 1–15%) and generally occurs within two years of surgery [1, 4–11]. The primary risk factors for urethral second primary tumors after radical cystectomy include prostatic involvement by urothelial carcinoma, tumor multifocality, and cutaneous urinary diversion (as opposed to orthotopic bladder substitution). Clark and others reviewed 1054 patients after radical cystectomy and found that urethral cancers were detected in 4% of patients at a median of 18.5 months after cystectomy, with 42% of the urethral cancers diagnosed within one year [7]. Boorjian et al. similarly reviewed 1506 patients who underwent radical cystectomy and found urethral cancers in 5.6% of patients detected at a median of 13.3 months after cystectomy. Importantly, this risk is lifelong [9].

Risk factors for developing a urethral cancer following radical cystectomy

Male risk factors

Several studies have reported on pathologic variables identified at radical cystectomy that predict for the possibility of later developing a urethral tumor. For the most part, the findings were not uniform amongst the studies except for the presence of prostatic involvement by urothelial carcinoma [12–16]. A multivariate analysis of 729 male radical cystectomies reported that a past history of recurrent non-muscle-invasive bladder cancer, tumor multifocality, CIS, and urothelial cancer of the prostate independently predicted for a metachronous urethral cancer [15]. A study similar in design emphasized that the risk of urethral cancer was dependent upon the depth of urothelial cancer involvement of the prostate. Specifically, the five-year risk of urethral cancers following radical cystectomy was only 6% if there was no prostate involvement, while the risk increased to 15% with ductal involvement and 21% with stromal involvement. Tumor multifocality and carcinoma in situ of the bladder were not associated with the risk of developing a latent urethral cancer in this study [10]. Other studies have also suggested that neither multifocality nor CIS of the bladder increases the risk of developing a urethral tumor, however these factors are associated with the finding of a concurrent diagnosis of urothelial cancer of the prostate which, in turn, impacts on the risk of developing a urethral tumor following radical cystectomy [16].

The finding that prostate involvement by urothelial carcinoma increased the risk of a urethral cancer following radical cystectomy led to concerted efforts to better identify such patients pre-operatively. A diagnosis of urothelial carcinoma involving the prostatic urethra can be made in a myriad of ways prior to radical cystectomy, including prostate needle biopsy, fine needle aspiration, and transurethral resection (TUR) [4, 17–20]. Given these multiple modalities for diagnosis, the incidence and accuracy of detection of urothelial carcinoma of the prostatic urethral mucosa, ducts, and stroma vary widely. Wood and colleagues compared the accuracy of prostate needle biopsy, fine needle aspiration, and TUR biopsies of the prostate to detect urothelial carcinoma of the prostate in 25 men undergoing radical cystectomy. The accuracy of the three detection methods was 20%, 40%, and 90%, respectively [18]. Liedberg and others reported on 154 cystectomy patients and found pre-operative TUR biopsies of the prostatic urethra correctly identified 66% of patients with urothelial cancer of the prostate/prostatic urethra with 89% specificity and similar accuracy of detection of stromal and non-stromal
involvement: 66% and 65%, respectively [17]. Donat et al. performed TUR biopsies prior to radical cystectomy in 246 men and reported the sensitivity for prostatic stromal invasion was only 53%, with specificity of 77%, positive predictive value of 45%, and negative predictive value of 82%. The authors concluded that TUR biopsy did not accurately determine prostate involvement by urothelial carcinoma [4]. Therefore, the cumulative data suggested TUR biopsy did not reliably act as a surrogate of predicting which patients are at greatest risk of developing a metachronous urethral cancer post radical cystectomy.

As a result of these findings, additional studies focused on whether the presence of tumor at the apical urethral margin at radical cystectomy was more predictive for urethral recurrence. This was especially relevant in patients being considered for orthotopic bladder substitution. A prospective study first reported in the late 1990s determined that intraoperative frozen section of the apical urethral margin was more accurate than a pre-operative TUR evaluation of the prostatic urethra [20]. Several studies later confirmed that frozen section of the apical urethral margin identified most, if not all, patients who later developed a second primary tumor of the urethra (up to 100% sensitivity and specificity). These figures are consistently superior to the pre-operative TUR of the prostatic urethra (53% sensitivity, 77% specificity, 45% positive predictive value, and 77% negative predictive value) in predicting for urethral recurrence [4, 21]. A more recent retrospective study of 294 patients confirmed that a positive urethral margin is the strongest independent risk factor for diagnosis of a subsequent urethral cancer when compared with prostatic urethral and stromal invasion [13]. This finding emphasizes the importance of achieving a tumor-free urethral margin at radical cystectomy. Patients must be made aware that the presence of disease at frozen section will necessitate a cutaneous diversion and possible urethrectomy (either simultaneously or in a staged procedure).

In summary, the literature does not support the routine use of pre-operative transurethral prostatic urethral biopsies, as intraoperative frozen section of the apical urethral margin is most predictive of urethral recurrence in patients considering orthotopic urinary diversion. But it is important to note that a recent report demonstrated an alternative complementary rationale to consider TUR of the prostatic urethra as a means of identifying patients pre-operatively who are unlikely to have a positive apical urethral margin on frozen section. A total of 169 patients underwent TUR biopsy of the prostatic urethra and 120 had a negative TUR biopsy. Only two (1.7%) of these patients had a positive apical urethral margin on frozen section. The authors suggested that positive apical urethral margins are uncommon following radical cystectomy and that a negative TUR biopsy can reduce the need and the additional operative time required for intraoperative frozen section [22].

Female risk factors

Urethrectomy in the female is associated with no additional morbidity at the time of radical cystectomy and thus the urethra was traditionally removed en bloc with the bladder and anterior vaginal wall. However, in recent years, orthotopic bladder substitution in women has become more common. Accordingly, several studies have evaluated the incidence of synchronous or metachronous urethral tumor in women after radical cystectomy.

Stein and colleagues reviewed archival specimens from 67 women who underwent radical cystectomy and en bloc urethrectomy and found a highly significant association between tumor involving the bladder neck and concurrent tumor in the urethra ($p < 0.0001$). Importantly, all patients without tumor involvement of the bladder neck had no urethral tumor [23]. A similar finding was reported by Stenzl and colleagues, who found that tumor at the bladder neck ($p < 0.0001$) and/or trigone ($p < 0.035$) were most often associated with concurrent tumor in the urethra at radical cystectomy. It is noteworthy that only 2% of the 356 women included in the study had concurrent tumor in the urethra [24]. In a recent univariate analysis, both tumor at the bladder neck and tumor multifocality predicted for urethral cancer following radical cystectomy in the retained urethra [25]. Thus, the only consistent risk factor for synchronous or metachronous urethral tumor in women is tumor involving the bladder neck and even then the rate is low. Therefore, unless there is gross tumor involving the urethra, preservation of the distal urethra with the intent of performing an orthotopic diversion is appropriate in women as long as the frozen section demonstrates no tumor.
Impact of urinary diversion type on metachronous urethral cancers

Retrospective studies have reported a higher incidence of urethral cancer in patients undergoing cutaneous diversion when compared to orthotopic substitution. Freeman and colleagues published the first complete report on this subject in 1996. The study included 436 patients and urethral cancers occurred in 2.9% of orthotopic substitutions, which was significantly lower than the 11.1% rate in patients with cutaneous diversions. Even in patients with urothelial cancer involvement of the prostate, orthotopic substitution was associated with lower urethral cancer rates when compared to cutaneous diversions [10]. Stein and colleagues studied 768 consecutive male patients undergoing radical cystoprostatectomy, including 51% with orthotopic urinary diversion and 49% with cutaneous urinary diversion. Overall, 6% of patients developed a urethral second primary at a median of two years after cystectomy, including 8% with cutaneous urinary diversion compared to only 4% of patients with orthotopic urinary diversion. The estimated five-year risk of urethral cancer was 5% without prostatic urethral involvement at cystectomy but increased to 12% with prostatic mucosal/ductal involvement and 18% with prostatic stromal invasion. Any prostate involvement with urothelial carcinoma was associated with significantly increased risk of a subsequent diagnosis of urethral cancer [5]. Orthotopic urinary diversion was associated with significantly lower risk of urethral cancer compared to cutaneous urinary diversion. Patients without prostate involvement with orthotopic urinary diversion (lowest risk group) had an estimated 4% risk of cancer in the retained urethra versus an estimated 24% risk in patients with invasive prostate involvement and cutaneous urinary diversion (highest risk group). Prostatic involvement and type of urinary diversion were significant independent predictors of urethral cancer on multivariate analysis [5]. Similarly, urethral cancer after radical cystectomy and orthotopic bladder substitution in women is uncommon [6].

Post radical cystectomy monitoring of the urethra

It is generally agreed that the urethra should be monitored for life following radical cystectomy. Monitoring can include a surveillance approach in the absence of symptoms that relies on urethral cytology, either a voided (orthotopic substitution) or washed specimen or routine urethroscopy, at defined intervals. An alternative approach is to perform urethral cytology and/or urethroscopy only when indicated by patient history and physical (i.e. bloody urethral discharge, hematuria, pain, a palpable mass, or change in voiding habit).

Urethral cancer after radical cystectomy may be uncommon but carries a poor prognosis if diagnosed beyond the in situ stage. The optimal surveillance interval and method for the retained urethra after radical cystectomy lack consensus but patients who are asymptomatic at diagnosis may have higher-stage disease and decreased survival when compared to patients who are asymptomatic and discovered during surveillance [3, 9, 26, 27]. However, patients with symptomatic urethral cancers have no difference in median time to diagnosis when compared to asymptomatic patients with cytologic abnormalities [27]. Clark and colleagues reviewed 1054 patients after radical cystectomy and urinary diversion and assessed the presentation of patients with second primary tumors of the urethra and found the majority of patients were symptomatic (57%), including bloody urethral discharge, pain, or palpable mass. Thirty-one percent of patients were asymptomatic with abnormal cytology on urethral washings, with the remaining 12% of patients having a prophylactic urethrectomy based on radical cystectomy pathologic findings. Overall, 87% of patients with urethral cancers in this study underwent urethrectomy but 76% of patients were dead at a median follow-up of 26 months, with only 21% alive and disease-free. Median overall survival in patients with cancer of the retained urethra after radical cystectomy was only 28 months after the diagnosis of urethral cancer. Urethral stage at diagnosis was the most important predictor of overall survival [7]. Boorjian and others reviewed 1506 patients who underwent radical cystectomy and found the five-year cancer-specific survival following the diagnosis of urethral cancer determined by cytology was 80% compared to only 41% with symptomatic recurrence.
Further, symptomatic urethral cancers were associated with significantly higher stage of disease at urethrectomy. These investigators concluded that urethral cancer is uncommon, but the detection of asymptomatic urethral tumors was associated with significantly lower-stage disease and improved survival, thus they recommended lifelong surveillance of the urethra after radical cystectomy [9].

### Treatment for cancer of the retained urethra

A complete urethrectomy is the treatment of choice for a urethral cancer following radical cystectomy, regardless of stage. The procedure should include removing the entire length of urethra and the urethral meatus. Previous reports suggested up to a 27% risk of glanular urethral cancer if a subtotal urethrectomy was performed [28].

In patients with a non-invasive urethral cancer, consideration of a urethra-preserving strategy (i.e., transurethral resection) may be appropriate [29]. In a prospective study of a small number of patients with CIS of the urethra after radical cystectomy, the administration of intraurethral BCG weekly for six weeks resulted in an initial 80% complete remission rate but durability of the response was not determined [30].

Urethrectomy is indicated in men with invasive urethral disease despite the poor overall and disease-specific survival. In a large series of patients, Clark and colleagues reported a median survival of 28 months in patients with a urethral cancer following radical cystectomy. The factor most predictive of survival in this study was the stage of the urethral cancer, with invasive disease carrying the worst prognosis [7]. A more recent European publication found the median survival was 53.8 months with a five-year actuarial survival of 43% [15]. An analysis of the SEER database investigated the timing of urethrectomy as a possible predictor of improved survival in 2401 male patients following radical cystoprostatectomy. The use of concurrent urethrectomy at the time of radical cystoprostatectomy compared with salvage urethrectomy was not found to confer any significant independent survival benefit (hazard ratio: 0.775; 95% CI, 0.592–1.014; *p* = 0.0632) [3]. In women, given the very low rate of urethral cancers following cystectomy, a prophylactic urethrectomy without evidence of malignancy at the urethral margin does not have a significant impact on the oncologic long-term outcome after radical cystectomy [24, 31].

### Conclusion

The need to perform a concurrent urethrectomy at the time of radical cystectomy is uncommon, however almost 10% of patients develop a second primary tumor of the retained urethra during follow-up and a delayed urethrectomy may be necessary. The risk of developing a urethral cancer is higher in men with urothelial cancer involvement of the prostate and women with bladder neck involvement. For reasons that are not entirely clear, patients with an orthotopic bladder substitution are at lower risk of a metachronous urethral cancer. Lifelong monitoring of the retained urethra is necessary following radical cystectomy but whether routine surveillance urethral cytologies in all patients is necessary and provides a survival benefit remains unclear. Urethral cancer is associated with relatively poor overall and disease-specific survival and most urethral cancers are best treated by complete urethrectomy and meatectomy.

### Useful web links

1. [http://www.uroweb.org/guidelines/online-guidelines](http://www.uroweb.org/guidelines/online-guidelines)

### References


CHAPTER 17

The role of radical cystectomy in patients with unresectable or regionally metastatic urothelial carcinoma of the bladder

Scott Delacroix, Jr1, Nathan Lawrentschuk2, and Ashish M. Kamat3
1 Department of Urology, Louisiana State University School of Medicine, New Orleans, LA, USA
2 Department of Surgery, Olivia Newton-John Cancer Research Institute, Austin Hospital and Peter MacCallum Cancer Centre, Division of Cancer Surgery, Melbourne, Australia
3 Department of Urology, MD Anderson Cancer Center, Houston, TX, USA

KEY POINTS

• Survival in patients with Stage 4 carcinoma of the bladder is rare.
• Approximately 20% of patients with bladder cancer will present with locally advanced non-organ-confined disease, 4% with distant metastases, and about 25% with unsuspected (occult) positive regional nodes discovered at the time of cystectomy.
• There are no randomized trials of surgical consolidation after systemic chemotherapy in patients with cT4b or clinical node-positive disease (cN+ or M1-retroperitoneal nodes).
• In patients with unresectable or metastases limited to regional or retroperitoneal nodes, an aggressive multidisciplinary pre-surgical treatment pathway may allow select patients an opportunity for durable disease-free survival.
• In contrast to a neoadjuvant treatment pathway, the pre-surgical multidisciplinary pathway reserves aggressive consolidation of systemic disease for patients most likely to benefit.
• The role of high-quality radical cystectomy and lymph node dissection in patients presenting with unresectable (cT4b) or regionally metastatic node-positive disease is as an important but secondary step contingent upon an aggressive multidisciplinary pre-surgical systemic treatment strategy.

Introduction

Patients with bladder cancer who have disease that extends outside the boundaries of the bladder and into adjacent organs or those with clinically evident metastases to the regional nodes have traditionally been considered to be unresectable, i.e. not candidates for radical cystectomy with a curative intent. Over time, the role of high-quality radical cystectomy and lymph node dissection in these patients (cT4b or cN+) has emerged as an important but secondary step contingent upon an aggressive multidisciplinary pre-surgical systemic treatment strategy.

In patients with organ-confined disease, the five-year disease-specific survival (DSS) of radical cystectomy with extended pelvic lymphadenectomy is approximately 80–85%. However, approximately 20% of patients with bladder cancer will present with locally advanced non-organ-confined disease, 4% with distant metastases, and about 25% with unsuspected (occult) positive regional nodes discovered at the time of cystectomy [1–6]. Surgery cures only a minority of those cases with low-volume
pelvic nodal (N1) or locally advanced disease (stage pT3b–4). For those with extensive node-positive (N2–3) or metastatic (M+) bladder cancer, the chances of cure with surgery alone are low. The five-year survival of non-organ-confined bladder cancer following surgery alone is reported to be in the vicinity of 50% for node-negative patients and 23% in node-positive patients, even in series in which a high-quality extended pelvic nodal dissection is standard practice [1–6]. The use of neoadjuvant chemotherapy (NAC) in patients with invasive tumors and clinically node-negative disease (T2–T4a, cN0M0) has been shown to improve overall survival. When including all patients with cT2–T4 CNOM0, there is an approximately 5–6% improvement in overall survival [7–9], with an increasing advantage to NAC seen as stage increases [7, 10, 11]. It is hypothesized that the benefit of systemic therapy in conjunction with high-quality surgical extirpation and lymph node dissection is likely secondary to the treatment of micrometastatic disease in conjunction with downstaging of the primary tumor. Thus, the administration of multi-agent cisplatin-based chemotherapy in conjunction with surgery with curative intent has become the standard of care for high-risk muscle-invasive UCB [8, 12].

There are no contemporary randomized trials assessing the role of systemic therapy prior to surgery in patients with T4b (unresectable) or clinically node-positive/regional metastatic disease, since most such studies consider these as exclusion factors. For the purposes of this chapter, unresectable is defined as cT4b disease with direct invasion of adjacent pelvic organs or fixation to the pelvic muscular sidewall or pelvic bones as assessed by exam under anesthesia (EUA) or by pre-operative cross-sectional imaging. Although cT4b tumors can be considered “technically” resectable, the risk of positive surgical margins is great and ultimately associated with an unacceptable risk of local and distant recurrence [13]. Regionally metastatic disease is defined as patients with clinically positive lymph nodes below the bifurcation of the aorta (cN1, 2, 3). An additional cohort includes patients with non-regional clinically positive nodal disease confined to the infra-renal retroperitoneal lymph nodes (M1-retroperitoneal nodes). The management of patients with unresectable (cT4b) clinically detected regionally metastatic disease (cN1, 2, 3), and retroperitoneal nodal disease (cM1-retroperitoneal nodes) with primary transitional cell type urothelial carcinoma are the topic of this chapter.

Pre-surgical versus neoadjuvant chemotherapy

Any chemotherapy given prior to surgery can be considered “pre-operative chemotherapy.” By definition, however, the term neoadjuvant chemotherapy should be reserved for chemotherapy given in the setting of a resectable high-risk primary tumor and clinically node and distant metastatic negative disease. The overwhelming majority of patients receiving treatment under an NAC pathway will ultimately undergo local therapy with a curative intent (e.g., radical cystectomy and regional lymphadenectomy or pelvic radiation) after a specified number of cycles (usually 3–4) of therapy. On the other hand, patients with disease that is initially considered non-resectable or metastatic who undergo chemotherapy usually receive more cycles and are considered candidates for local extirpation based on response to therapy. In these patients, the targeted duration of systemic therapy is six cycles of cisplatin-based multi-agent chemotherapy in accordance with clinical trial of unresectable and/or metastatic disease but may be altered dependent on response and toxicity.

At many centers, the pre-surgical approach is applied to this highest of risk cohort [14–16]. Patients receive pre-surgical chemotherapy to achieve a significant response. Those patients with significant responses to chemotherapy (resolution of nodal disease and downstaging of unresectable disease) are then offered consolidative surgery. This approach yields disease-free survival rates at five years of approximately 33% [17]. Thus, although the terms are often used interchangeably, neoadjuvant chemotherapy and pre-surgical chemotherapy are two distinct treatment paradigms with differing goals and rationales.

Outcomes of surgical consolidation after systemic chemotherapy

There are no randomized trials of surgical consolidation after systemic chemotherapy in patients with cT4b or clinical node-positive disease, and the paradigm of surgical consolidation of residual regional or distant metastatic urothelial carcinoma has evolved from experiences in other disease types and observations on the natural history of this sub-group of patients. Dimopoulos et al. reported the patterns of failure after cisplatin-based
multi-agent chemotherapy in 58 patients with regionally and distant metastatic disease [18]. Of those patients presenting with regional metastases, 74% recurred regionally while only 26% recurred with visceral metastases. These findings suggested that select patients with urothelial tumors and regional metastases might benefit from surgical consolidation after pre-surgical chemotherapy.

Sweeney et al. reported on a series of 11 patients with M1-retroperitoneal nodal disease who underwent pre-surgical chemotherapy followed by consolidative retroperitoneal lymph node dissection [19]. All patients included had achieved at least a partial response to systemic therapy (>50% reduction in burden of disease and the absence of progression in any additional sites). Patients received systemic chemotherapy until maximal response and then received an additional two cycles followed by restaging evaluation before consolidative surgery. All but one patient received a multi-agent cisplatin-based regimen with a median of eight cycles of chemotherapy (range 3–10) delivered. Four-year disease-specific and recurrence-free survival rates were 36% and 27%, respectively. No patient with residual disease in more than two nodes survived for more than 13 months.

De Vries et al. reported on a series of 14 patients with metastatic urothelial carcinoma confined to the retroperitoneal lymph nodes [20]. All patients received pre-surgical chemotherapy with multi-agent cisplatin-based regimens; 5 patients achieved a clinical complete response and 9 had a major partial response (>50% reduction without development of new lesions or progression in any one lesion). In this series, the five-year disease-specific survival rate was 24%.

Nieuwenhuijzen et al. reported on a series of 52 patients with histologically confirmed clinically positive regional lymph nodes who received systemic chemotherapy followed by surgery [21]. All patients either underwent percutaneous biopsy/fine needle aspiration or underwent lymph node dissection with aborted cystectomy followed by administration of systemic chemotherapy. This was a formal pre-operative treatment pathway in which only patients with clinical CR or PR were offered consolidative surgery. After a median of four cycles of MVAC chemotherapy, 29% of patients had a clinical complete response and 57% had a partial response while 14% had stable or progressive disease, resulting in five-year survival rates of 42%, 19%, and 0%, respectively. In this series, all patients with residual nodal disease after pre-surgical chemotherapy (ypN+) died within two years.

Meijer et al. reported on a series of 152 patients with locally advanced or clinically node-positive disease (cN+ = 115, 76%) treated with at least two cycles of systemic chemotherapy [22]. Clinical complete response to chemotherapy was seen in 31.6%, partial response in 52%, stable disease in 7.9%, and progressive disease in 8.6%. The median overall survival based on clinical response was 49 months for CR, 17 months for PR, 10 months for SD, and 8 months for PD.

In those patients with clinical complete responses to chemotherapy (ycN0), 37.5% were found to still harbor residual disease (ypN+). Median overall survival based on pathologic response after surgery was 74 months for pCR, 22 months for pPR, 15 months for pSD, and 10 months for pPD. Patients with clinical positive lymph nodes (cN+) at presentation who did not achieve a clinical complete response in the lymph nodes (ycN+) had significantly worse outcomes when compared to those that achieved a clinically complete response (ycN0). The median OS for ycN+ (n = 35) was 8 months versus 23 months for ycN0 (n = 117) and the five-year OS was 9.6% for ycN+ versus 33.5% for ycN0 (p < 0.001). This series highlights the importance of systemic therapy and response to systemic therapy on the outcomes of patients with extravesical disease.

It must be noted that although patients with residual N+ disease after surgery have significantly worse outcomes than those with residual disease, a subset of patients who harbor residual microscopic disease at the time of consolidative surgery may still derive benefit from further chemotherapy in the adjuvant setting, as found in the series by Kassouf et al. [23]. Patients with ypN+ disease who received adjuvant chemotherapy had a significantly prolonged recurrence-free survival (13 versus 5 months) and a trend toward improved overall survival.

Unresectable T4b disease
In a series of 23 patients who initially presented with unresectable (cT4bN0) disease, Black et al. reported a five-year DSS of 60% with the integration of systemic therapy at MD Anderson Cancer Center [13]. These outcomes were achieved with careful patient selection and the utilization of the response to chemotherapy as the primary criterion for proceeding with consolidative surgery.
The majority of these patients were clinically deemed to have been downstaged enough to undergo surgery. Not surprisingly though, the majority of patients (n = 17/23) were still found to have invasive disease at the time of consolidative surgery. Significant predictors of reduced DSS included positive surgical margins (HR 5.34; CI 1.25–22.83) and the presence of pathologic nodal metastases (HR 29.33, 95% CI 3.13–275.19).

Dodd et al. reported on a cohort of 203 patients with unresectable or metastatic TCC of whom 50 (24%) underwent post-chemotherapy consolidative surgery with curative intent (palliative indications excluded) [16]. Indications for a pre-surgical consolidative approach included presentation with subdiaphragmatic nodal disease (64%), unresectable primary tumor (8%), or solitary visceral metastatic disease (28%). The majority of patients undergoing consolidative surgery achieved a major partial response (defined by the authors as a greater than 50% decrease in the sum of the longest perpendicular diameters of all measured lesions without simultaneous increase in the size of any lesion or the appearance of new lesions when assessed radiographically at least four weeks after pre-surgical chemotherapy). An analysis by extent of disease at presentation revealed a five-year disease-specific survival of 75% in patients with isolated T4b disease at presentation, 38% for patients with clinically node-positive regional lymph nodes (cN1, N2, N3), 18% for patients with non-regional lymph node metastasis (cM1-retroperitoneal nodes), and 11% for patients with an isolated solitary site of visceral metastases with primary tumor in place. Interestingly, an additional cohort of patients with metachronous isolated metastatic disease after prior treatment of the primary tumor (i.e. prior cystectomy) had a 30% five-year DSS after consolidative surgery directed at the recurrent/metastatic site alone.

No patients who achieved less than a major response (<50% reduction) to multi-agent cisplatin chemotherapy survived for five years [16]. Response to systemic therapy correlated with survival after consolidative surgery. Regardless of the sites of disease at presentation, a complete pathologic response with pre-surgical chemotherapy (n = 30) was associated with a 33% five-year survival (n = 10/30). None of the long-term survivors after consolidative surgery had residual pathologic disease in either the primary or nodal sites. All patients with persistent disease in both the lymph nodes and primary site experienced rapid recurrence and death.

Herr et al. reported on a cohort of 207 patients with unresectable primary bladder tumors (cT4bNxM0) or locally advanced tumors with significant regional nodal disease (cT3–4, cN2–3M0) [24]. Of these patients, 80 (39%) ultimately underwent surgical consolidation; the reasons for not proceeding with surgery (n = 127) included disease progression, performance status precluding surgery, and patient refusal (n = 12). One-third of the patients had complete response confirmed at consolidative surgery (ypT0N0). As in other studies, despite a complete response assessed clinically to pre-surgical chemotherapy, patients still had a significant risk of harboring occult residual disease (37.5%). However, unlike the series from Nieuwenhuijzen and Meijer [21, 22], 29% of patients with cPR or cCR who were ultimately found to have residual nodal disease (ypN+) were alive at five years. This indicates a potential therapeutic role to consolidative surgery; a glimpse of the extent of this benefit can be seen from the outcomes of the 12 patients who refused surgery. Of the 12 patients that refused consolidative surgery, 10 had what was deemed a complete response to chemotherapy, yet only one patient (8%) was alive at five years. Thus, surgical consolidation appears to be an integral part of a pre-surgical treatment pathway, and provides an added overall therapeutic benefit in subset patients.

Adjuvant radiation therapy

Despite initial promising reports, there is no significant evidence showing a survival benefit to pre-operative radiation therapy compared to systemic therapy on patients with unresectable or regionally metastatic transitional cell carcinoma of the bladder [25–29]. In the post-operative setting, adjuvant therapy trials using radiation after radical cystectomy and chemotherapy for bladder cancer are in development. However, inclusion and stratification factors have not been clearly established for further trial development. Christodouleas and colleagues [30] evaluated and refined a published risk stratification for loco-regional failure by applying it to a multi-center patient cohort. They found that pT classification above or below pT3, margin status, and the number of involved lymph nodes (with ten as threshold) are essential components in study design.
Proposed clinical algorithm

Current guidelines for patients with clinically positive regional metastases or unresectable disease at the time of presentation are shown in Table 17.1. While the EAU recommends cystectomy only with palliative intent in patients with T4b disease, the NCCN recommends systemic chemotherapy with a consideration of consolidative cystectomy or radiation therapy if a response is seen [31, 32]. For patients with N+ and M-nodal disease both guidelines suggest administration of systemic chemotherapy, with the NCCN guidelines adding consolidation (radiation or surgery) if there is a complete response to chemotherapy. Based on the available literature, we propose a clinical algorithm for patients with unresectable or regionally metastatic transitional cell carcinoma of the bladder (Figure 17.1 and Table 17.2). The proposed algorithm outlines a pre-surgical pathway of systemic chemotherapy (metastatic regimen, or clinical trial if available) with surgical consolidation considered for patients with significant responses to chemotherapy. Patients should be counseled that consolidation with curative intent is possible only after assessing the response to therapy and that the duration (number of cycles) of systemic therapy will depend on the response rather than a pre-defined number of cycles as is the case in NAC. PET-CT is becoming increasingly important to diagnose metastatic visceral and lymph node deposits [33]. An argument may be made to biopsy “hot” nodes pre-chemotherapy as a way to monitor treatment response, but recognizing that increased uptake is sensitive for deposits in these cases also allows for serial imaging. The role of biopsy is limited perhaps to centers without easy access to PET-CT or for study purposes.

cT4bN0

Accurate clinical staging of patients into the T4b category is paramount and here the importance of a carefully conducted examination under anesthesia (EUA) is critical. It is the authors’ experience that patients are sometimes inaccurately put into this category by virtue of inappropriately timed imaging (e.g. after a major TUR, with a CT scan showing stranding extending to the surrounding structures). In patients who are truly T4b, an upfront discussion regarding its implications is important; they should be counseled on the fact that upfront surgical treatment has an unacceptably high rate of positive margins and residual disease which is sub-optimally treated with adjuvant chemotherapy. If the patient is willing, a clear path encompassing systemic chemotherapy (metastatic regimen, or clinical trial if available) followed by consideration of local consolidated therapy should be offered.

Patients are re-staged after 3–4 cycles of pre-surgical chemotherapy, with cross-sectional imaging and repeat EUA and possible TUR with additional cycles given to maximal response. High-quality radical cystectomy with lymph node dissection is then recommended for patients who have a clinical response and downstaging to resectable disease (i.e. not T4b). Stable (unresectable) disease despite systemic therapy should prompt consideration

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>T2–T4a N0M0</th>
<th>Stage T4b</th>
<th>Metastatic (N+, M+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAU Guidelines 2011</td>
<td>Preferred: Radical cystectomy with neoadjuvant chemotherapy. Alternative: Bladder preservation with chemo-radiation</td>
<td>Palliative cystectomy only</td>
<td>Chemotherapy if appropriate first line; post-chemotherapy surgery after a partial or complete response may contribute to long-term disease-free survival in select patients</td>
</tr>
<tr>
<td>NCCN Guidelines 2013</td>
<td>Preferred: Radical cystectomy with neoadjuvant chemotherapy. Alternatives: Bladder preservation with chemo-radiation or if unfit TURBT or chemo-radiation or chemo alone</td>
<td>Chemotherapy then consider consolidative cystectomy or radiation therapy if response</td>
<td>N+ and M–nodal disease: Consider biopsy of nodes and chemotherapy with consolidation (radiation or surgery) if complete response to chemotherapy</td>
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of alternate chemotherapeutic regimens while local, regional, or distant progression despite systemic therapy should prompt a discussion regarding non-curative goals of therapy.

**cTanyCN1–3 and M1-retroperitoneal**

In patients presenting with clinical node-positive disease, consideration should be given to a percutaneous biopsy to avoid mis-classification of nodal enlargement from prior intravesical therapy or inflammatory response into this category. If the patient is willing, a clear path encompassing systemic chemotherapy (metastatic regimen, or clinical trial if available) followed by consideration of consolidative therapy should be offered. Patients are restaged after 3–4 cycles of pre-surgical chemotherapy with cross-sectional imaging, with the aim being a minimum of six cycles of chemotherapy in such patients (N+, M1). Since it has been demonstrated in prior reports that patients with significant residual disease after chemotherapy do poorly even with surgery, cross-sectional imaging pre- and post-chemotherapy with FDG-PET imaging may be beneficial in these select patients [34, 35].

In patients with a slower than expected response to chemotherapy, consideration for repeat EUA and TUR to assess the response in the primary tumor can be useful to guide the choice of alternate regimen. This could also be assessed by percutaneously guided biopsy of the nodal sites with the least response. In those patients with major response yet biopsy-proven or PET-suspected residual disease, strong consideration should be given to...
additional systemic therapy followed by re-staging [21, 24]. In patients who undergo a major response, high-quality radical cystectomy with extended lymph node dissection (removing all diseased nodes in addition to regional nodes) is then recommended. It is important to plan surgery in such a way that the template of node dissection involves all nodal basins that were suspicious prior to the start of chemotherapy to avoid leaving behind occult disease. Additional consolidation with bilateral full retroperitoneal lymph node dissection may have a therapeutic role in highly select patients after pre-surgical chemotherapy for M1 disease. Regional or distant progression despite systemic therapy should prompt a discussion regarding non-curative goals of therapy.

## Conclusion

Long-term survival in patients with Stage 4 carcinoma of the bladder is not common. In patients with unresectable or metastases limited to regional or retroperitoneal nodes, an aggressive multidisciplinary pre-surgical treatment pathway may allow select patients the opportunity for disease-free survival. Palliative or upfront surgical resection is not recommended. In the absence of an available clinical trial, these patients should be treated on a multidisciplinary pathway which allows for systemic chemotherapy and aggressive surgical consolidation for those patients most likely to benefit.

### Useful web links

1. [http://www.uroweb.org/guidelines/online-guidelines](http://www.uroweb.org/guidelines/online-guidelines)

### References

Radical cystectomy for unresectable/regionally metastatic UC


PART III

Primary bladder-sparing therapy
**CHAPTER 18**

**Radical transurethral resection**

Eduardo Solsona and Harry W. Herr

*Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

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**KEY POINTS**

- Radical transurethral resections consist of a fractionated and complete transurethral resection including the exophytic part of the tumor, followed by the complete resection of the endophytic part until the detrusor muscle is apparently cleaned of macroscopic tumor, and finally five or more biopsies from the healthy-appearing tumor bed. These samples should be sent separately to the pathologist, who should report that the tumor invades the muscularis propria from the second biopsy sample, and negative biopsies obtained from apparently healthy muscle from the tumor bed should be included in the third biopsy set.

- Restaging TUR should be performed from two to six weeks after initial TURBT in cases of a complete TURBT when a radical TURBT was not performed.

- Restaging TUR should be performed, at least, in the first and second endoscopic evaluation.

- Intravesical BCG should be indicated in cases of carcinoma in situ associated with the primary tumor, but this is not a contraindication for bladder preservation.

- Inclusion criteria for patients with muscle-invasive bladder cancer are essential for being included in a bladder-preservation program.

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**Introduction**

Transurethral resection is the mainstay for diagnosis and staging of bladder cancer as well as being the initial standard treatment for non-muscle-invasive bladder cancer. Radical cystectomy and pelvic lymphadenectomy remain the standard of care for patients with muscle-invasive disease; however, despite significant improvements in peri- and post-operative care, cystectomy is a morbid procedure [1]. Orthotopic urinary diversions and nerve-sparing procedures help to mitigate the two major sequelae of radical cystectomy – incontinence and impotence – however, not all patients are suitable for these technical improvements and their outcomes are still far from ideal.

Bladder preservation emerged as an alternative approach to radical cystectomy in order to decrease morbidity and to improve quality of life by preserving natural bladder and sexual functions. Bladder-preservation approaches encompass radical transurethral alone [2, 3], radiotherapy [4], partial cystectomy [5], complete transurethral resection plus systemic chemotherapy [6, 7], and complete transurethral resection plus radio-chemotherapy [8, 9]. Bladder sparing is not widely utilized among the urological community, except in patients who are unfit for cystectomy, and randomized trials comparing preservation programs and radical cystectomy are not available. Furthermore, bladder-sparing strategies require cooperation among different disciplines and a clear definition of inclusion criteria in order to be successful.
Radical TURBT

Radical TURBT entails a visibly complete (R0) resection of all invasive bladder carcinoma, as shown in Figure 18.1, where the lateral and deep margins are microscopically negative for tumor. Radical TURBT may be curative for some muscle-invasive cancers and is a vital prognostic and therapeutic component of successful bi- and tri-modal therapy.

The rationale for radical TURBT as a therapeutic approach in patients with muscle-invasive bladder tumors is based on the 10% to 15% incidence of pT0 in cystectomy specimens [10–12]. In cT2 patients not receiving neoadjuvant chemotherapy, the incidence of pT0 was 12% and < pT2 in 32% [13]. When patients received a complete (R0) TUR rather than biopsy only or incomplete TUR prior to radical cystectomy, pT0 rates increased to 20% in all patients and 31% in cT2 patients [14]. These data suggest that a substantial proportion of patients with muscle-invasive bladder cancer can be controlled with complete TURB alone, especially when the tumor is clinically organ-confined.

Further, in cT2 patients, the incidence of micrometastasis in pelvic lymph nodes is low, ranging from 6% to 9% after a complete TURBT [14, 15]. On the other hand, the absence of residual tumor in cystectomy specimens does not necessarily mean that patients are cured, since the five-year cancer-specific survival rate ranges from 82–92% [10–12]. Cure rates over 80–90% should be the goal for patients treated by radical TURBT.

Caveats to this rationale

The patients selected for radical TURBT will be those in whom a pT0 cystectomy specimen is predicted.

The main problem of radical TURBT as a therapeutic approach is the correct identification of candidate

![Figure 18.1](image)

**Figure 18.1** a) Necrotic 3-cm invasive carcinoma right base of bladder. b) Resection into lamina propria and superficial muscle. c) TUR into deep muscle. d) TUR into normal fat deep to invasive cancer.
patients, as we know that the clinical understaging error of TURBT compared to cystectomy specimens is 31% [16]. Moreover, the pathological tumor spread is double: frontal growth, which is easier to control with a complete TURBT when surgical margins are respected, and a digital spread, in which case, particularly if associated with the presence of independent micro-foci, a complete resection may be difficult to achieve, even if we perform a macroscopically complete resection. In fact, retrospective studies using TURBT showed that five-year survival rates ranged from 31% to 53%, but this rate increased to 54–63% in patients with clinical stage T2a [17–24]. However, this survival rate is inferior to the 73% ten-year disease-free survival reported on cT2 patients treated with cystectomy [25], demonstrating the limited value of TURBT in some patients. On the contrary, although cystectomy is overall superior to TURBT, these data demonstrate the feasibility of radical TURBT in selected patients with low-volume muscle-invasive disease.

**Prospective studies: inclusion criteria**

Attempting to overcome the limitations of clinical identification of potential pT0 after TURBT, three prospective series established inclusion criteria with this aim. Two series implemented a restaging TUR performed on visible tumor or scar, with deep tissue biopsies of the bed and including 1–2 cm of normal-appearing surrounding mucosa, within the first six weeks after initial TURBT. If the pathologist confirmed the absence of invasive cancer, patients were included in a surveillance program [2, 26]. The other series used as inclusion criteria the results of a fractionated TURBT which consisted of: first, resection of the exophytic part of the tumor; secondly, complete resection of the endophytic part, including the surrounding normal mucosa until the muscularis propria was apparently free of the tumor; finally, once the muscularis propria is macroscopically tumor-free, five or more biopsies are taken of deep muscle and perivesical fat. Patients who had tumor invasion of the muscularis propria in the second set of biopsies and negative biopsies on healthy-appearing muscularis propria in the third set of biopsies were included in a strict surveillance program [3]. The absence of hydroureteronephrosis and lymph nodes on CT or MRI scans and patients with clinically organ-confined tumors were common inclusion criteria in the three prospective studies. In Herr’s series, patients with residual bladder pTis and pT1 were also included in the bladder-preservation program and they received intravesical BCG [15]. In Solsona et al.’s series [3], all patients underwent systematically random bladder biopsies and patients with bladder pTis received intravesical BCG. Although the inclusion criteria used in the three prospective series were not completely identical, the aim of both sets of criteria is essentially the same: to identify patients with potential pT0.

**Prospective studies: results**

Initial results from the three prospective studies were comparable, with small differences in length of follow-up. Progression rates of 33%, 17%, and 28%, cancer-specific survival rates of 82%, 93%, and 81%, and bladder-preservation rates of 67%, 59%, and 75% were reported by Herr [2], Leibovici [26], and Solsona et al.’s series [27], respectively (Table 18.1).

In bladder-preserving strategies, the follow-up length and patient’s age are important in order to avoid interpretation bias in the final results, as elderly patients and

**Table 18.1** Prospective studies: initial outcome.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>45</td>
<td>133</td>
<td>27</td>
</tr>
<tr>
<td>Recurrence -cTa-1- (%)</td>
<td>21 (46.6)</td>
<td>35 (26.2)</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>Progression (%)</td>
<td>15 (33.3)</td>
<td>37 (27.7)</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>-cT ≥ M0</td>
<td>13 (28.8)</td>
<td>30 (22.4)</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>-cT0M1</td>
<td>2 (4.4)</td>
<td>7 (5.3)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Cancer-specific survival (%)</td>
<td>37 (82.2)</td>
<td>107 (80.5)</td>
<td>2 (93)</td>
</tr>
<tr>
<td>Bladder preservation (%)</td>
<td>30 (67)</td>
<td>100 (75.2)</td>
<td>19 (70)</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>5.1 (3–7 yrs)</td>
<td>83 (11–183 mos)</td>
<td>29 mos</td>
</tr>
</tbody>
</table>
short follow-up can artificially improve the patient’s survival and bladder-sparing rates. With this in mind, two prospective series [15, 27] reported their results with a minimal follow-up of ten years (Table 18.2). Bladder-preservation rates decrease about 10% over time, related to the incidence of non-muscle-invasive bladder cancer (66%) and local progression (27%), for which some patients require salvage cystectomy.

More recently, Solsona et al. [28] updated their series, with a minimum follow-up of 15 years, showing a cancer-specific survival rate of 79.5%, a progression rate of 30%, and a bladder-preservation rate of 58% (Table 18.3). These data, with long-term follow-up, confirm the feasibility of TURBT as monotherapy in a selected group of patients with invasive bladder cancer that meets strict inclusion criteria. In Herr and Solsona’s series, differences in inclusion criteria account for the different results. In Herr’s series, patients with residual pT1 were reported (26%); however, in Solsona’s series residual pT1 was not documented as restaging TURBT was not done systematically. Residual pT1 tumor on restaging radical TURBT is a predictive factor for progression and decreased survival [15, 29].

Age can have an impact on the final results. To assess this potential impact on survival, stratified age analysis was performed, showing that median and quartile age have a negative impact on overall survival (Figure 18.2), but age did not impact cancer-specific survival (Figure 18.3), lending support to the contention that TURBT is equally effective in young and elderly patients.

The strength of these results was confirmed in a sequential study carried out by Solsona et al. [28], demonstrating that the majority of events occurred during the first five years and cancer-specific survival rates slightly decreased from five to ten years (Table 18.4).

Although there are no randomized trials available comparing cystectomy and radical TURBT, in patients who had no residual muscle-invasive tumor on restaging TUR, Herr [15] compared 99 patients included in a surveillance program with 52 who elected immediate radical cystectomy; ten-year disease-specific survival was similar (76% vs. 71%, \( p = 0.3 \)) in both groups (Figure 18.4). Although this is not a randomized trial, patients met the same inclusion criteria, suggesting that selected patients with muscle-invasive bladder cancer treated by radical TURBT can achieve survival comparable to radical cystectomy.

Table 18.2 Prospective studies: ten-year outcome.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Herr [15]</th>
<th>Solsona [27]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation at</td>
<td>10-yr</td>
<td>10-yr</td>
</tr>
<tr>
<td>% recurrence</td>
<td>66</td>
<td>27.0</td>
</tr>
<tr>
<td>% progression</td>
<td>34</td>
<td>28.5</td>
</tr>
<tr>
<td>-T ≥ 2</td>
<td>–26</td>
<td>–23.3</td>
</tr>
<tr>
<td>-T0M1</td>
<td>–8</td>
<td>–5.2</td>
</tr>
<tr>
<td>% cancer-specific survival</td>
<td>75</td>
<td>79.5</td>
</tr>
<tr>
<td>% bladder preservation</td>
<td>57</td>
<td>64.9</td>
</tr>
</tbody>
</table>

Table 18.3 Patients’ status at the end of follow-up > 15 years.

<table>
<thead>
<tr>
<th>Patients’ status</th>
<th>No. patients (%)</th>
<th>Md (ms), FU (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence (Ta-Tis)</td>
<td>40 (30)</td>
<td>21 (3–247)</td>
</tr>
<tr>
<td>Progression (T ≥ 2)</td>
<td>40 (30)</td>
<td>–26 (3–135)</td>
</tr>
<tr>
<td>–T ≥ 2M0</td>
<td>–30 (22.5)</td>
<td>–29 (4–135)</td>
</tr>
<tr>
<td>–T ≥ 2M1</td>
<td>–3 (2.2)</td>
<td>–12 (3–36)</td>
</tr>
<tr>
<td>–T0M1</td>
<td>–7 (5.2)</td>
<td>–21 (11–30)</td>
</tr>
<tr>
<td>Cancer-specific mortality</td>
<td>27 (20.3)</td>
<td>34 (11–183)</td>
</tr>
<tr>
<td>Lost follow-up</td>
<td>9 (6.7)</td>
<td>159 (120–238)</td>
</tr>
<tr>
<td>Alive free of tumor</td>
<td>14 (10.7)</td>
<td>220 (192–264)</td>
</tr>
<tr>
<td>Died free of tumor</td>
<td>83 (62.4)</td>
<td>99 (44–305)</td>
</tr>
<tr>
<td>Bladder preservation</td>
<td>77 (57.8)</td>
<td>87 (11–305)</td>
</tr>
</tbody>
</table>

Candidates for TURBT

In spite of the excellent results at long-term follow-up of the two prospective series, the progression rate was high at 30% and 34% and this had a negative impact on survival in both series, with 70% of these patients dying of disease. However, salvage radical cystectomy saved 53% to 87% of patients who failed locally [15, 29]. In both series similar percentages of patients, 8% and 5.3%, developed distant metastasis without local invasive recurrence. Although radical cystectomy was an excellent rescue therapy in patients fit for this procedure, this obviously has a negative impact on bladder preservation.

Being aware of this concern, several studies assessed different factors in order to better define the incidence of pT0 in cystectomy specimens related to clinical stage. When patients were differentiated in cT2a and cT2b, the incidence of pT0 was 42% and 11%, respectively [14]. These data suggest that patients with clinically organ-confined tumor were the most suitable for a complete TURBT, particularly in cT2a. These patients
Overall survival

Figure 18.2 Overall survival according to median and quartile age.
**Figure 18.3** Cancer-specific survival according to median and quartile age.
are best defined by a radical or restaging TURBT, insisting on microscopically negative lateral and deep tumor margins.

In the Solsona series, uni- and multivariate analysis to predict understaging (invasive recurrence at first cystoscopy) and true progression (invasive recurrence after at least a negative cystoscopy) were carried out. In this analysis, no independent predictive factor for understaging was identified, but more than 3 cm of sessile tumor ($p = 0.0236$) was related to a greater risk of understaging. This was not true for papillary tumors ($p = 0.64$) [30]. The understaging in the first 59 patients was 12% and this rate decreased to 7% in the whole series of 133 patients when patients with sessile tumors of more than 3 cm were excluded [30]. Regarding true progression, bladder pTIS was independently predictive (HR = 2.27; $p = 0.013$), however in an updated analysis including all patients with long-term follow-up, pTIS lost its predictive value ($p = 0.132$) [28].

In the Herr series [15], 73 patients who had no tumor (cT0) on restaging TUR fared significantly better than 26 patients having persistent cT1 disease ($p = 0.003$) (Figure 18.5). This difference was also observed on local progression-free survival ($p = 0.001$). Of patients with cT0, 50 (68%) survived with bladder intact and only 7 (27%) of those with cT1 on restaging TURBT ($p = 0.001$).

Herr et al. [31] also found that in stage cT2 tumors, p53 overexpression was a predictor of successful bladder preservation. However, in a separate analysis, p53 overexpression was tested in a pilot study of 60 patients from Solsona’s series [32]. Among them, 10/18 (56%) patients with p53 overexpression and 16/42 (38%) patients with negative p53 developed progression, but the difference was not statistically significant [32]. Additional evaluation has failed to support the use of p53 as a prognostic marker in patients with urothelial cancer [33, 34].

In summary, patients with muscle-invasive bladder cancer most suitable for bladder preservation with radical TURBT will be those with clinical cT2 receiving a complete TURBT with pathological confirmation (negative biopsies on healthy-appearing tumor bed or restaging TURBT). Patients with sessile morphology more than 3 cm and those with residual T1 tumor are best treated by immediate cystectomy.

### Table 18.4 Survival and bladder preservation at 5, 10, and 15 years.

<table>
<thead>
<tr>
<th>Events</th>
<th>5 yrs.</th>
<th>10 yrs.</th>
<th>15 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (%)</td>
<td>73.7</td>
<td>39.8</td>
<td>24.8</td>
</tr>
<tr>
<td>Cancer-specific survival (%)</td>
<td>81.9</td>
<td>79.5</td>
<td>79.5</td>
</tr>
<tr>
<td>Progression-free survival with bladder preserved (%)</td>
<td>75.5</td>
<td>64.9</td>
<td>57.8</td>
</tr>
<tr>
<td>Local progression-free survival with bladder preserved (%)</td>
<td>81.8</td>
<td>70.2</td>
<td>61.9</td>
</tr>
<tr>
<td>Progression (%)</td>
<td>25.5</td>
<td>27.7</td>
<td>30.0</td>
</tr>
<tr>
<td>Recurrence (%)</td>
<td>25.6</td>
<td>28.6</td>
<td>30.0</td>
</tr>
</tbody>
</table>

![Figure 18.4](image-url) Survival comparison between TURBT alone and cystectomy in patients who met the same inclusion criteria.
TURBT as a prognostic factor

The excellent results achieved in prospective studies pose the dilemma of whether a radical TURBT has a therapeutic value by itself or whether it has a prognostic value for selecting patients with good prognosis in whom a more aggressive approach could constitute overtreatment.

In multimodal bladder preservation strategies, the quality of TURBT was an important predictive factor for five-year survival. A complete TURBT was related to a better survival when compared to a TURBT with residual tumor (57% vs. 43%, \( p = 0.003 \)) [35]. These findings are supported by another study which, by stratifying patients by complete TURBT, or micro- and macroscopic residual tumor, demonstrated five-year survival rates of 70%, 47%, and 33% \( (p < 0.001) \), respectively [36]. These data suggest that in patients treated with tridmodal therapy, a complete TURBT was an excellent prognostic factor for survival.

In radical cystectomy series, a complete TURBT has been associated with a higher incidence of downstaging \( (p \leq 1) \), 70.6% vs. 16.7% [37], and a lower incidence of positive lymph nodes, 9.7% vs. 14.7% [14] when compared with residual tumor after TURBT. Downstaging, especially the attainment of P0, after a complete TURBT was also related to a better recurrence-free survival \( (p = 0.04) \), even after adjusting for lymph node status (HR = 0.33, \( p = 0.07 \)) and chemotherapy applied (HR = 0.29, \( p = 0.044 \)) [38]. In patients with clinical cT2 and pathologically \( p \leq 2\)N0 – without neo or adjuvant chemotherapy – downstaging \( (p \leq 1) \) after TURBT was an independent predictive factor for recurrence-free (HR = 0.20, \( p = 0.002 \)) and cancer-specific survival (HR = 0.24, \( p = 0.02 \)) [13]. These data also suggest that, in patients with clinical T2 tumors, downstaging by TURBT to P0 is an excellent prognostic indicator that identifies patients with a lower incidence of positive lymph nodes and better survival compared to patients with invasive residual tumor after TURBT.

Solsona’s strategy for bladder preservation in patients with muscle-invasive bladder cancer was based on the type of TURBT; when a complete TURBT was achieved and biopsies of the muscularis propria were negative for tumor, patients were included in a surveillance program, whereas those with positive biopsies were offered three cycles of systemic chemotherapy or radical cystectomy [7]. When comparing the cancer-specific survival of these three groups, a significantly higher survival rate was achieved in patients treated with radical TURBT alone than in those receiving TURBT plus systemic chemotherapy or in those treated by cystectomy (Figures 18.5 and 18.6). All patients included in these three groups met the same inclusion criteria, biopsies on apparently healthy muscularis propria after a complete TURBT was the only discriminating factor and this was the only independent predictive factor for cancer-specific survival in multivariate analysis (HR = 2.643, \( p = 0.0007 \)) [30]. Therefore, biopsies of the muscularis propria probably identify a subgroup of patients with good prognosis in whom a microscopic complete TURBT is feasible and reliable.

Pooling all these data, downstaging to pT0 by a complete TURBT evaluated microscopically by negative biopsies on healthy-appearing muscularis propria or negative restaging TURBT will preselect a favorable cohort of patients with a better prognosis for whom a
complete TURBT is possible and sufficient to provide similar survival outcomes to more aggressive therapies, such as cystectomy or TURBT plus chemotherapy or radio-chemotherapy, which may represent an overtreatment for this particular group of patients.

TURBT and neoadjuvant chemotherapy

A complete and fractionated TURBT with negative biopsies on muscularis propria free of tumor or cT0 on restaging TURBT in selected patients with muscle-invasive bladder cancer have shown excellent survival and bladder-preservation rates. However, the progression rate is as high as 30–34% [15, 28]. The majority of this progression occurred during the first two to three years, suggesting an important understaging, as reported by Herr in a comparative study between TURBT and cystectomy [15] and as shown by the appearance of distant micro-metastasis in 5–8% of patients without tumor recurrence in the bladder tumor [15, 28]. Keeping in mind these issues, in 60 patients with complete TURBT and minimal residual invasive tumor after restaging TURBT or cT0 on radical TUR or partial cystectomy after four cycles of neoadjuvant cisplatin-based chemotherapy, Herr and colleagues reported 92% of 120 patients survived a median of 68 months and 86% retained their bladder.

Follow-up of patients treated with TURBT

The implementation of a bladder-preservation protocol encumbers the urologist with the longitudinal burden of surveillance because local (non-muscle and muscle-invasive) recurrence as well as a risk of distant metastasis remain persistent threats for patients treated using this strategy. Early detection of local recurrence can lead to successful salvage therapy. In all series [15, 28, 34, 35], local progression and recurrence were observed after five and ten years. The long-term follow-up of Solsona's series allowed a sequential assessment of recurrence and progression. As a whole, the vast majority of local and systemic recurrence occurred during the first three years, 70% of patients developed local progression and 100% distant metastasis without synchronous bladder tumor. In contrast, 30% of these patients developed local progression from 36 to 180 months but none after this period. Herr also observed that 74% of patients developed local invasive recurrence during the first 5 years and the remaining 26% from 5 to 15 years. Non-muscle-invasive bladder cancer recurrence followed a similar trend to the local invasive progression but it also took place after 180 months (Table 18.5).
According to these data, a follow-up schedule was developed, suggesting a three-monthly endoscopic evaluation and semi-annual imaging. After three years, annual surveillance for upper tract or distant disease imaging is not necessary. The endoscopic interval can be increased to one every six months for 5 years and then annually for up to 15 years, as only 5% and 7% of patients at risk will develop local progression in these two periods, respectively.

### Summary

In patients with invasive bladder cancer, radical TURBT (complete and fractionated) with negative biopsies on healthy-appearing muscularis propria of the tumor bed or restaging TURBT with cT0 in biopsy specimens is a reasonable therapeutic option in selected patients who meet strict inclusion criteria. However, bladder recurrences and local progression remain risks in the retained bladder, requiring lifelong surveillance. A promising alternative therapy to radical TURBT alone is TURBT combined with systemic chemotherapy to treat undetected local, nodal, or distant disease. Initial radical TURBT with a complete restaging TURBT is an essential component of bladder-sparing treatments.

### Useful web links


### References


CHAPTER 19
Partial cystectomy

Ahmed Haddad, Yair Lotan, and Arthur I. Sagalowsky
Department of Urology, The University of Texas Southwestern Medical Center, Dallas, TX, USA

KEY POINTS
• Partial cystectomy represents a less morbid alternative to radical cystectomy in the management of highly selected cases of muscle-invasive bladder cancer.
• Partial cystectomy is indicated for small, solitary tumors in the mobile portion of the bladder, with negative random bladder biopsies and with normal bladder capacity.
• Patients with either urachal adenocarcinoma or urothelial tumors in bladder diverticula may also be candidates for partial cystectomy.
• Key technical considerations are adequate mobilization of the bladder and the application of parallel clamps to the bladder beyond the tumor under cystoscopic guidance. These steps prevent tumor cell spillage and ensure negative resection margins.
• Laparoscopic and robotic approaches to partial cystectomy have been described. However, long-term follow-up for patients undergoing these minimally invasive procedures is not available.
• Carefully selected patients who undergo partial cystectomy have long-term survival rates comparable to those from radical cystectomy.

Introduction

The American Cancer Society estimates that the lifetime risk of developing bladder cancer in the United States is 1 in 26 for men and 1 in 90 for women [1]. On average, 15 to 30% of all patients with bladder cancer are diagnosed with muscle-invasive tumors, and radical cystectomy with pelvic lymph node dissection represents the gold standard therapy for this group of patients [2]. Perioperative complications occur in 25–75% of patients treated by radical cystectomy; and 30-day mortality rates associated with this procedure range from 1–3% [3, 4]. Various bladder-preservation therapies have been proposed in an attempt to minimize the morbidity associated with the surgical management of muscle-invasive bladder cancer (MIBC). Options for bladder-preservation therapy include trimodality therapy (aggressive transurethral resection (TUR) followed by chemotherapy/radiotherapy) or, in select patients, TUR or partial cystectomy (alone or with chemo-radiation therapy) [5, 6]. The advantage of partial cystectomy over TUR is that it allows for complete pathologic staging of the tumor and pelvic lymph nodes. In carefully selected patients, partial cystectomy can achieve comparable survival outcomes to radical cystectomy, with significantly less morbidity [7, 8]. In this chapter we discuss the selective role of partial cystectomy in MIBC and its role in the specific cases of tumors in bladder diverticula and urachal adenocarcinomas.
**Indications**

The most important factor in performing a successful partial cystectomy is proper patient selection. Bladder cancer is an aggressive disease that places the entire urothelium at risk. Current treatment options such as radical cystectomy, radiotherapy, and systemic chemotherapy do not significantly change the overall survival rates once there is metastatic disease [9, 10]. Strict criteria should be employed when considering patients for partial cystectomy. These criteria exclude the majority of patients with MIBC, with previous reports estimating that only 5.8% to 18.9% of patients with MIBC were suitable candidates for partial cystectomy [11]. Early recurrences may be due to inadequate surgical margins or to new tumor from the inherent urothelial field change effect of urothelial carcinoma.

The indications for partial cystectomy in MIBC have not changed significantly in 30 years [12]. Ideal candidates for partial cystectomy are patients with a solitary invasive tumor in the mobile portion of the bladder (dome), with negative random bladder biopsies and normal bladder capacity. Patients with a prior history of urothelial carcinoma are at increased risk for further recurrence and progression following partial cystectomy [8, 13]. However, partial cystectomy may be considered after unifocal recurrence at the same site as the prior tumor in patients with medical comorbidities that would preclude radical cystectomy. Tumors larger than 4 cm are associated with increased recurrence after partial cystectomy [14]. Large lesions increase the difficulty of complete resections with negative margins and there is a practical limit to the size of lesion that will allow for a partial cystectomy. While the need for ureteral reimplantation can increase the difficulty of the procedure, it is not an absolute contraindication [15]. Herr and others have recommended expanding the indications for partial cystectomy to include those patients who responded well to neoadjuvant chemotherapy [16, 17]. Partial cystectomy may also be indicated for tumors that are inaccessible to complete TUR, either due to tumor size or location [15]. As discussed below, patients with urachal adenocarcinomas or urothelial tumors in bladder diverticula are special instances where partial cystectomy may be suitable.

**Cancer in bladder diverticulum**

Partial cystectomy offers a good treatment option for patients with isolated tumors in a diverticulum or those difficult to resect (Figure 19.1a). Tumors in bladder diverticula are difficult to treat endoscopically due to limitations in access through sometimes narrow diverticular openings and the risk of perforation of the thin diverticular wall. The absence of a muscular layer allows invasive tumors to become locally advanced or to metastasize earlier [18, 19]. Thus, tumors in diverticula should be treated early, since spread beyond the lamina propria (pT1) in bladder diverticula would involve the perivesical fat (pT3), resulting in progression to a stage that would no longer be organ-confined. If the ureter enters near or within the diverticulum, ureteral reimplantation may be required. Partial cystectomy is not ideal for large, high-grade or invasive tumors in diverticula as the most important predictor of outcome is the stage of the tumor [20]. The literature on management of tumors in diverticula with partial cystectomy is limited to a few small case series, and 2–5-year cancer-specific survival has ranged from 16–80% [19–22]. In order to improve outcomes, Garzotto et al. recommended combining partial cystectomy with chemotherapy or radiation therapy [23]. Unfortunately, there are no randomized trials evaluating combination therapies as compared with partial cystectomy.

**Adenocarcinoma and urachal tumors**

Adenocarcinomas of the bladder are rare and aggressive cancers. They can be primary or urachal in origin [24]. In one of the largest series of adenocarcinoma of the bladder (n = 185), el-Mekresh and colleagues found an overall five-year disease-free survival of 55% [25]. They recommended radical cystectomy over partial cystectomy in managing these tumors. While partial cystectomy was appropriate for some patients, Xiaoxu et al. found poor three-year survival rates (33%) after partial cystectomy for primary adenocarcinoma of the bladder [26].

There is generally less controversy about performing partial cystectomy for urachal tumors, in large part because they are commonly located in an area of the bladder where the procedure is technically possible (Figure 19.1b). Urachal cancers comprised only 0.22% of all bladder cancers diagnosed at a single institution [27]. Compared to
non-urachal primary adenocarcinomas of the bladder, urachal adenocarcinomas are more likely to present with metastasis (30% vs 15%) [28]. The primary determinant of treatment outcome is the initial tumor stage (organ-confined versus extravesical and/or node-positive) rather than the extent of the surgery (partial versus radical cystectomy). For disease of equal pathologic stage, partial cystectomy for urachal adenocarcinoma provides equivalent outcomes to radical cystectomy in most series [27, 29]. Bruins et al. reported on 152 patients with urachal adenocarcinoma including 53% of patients who underwent partial cystectomy. The five-year overall survival was 45%, and radical cystectomy did not provide a survival advantage over partial cystectomy [29]. Similarly, Henly et al. found no difference in five-year survival between partial and radical cystectomy (43% and 50%, respectively) [27].

Partial cystectomy for urachal adenocarcinoma should include en bloc excision of the entire urachus and umbilicus, posterior rectus fascia, and overlying peritoneum [30]. When these principles are adhered to, outcomes for locally confined disease are excellent. Incomplete resection of the umbilicus is consistently associated with higher relapse rates [30, 31]. In a study of 49 cases of urachal carcinoma at the Mayo Clinic, median survival was significantly better for tumors confined to the urachus compared with extrarachal spread (median survival 10.8 years vs 1.3 years, p < 0.001) [32]. For this reason, aggressive therapy, with neoadjuvant or adjuvant systemic

Figure 19.1 Examples of tumors successfully treated with partial cystectomy. a) Axial CT image of tumor in diverticulum. The tumor is visualized as a thickening at the neck of the diverticulum. b) Axial CT image of urachal adenocarcinoma. The tumor is seen as an enhancing mass at the dome of the bladder. c) Coronal T2 weighted MRI of large benign fibromyxoid tumor involving the dome of the bladder. d) Sagittal CT image of benign leiomyoma involving the anterior wall of the bladder.
chemotherapy (cisplatin and 5-fluorouracil or FOLFOX [folinic acid, fluorouracil, and oxaliplatin]) is advocated in patients with advanced disease at presentation [33].

Other non-urothelial tumors

Partial cystectomy has also been utilized successfully for management of non-urothelial tumors of the bladder. There are a multitude of case reports describing the use of partial cystectomy for benign lesions such as leiomyoma [34], inflammatory pseudotumor [35], pseudosarcomatous fibromyxoid [36], neurofibroma [37], pheochromocytoma [38], and paragangliomas [39] (Figure 19.1c and d). Some patients with bladder sarcoma may be eligible for partial cystectomy. However, the cornerstone of sarcoma management is wide excision and negative surgical margins during the first surgery. Thus, patients must be very carefully selected to avoid recurrences [40, 41]. Partial cystectomy is often necessary in cases with non-urologic malignancies such as locally invasive colorectal carcinoma. These patients can have good local control following partial cystectomy without a decrease in survival provided negative margins are obtained [42, 43].

Pre-operative considerations

The main objective of pre-operative evaluation is proper staging of the bladder tumor. Cystoscopy with random bladder biopsy can exclude patients with multifocal disease or CIS. Bimanual examination under anesthesia allows for evaluation of the extent of tumor involvement and bladder mobility. In cases where there is a concern regarding bladder function, an evaluation of bladder capacity is in order. Pre-operative testing should include a CT scan or MRI and chest radiograph to evaluate for evidence of metastatic disease. Sagittal MRI is the best imaging modality for assessment of local extension along the urachal tract.

Surgical technique

The surgical technique for open partial cystectomy has been described previously [11, 44]. The main objectives include:

1. Full mobilization of the bladder;
2. Complete excision of the tumor with a clear margin of normal bladder;
3. Prevention of tumor cell spillage;
4. In the case of urachal tumors, removal of the urachal tract and umbilicus;
5. Watertight closure of the bladder in two layers with absorbable suture;
6. Bilateral pelvic lymphadenectomy;
7. Insertion of a pelvic drain;
8. Use of a Foley catheter in preference to a suprapubic tube due to the risk of spilling tumor cells into the pelvis or along the suprapubic tube tract.

The bladder can be approached either extra- or intraperitoneally. In the extra-peritoneal approach, the parietal peritoneum is peeled from the bladder with blunt and sharp dissection, leaving the peritoneum attached only over the area adjacent to the tumor. Next, the peritoneum is cut so that a patch is left adherent to the bladder overlying the tumor. The peritoneal defect is then closed and the peritoneum and contents packed out of the way. The bladder should be fully mobilized. Ligation of the ipsilateral superior vesical artery and occasional ligation of the vas deferens behind the bladder base on the affected side help achieve the necessary mobilization (Figure 19.2a).

We recommend that the risk of tumor spillage be minimized by never opening the tumor-bearing portion of the bladder or the bladder remnant in the operative field. While one surgeon identifies the tumor cystoscopically, the other places clamps, such as a Satinsky clamp, to isolate the tumor with a margin of normal-appearing bladder [45]. Two parallel sets of clamps are applied with one closing the normal bladder and the other closing the tumor side (Figure 19.2b and c). The tumor is removed and the cut edge is oversewn without opening the bladder. Ensuring a negative margin is essential, since most patients with a positive margin will suffer recurrence [7]. A 2-cm negative macroscopic margin was recommended in older studies. However, a negative microscopic margin is sufficient and may be obtained by the parallel clamp technique described above while still maintaining maximal safe volume of the bladder remnant. Frozen sections of the resected margin are sent routinely in all cases to confirm a negative margin has been obtained. Current guidelines recommend that all cases of partial cystectomy should have a complete lymphadenectomy employing the same template as for radical cystectomy [46]. Despite these guideline recommendations, recent population
studies have shown that a lymphadenectomy is performed in under 25% of partial cystectomies [47, 48]. The benefit of instillation of intravesical chemotherapy such as mitomycin-C into the bladder prior to beginning the procedure to reduce the number of viable cancer cells and to lower the risk of tumor spillage or recurrence, while logical, is not proven [45]. Any instilled mitomycin-C must be carefully irrigated from the bladder prior to cystotomy to prevent intraperitoneal spillage of mitomycin-C, which leads to an intense chemical peritonitis. Localized radiotherapy to the abdominal wall (25 Gy fractionated over five doses) has also been described to prevent local abdominal wall recurrence [14]. This, however, is not standard. Further, with proper case selection and application of the surgical principles to avoid tumor spillage, abdominal wall recurrences are low in contemporary series.

Recently, laparoscopic and robotic approaches for partial cystectomy in patients with invasive bladder tumors have been described [49–52]. These studies demonstrate the technical feasibility and safety of these minimally invasive procedures. Outcome measures are not robust to date due to the small sample size and very limited follow-up. Mariano et al. described six patients who underwent laparoscopic partial cystectomy for urothelial carcinoma (pT1–3). Negative resection margins were obtained in all patients. During the follow-up period of 12–50 months, only one patient developed metastatic disease [49].

A variety of techniques has been described to ensure negative margins with laparoscopic or robotic partial cystectomy. One group described undocking the robot to allow the use of a resectoscope and the Collins knife to demarcate tumor margins while the assistant used the robotic camera to view the bladder extravesically [51]. However, this technique has a risk of tumor spillage. Kim et al. described tattooing the margins using a cystoscopic fine needle with India ink [53]. Correct port placement is an important technical consideration for all the laparoscopic partial cystectomies. This is particularly true for
patients with urachal tumors. The distance of the camera port above the umbilicus must allow for complete excision of the umbilicus and entire urachal tract en bloc with the bladder dome [50]. Longer follow-up will be needed to determine if the minimally invasive approaches provide comparable outcomes to open partial cystectomy.

### Perioperative complications

In older series, operative mortality with partial cystectomy was 5–20% (Table 19.1). The morbidity and mortality in contemporary series are considerably less. In 58 patients undergoing partial cystectomy for MIBC at Memorial Sloan-Kettering Cancer Center, Holzbeierlein et al. reported no perioperative deaths, and complications were limited to two urinary tract infections requiring intravenous antibiotics, one wound dehiscence, one case of atrial fibrillation, and two cases of prolonged ileus [7]. There was no perioperative mortality in another series of 25 patients undergoing partial cystectomy, with few post-operative complications—lymphocele (4%), ileus (8%), and distal ureteral stricture (4%) [14]. Following careful closure of the bladder, urinary leakage is infrequent. In cases where the ureter is reimplanted, ureteric fistula and ureteral anastomotic strictures have occurred [54]. Decreased bladder capacity can cause problems with bladder function. Cummings et al. found that 18% (19/101) of their patients experienced compromised bladder function with significant storage symptoms, and five patients required palliative diversion [55]. Smaldone et al. reported that 20% of patients complained of storage symptoms at a median follow-up of 43 months [14]. In the Memorial series, none of the patients required a separate procedure for insufficient bladder capacity [7].

### Follow-up and outcomes

Recurrent tumors in the bladder remnant are seen in 29–78% of patients following partial cystectomy for MIBC (Table 19.1). Most recurrences are new tumors

<table>
<thead>
<tr>
<th>Authors</th>
<th>Years of accrual</th>
<th>Number of patients</th>
<th>Operative mortality (%)</th>
<th>Stage</th>
<th>Bladder recurrence (%)</th>
<th>Salvage cystectomy (%)</th>
<th>5-yr OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma et al. [13]</td>
<td>2000–2010</td>
<td>101</td>
<td>0</td>
<td>T2–3</td>
<td>45.5</td>
<td>10</td>
<td>58</td>
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<tr>
<td>Knoedler et al. [56]</td>
<td>1980–2006</td>
<td>86</td>
<td>N/A</td>
<td>T1–4</td>
<td>38</td>
<td>19</td>
<td>36</td>
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<tr>
<td>Fahmy et al. [48]</td>
<td>1983–2005</td>
<td>714</td>
<td>N/A</td>
<td>N/A</td>
<td>30.7</td>
<td>23.7</td>
<td>49.8</td>
</tr>
<tr>
<td>Smaldone et al. [14]</td>
<td>1995–2005</td>
<td>25</td>
<td>0</td>
<td>T1–2</td>
<td>44</td>
<td>N/A</td>
<td>70</td>
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<tr>
<td>Capitanio et al. [47]</td>
<td>1988–2004</td>
<td>1573</td>
<td>N/A</td>
<td>T1–4</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Kassouf et al. [8]</td>
<td>1982–2003</td>
<td>37</td>
<td>N/A</td>
<td>T2–3b</td>
<td>29.7</td>
<td>13.5</td>
<td>67</td>
</tr>
<tr>
<td>Holzbeierlein et al. [7]</td>
<td>1995–2001</td>
<td>58</td>
<td>0</td>
<td>Ta–4</td>
<td>19</td>
<td>6.9</td>
<td>69</td>
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<tr>
<td>Dandekar et al. [64]</td>
<td>1984–1993</td>
<td>32</td>
<td>3.1</td>
<td>T2–3b</td>
<td>43.8</td>
<td>N/A</td>
<td>50</td>
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<tr>
<td>Kaneti [54]</td>
<td>1958–1978</td>
<td>55</td>
<td>7.3</td>
<td>Ta–4</td>
<td>38.0</td>
<td>1.6</td>
<td>47.1</td>
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<tr>
<td>Lindahl et al. [15]</td>
<td>1955–1975</td>
<td>45</td>
<td>4.4</td>
<td>Ta–4</td>
<td>70.0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Schoborg et al. [65]</td>
<td>1962–1977</td>
<td>117</td>
<td>0.0</td>
<td>T1–3</td>
<td>78.0</td>
<td>7.7</td>
<td>40</td>
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<tr>
<td>Faysal and Freiha [66]</td>
<td>1958–1973</td>
<td>54</td>
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<td>T2–4</td>
<td>29.0</td>
<td>3.7</td>
<td>48</td>
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<tr>
<td>Merrell et al. [67]</td>
<td>1950–1974</td>
<td>49</td>
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<td>T1–3</td>
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<td>N/A</td>
<td>60</td>
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<tr>
<td>Brannan et al. [68]</td>
<td>1945–1971</td>
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<td>T1–4</td>
<td>N/A</td>
<td>N/A</td>
<td>43.3</td>
</tr>
<tr>
<td>Cummings et al. [55]</td>
<td>1955–1965</td>
<td>153</td>
<td>3.0</td>
<td>T1–4</td>
<td>75.6</td>
<td>N/A</td>
<td>41.9</td>
</tr>
<tr>
<td>Utz et al. [62]</td>
<td>1952–1959</td>
<td>104</td>
<td>9.6</td>
<td>Ta–3</td>
<td>32.7</td>
<td>N/A</td>
<td>41.8</td>
</tr>
</tbody>
</table>
and occur in the bladder secondary to the multifocal nature of bladder cancer. The majority of recurrences in the bladder are non-invasive (52–69%) and can be treated endoscopically with or without intravesical BCG or chemotherapy [8, 56]. Long-term follow-up with cystoscopy and cytology is essential since recurrences within the bladder have been reported to occur more than ten years after partial cystectomy [8]. Cystoscopy and evaluation of urinary cytology should be continued at three-monthly intervals for at least two years, and then at appropriate intervals thereafter on a schedule similar to that for tumors managed endoscopically. We recommend regular CT or MRI scans of the abdomen and pelvis, plus chest X-rays, particularly in patients with high-grade or high-stage disease.

Five-year overall survival for patients with MIBC treated with partial cystectomy is 40–80% (Table 19.1). In a large case-controlled study of patients from the Surveillance Epidemiology and End Results-9 database, Capitanio et al. identified 1573 patients who underwent partial cystectomy and 5670 patients treated with radical cystectomy for bladder cancer. Approximately half of the patients in the partial cystectomy group had muscle-invasive disease. Similar five-year overall survival was seen in both the partial cystectomy (57.2%) and radical cystectomy (51%) groups (p = 0.21) [47]. In a study of 714 patients who underwent partial cystectomy from 1983–2005 in Quebec, the five-year overall survival was 49.8% [48]. In this study, 23.7% of patients went on to require a salvage radical cystectomy for recurrent disease at a median time of 17.6 months. Patients who underwent salvage radical cystectomy had a 50% increased mortality compared to those who had upfront radical cystectomy (HR = 1.5, p = 0.006).

Multimodality bladder-preservation approaches incorporating partial cystectomy with chemotherapy and/or radiation have been described [57–59]. Patients with adverse prognostic features such as extensive invasion of the perivesical fat or nodal metastases should be considered for adjuvant chemotherapy. However, the benefit of adjuvant therapy in this setting is unclear. The role of perioperative radiation therapy is also uncertain. Perioperative radiation therapy has been associated with improved survival in some series [60] but had no benefit in others [61, 62]. Partial cystectomy may be performed safely after pre-operative doses up to 5000 cGy, and possibly higher, as long as the bladder volume is sufficient.

Patients with localized invasive disease recurrence should undergo salvage radical cystectomy if medically eligible. Bruins et al. reported on 72 patients who underwent salvage radical cystectomy following failed partial cystectomy [63]. Sixty-one percent of patients had organ-confined disease after salvage radical cystectomy, and five-year overall survival after salvage surgery was 41%. Thus, long-term survival is a possibility after failed partial cystectomy.

Partial cystectomy is a suitable treatment option in a minority of patients with MIBC. However, in these carefully selected patients, partial cystectomy provides equivalent long-term outcomes to radical cystectomy. Compared to radical cystectomy, partial cystectomy is associated with significantly reduced perioperative morbidity as well as the preservation of bladder and sexual function. Thus, partial cystectomy should be considered in appropriate candidates as an alternative to radical cystectomy.

Useful web links


References

Partial cystectomy


CHAPTER 20

Integrating chemotherapy and radiotherapy for bladder cancer

Lior Z. Braunstein¹, William U. Shipley², Nicholas D. James³, Andrea B. Apolo⁴, and Jason A. Efstathiou²

¹ Harvard Radiation Oncology Program, Boston, MA, USA
² Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA
³ School of Cancer Sciences, University of Birmingham, Birmingham, UK
⁴ Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

KEY POINTS

• Selective bladder-preservation trimodality therapy integrates transurethral resection of the bladder tumor (TURBT) along with chemotherapy and radiation for patients who are either poor candidates for radical cystectomy or who are otherwise highly motivated to preserve their native bladder.

• Trimodality therapy is a safe and effective option for many patients with bladder cancer, and the retained native bladder generally functions well with acceptable long-term toxicity to pelvic organs.

• In selected patients, bladder-preservation therapy with salvage cystectomy reserved for invasive recurrences has similar durable long-term outcomes to immediate radical cystectomy.

• Invasive local recurrences after definitive bladder preservation can often be salvaged via radical cystectomy with acceptable surgical outcomes.

• Studies based on elderly patients for whom radical cystectomy carries a high risk of morbidity show that combined chemoradiation is a well-tolerated and effective approach.

• Given that muscle-invasive bladder cancer (MIBC) is a systemic disease with failures often attributed to occult micrometastases at presentation, the addition of neoadjuvant or adjuvant chemotherapy to definitive chemoradiation merits further investigation.

• Biomarkers of radiation response are being actively studied and may soon facilitate the identification of those patients who are most likely to derive the greatest oncologic benefit from chemoradiation-based regimens.

Introduction

Modern oncologic principles are increasingly focused on organ preservation and optimizing functional outcomes. In an evolution from Halstedian en bloc resection, advances in conservative surgical techniques, radiation delivery, and systemic therapies have allowed for alternatives to radical surgical extirpation without compromising oncologic efficacy. Indeed, organ-sparing therapies are now the standard of care in cancers of the head and neck, breast, limb sarcomas, and anus.

Radical cystectomy has long represented the standard of care for muscle-invasive bladder cancer (MIBC). This operation, involving removal of the bladder and pelvic lymph nodes (along with the uterus and proximal vagina in women; or the prostate and seminal vesicles in men) has been extensively characterized with regard to long-term morbidity and oncologic efficacy. In light of data
showing higher perioperative risk with advanced age [1, 2] or with medical comorbidities [3], bladder-sparing approaches to MIBC have been developed through multidisciplinary collaboration. Trials of bladder-preservation therapy have employed a number of treatment algorithms, thereby giving rise to some differences between the predominant European and United States (US) practices. Whereas both approaches comprise a maximal transurethral resection of the bladder tumor (TURBT) followed by radiotherapy with concurrent sensitizing chemotherapy [4, 5], the prevalent US practice incorporates an interval cystoscopic assessment (with repeat biopsy) of treatment response after ~40 Gy before completing the chemoradiation course to ~65 Gy [4, 6]. Conversely, European practice generally integrates the cystoscopic assessment after chemoradiation has been completed (to ~65 Gy) [5, 7]. In either case, if residual or recurrent invasive disease is present at the time of cystoscopic evaluation, patients are counseled to undergo a salvage cystectomy (Figure 20.1).

Current cystectomy series in patients with clinically-staged MIBC demonstrate five-year pelvic control rates of up to 80% and five-year overall survival (OS) rates of 40% to 60% [8, 9]. Improvements in cystoscopic resections and radiotherapeutic delivery, along with advances in chemotherapeutic agents have made bladder preservation a feasible option for many patients. Long-term follow-up data show that bladder-sparing therapy does

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**Figure 20.1** The schema of selective bladder-preservation therapy comprises a) maximal transurethral resection of the bladder tumor (TURBT), followed by b) either an induction course of radiotherapy (~40 Gy) with concurrent sensitizing chemotherapy or a full course of chemoradiation to ~65 Gy with no treatment break. Treatment response to this combined-modality approach may then be evaluated by c) cystoscopy with re-biopsies either after ~40 Gy of induction chemoradiation or following the full dose of continuous chemoradiation. Those patients who undergo an assessment of treatment response and manifest persistent disease are counseled to proceed promptly to bladder removal. Conversely, patients without cystoscopic evidence of residual disease after induction chemoradiation undergo d) consolidative chemoradiation (~65 Gy) followed by e) an aggressive regimen of cystoscopic surveillance and tumor site re-biopsies, with f) immediate salvage cystectomy if an invasive local recurrence is detected.
not yield significant rates of late failure or bladder dysfunction [4, 10, 11]. Based on these findings and others discussed below, both the European Association of Urology [12] and the US National Comprehensive Cancer Network [13] advise considering bladder preservation for select patients with MIBC.

Selecting candidates for bladder-sparing therapy

Bladder-sparing therapy has demonstrated both safety and efficacy in patients with MIBC. For those patients who cannot tolerate surgery, and for those who are eligible for cystectomy and yet are motivated to preserve their bladders, combined-modality treatment offers a curative alternative. It should also be borne in mind that even the best surgical series in the fittest patients carry mortality rates of 1–2% [3], rising sharply in those older than 80 years (20% of MIBC) or with other comorbidities [2]. As bladder cancer is a smoking-related cancer, many patients will fall into one or the other (or both) of these categories. As treatment-related mortality with radiotherapy-based regimens is extremely low [4, 5], this is an important factor in case selection. Therefore, careful selection is required in this population to identify those with the highest likelihood of favorable outcomes with either surgery or bladder preservation.

As a general oncologic principle, the probability of loco-regional control with any treatment decreases as a function of the gross tumor burden. Consequently, a maximal resection, if feasible, is encouraged with combined-modality therapy for MIBC. Several reports have shown that achieving a grossly complete TURBT correlates with a complete response to chemoradiation and decreased need for salvage cystectomy [4, 7, 14]. A visibly incomplete TURBT, however, does not preclude bladder preservation. Indeed, in a series reported by the Massachusetts General Hospital, 57% of patients who had a visibly incomplete TURBT still attained a complete response after chemoradiation. In light of these data, a maximally safe TURBT is strongly recommended, though patients with residual gross disease may still consider proceeding to chemoradiation. In fact, in the UK BC2001 trial [5] there are detailed data on both the presence of residual mass and surgeon-reported completeness of resection. About 1/3 of patients had biopsy only or incomplete resection and a similar proportion had a residual mass. These surgical parameters did not affect the probability of benefit from chemoradiation compared to radiation alone. Overall, the invasive loco- regional disease-free survival at two years was 83% with chemoradiation. This suggests that the dogma of maximal TURBT may warrant re-examination.

Several studies have identified tumor-associated hydronephrosis as a poor prognostic factor for both bladder-sparing therapy and radical cystectomy. In a review of 415 bladder cancer patients treated at the University of Southern California with radical cystectomy between 1983 and 1993, five-year overall survival was 63% for patients without hydronephrosis, 45% for patients with unilateral hydronephrosis, and 31% for patients with bilateral hydronephrosis [15]. In other series, patients who initially presented with hydronephrosis had a lower likelihood of bladder preservation, a reduced probability of complete response to chemoradiation, and significantly worse overall survival [16–18]. However, in the absence of other curative options they may still be considered for treatment. In the UK these patients are generally managed by stenting followed by neoadjuvant chemotherapy.

Patients electing to undergo bladder-sparing therapy ideally should ideally be able to tolerate the multimodal combination of radiotherapy with concurrent chemotherapy. In a chemoradiation trial using mitomycin-C and 5-fluorouracil, BC2001 [5] showed that the addition of concurrent chemotherapy to radiation significantly improved loco-regional disease-free survival in comparison to radiation alone (67% vs. 54%, \( p = 0.03 \)). And although not adequately powered for these secondary endpoints, the addition of concurrent chemotherapy with radiation may have reduced two-year salvage cystectomy rates (11.4% vs. 16.8% with radiation alone, \( p = 0.07 \)) and improved overall survival (48% vs. 35% with radiation alone, \( p = 0.16 \)). The benefit of synchronous chemotherapy was most marked on invasive pelvic recurrences (muscle-invasive bladder or nodal recurrences) with a hazard ratio of 0.53 (95% CI 0.33–0.84, \( p = 0.007 \)) with minimal effect on non-invasive bladder recurrences.

Recent data suggest that on a population level, certain subgroups systematically fail to receive adequate definitive therapy for bladder cancer. In a recent analysis of over 28,000 new diagnoses from the National Cancer Database, elderly patients were significantly less likely to receive an aggressive curative
regimen than their younger counterparts (OR: 0.34 for age 81–90 vs. ≤ 50; p < 0.001) [19]. In fact, treatment by observation alone (including serial TURBT) was employed for nearly 40% of patients aged 81–89 and 25% of patients aged 70–79 years. These findings are generally attributed to comorbid illness and concerns regarding treatment tolerability in the elderly. Numerous studies, however, have shown that combined modality therapy is well-tolerated and effective in many elderly patients with MIBC [4, 5, 20], such that they should be carefully considered for trimodality therapy rather than embarking on a less-aggressive observational protocol.

**Chemotherapy concurrent with radiation therapy**

Two randomized clinical trials have shown that chemoradiation is superior to radiotherapy alone with regard to local bladder and pelvic tumor control [5, 21]. The addition of certain systemic agents (Table 20.1) is known to sensitize tumor cells to the effects of radiation, increasing cell kill and thereby synergistically enhancing treatment efficacy. Cisplatin is a well-studied and effective radio-sensitizing agent, although recent studies have identified alternative regimens that may be similarly effective and more tolerable [5].

Although cisplatin has long been the mainstay of chemoradiation for MIBC, many patients with impaired renal function or poor performance status cannot tolerate this agent. The Bladder Cancer 2001 (BC2001) trial was designed to evaluate an alternative radiosensitizing regimen to avoid the contra-indications of platinum-based therapy [5]. This phase III study randomized 360 patients with MIBC to undergo radiotherapy alone or with concurrent fluorouracil (500 mg/m² on days 1–5 and 22–26) and mitomycin-C (12 mg/m² on day 1 only). With a median age of 72 years and a median follow-up of 70 months, two-year loco-regional disease-free survival was 67% and five-year overall survival was 48% in the chemoradiation arm. Combined

<table>
<thead>
<tr>
<th>Table 20.1</th>
<th>Chemotherapy regimens for selective bladder-preservation therapy.</th>
</tr>
</thead>
</table>

### A. Continuous course chemoradiation

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Dose</th>
<th>Frequency</th>
<th>N</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>days 1–5</td>
<td>289</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>600 mg/m²</td>
<td>days 1–5</td>
<td>289</td>
<td>Rodel 2002</td>
</tr>
<tr>
<td>2</td>
<td>Mitomycin-C</td>
<td>12 mg/m²</td>
<td>day 1 only</td>
<td>182</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>500 mg/m²</td>
<td>days 1–5; wks 1 and 4</td>
<td>182</td>
<td>James 2012</td>
</tr>
<tr>
<td>3</td>
<td>Low dose gemcitabine</td>
<td>27 mg/m² (MTD)</td>
<td>days 1 and 4; weeks 1–6</td>
<td>23</td>
</tr>
</tbody>
</table>

### B. Split-course chemoradiation

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Dose</th>
<th>Frequency during induction chemoradiation</th>
<th>Frequency during consolidation chemoradiation</th>
<th>N</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cisplatin</td>
<td>70 mg/m²</td>
<td>days 1 and 22</td>
<td>day 1</td>
<td>91</td>
</tr>
<tr>
<td>2*</td>
<td>Cisplatin</td>
<td>15 mg/m²/day</td>
<td>days 1–3; 8–10; 15–17</td>
<td>days 1 and 2; 8 and 9</td>
<td>80</td>
</tr>
<tr>
<td>paclitaxel</td>
<td>50 mg/m²/day</td>
<td>days 1, 8, and 15</td>
<td>day 1 and 8</td>
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<td></td>
</tr>
<tr>
<td>3*</td>
<td>Cisplatin</td>
<td>15 mg/m²/day</td>
<td>days 1–3, 8–10, 15–17</td>
<td>days 1–2; 8 and 9</td>
<td>47</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>400 mg/m²/day</td>
<td>days 1–3, 15–17</td>
<td>days 1–3 and 8–10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Radiotherapy given in twice-daily doses of 1.5 Gy and 1.6 Gy
Integrating chemotherapy and radiotherapy for bladder cancer

therapy was well tolerated, with 36% of patients demonstrating acute Grade 3–4 toxicity and 8.3% of patients with late Grade 3–4 toxicity with no increase in either acute or long-term toxicity scores between the chemoradiation and radiation alone arms. Completion rates for radiation were not affected by the addition of chemotherapy. This landmark study provided level I evidence, establishing an effective and tolerable radiosensitization regimen for trimodality therapy.

More recently, a large multi-center trial in the US evaluated the utility of adding additional agents to a cisplatin-based chemoradiation regimen [6]. RTOG 0233 was a phase II study that randomized patients with MIBC to twice-daily radiation plus cisplatin with either paclitaxel or fluorouracil. As in the paradigm described above, patients underwent chemoradiation to 40.3 Gy, followed by a cystoscopic assessment of response. Patients with tumor downstaging to Ta, Tis, or T0 proceeded to consolidative chemoradiation to 64.3 Gy with the same chemotherapy regimen as allocated in the induction phase. Adjuvant cisplatin-gemcitabine-paclitaxel was administered after the completion of chemoradiation. Patients with residual T1 disease or worse after induction were counseled to undergo cystectomy and adjuvant chemotherapy. With a median follow-up of five years, 67% of patients in the paclitaxel arm completed the entire protocol including adjuvant chemotherapy, in comparison to 53% of patients in the fluorouracil arm. After induction, complete responses were achieved in 72% (95% CI: 57–84) of patients in the paclitaxel arm and in 62% (95% CI: 46–76) of patients in the fluorouracil arm without a statistically significant difference between the regimens. Notably, almost all patients completed the induction phase of treatment (98% in the paclitaxel arm; 96% in the fluorouracil arm). These data suggest that cisplatin-based chemoradiotherapy can yield high rates of complete response when supplemented by paclitaxel or fluorouracil.

There is a difference in radiation delivery between most US trials and the large European studies. While many European institutions design radiation fields to target only the whole bladder, US RTOG trials generally include larger fields to treat the pelvic lymph nodes. Indeed, pelvic lymphadenectomy is a widely accepted component of radical cystectomy for MIBC [24] with nodal involvement noted in up to 20–40% of patients [25, 26]. Despite the theoretical rationale for this practice, the added benefit of pelvic irradiation in the bladder-sparing setting remains to be determined. In the BC2001 trial [5], the planning target volume included the bladder + 1.5 cm (2 cm around the visible tumor) with no attempt to treat nodal volumes. Surprisingly, nodal relapse rates were low, at around 5% overall, suggesting that in radiographically node-negative patients, nodal radiotherapy may not be necessary.

Neoadjuvant and adjuvant chemotherapy

In an effort to improve upon the efficacy of bladder-preserving regimens, a number of studies have examined the efficacy of adding neoadjuvant and/or adjuvant chemotherapy to the overall therapeutic approach. There remains considerable debate regarding either of these approaches, although the literature offers some guidance.

Neoadjuvant chemotherapy is an attractive paradigm because it increases the possibility of tumor downstaging and offers the potential for early management of occult metastases. As with other disease sites, the disadvantages of early chemotherapy include the potential morbidity of systemic therapy, a delay in offering local management, and (if to be compared to cystectomy alone) compromised knowledge of the initial pathologic stage, which is the most accurate method of risk stratification by tumor presentation.

A landmark study by Grossman et al. [8] randomized patients with clinically staged MIBC to radical cystectomy alone vs. three cycles of MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) followed by radical cystectomy. The median survival of patients who received neoadjuvant chemotherapy was 77 months, in contrast to 46 months for those who underwent surgery alone ($p = 0.06$). Notably, the survival benefit attributed to MVAC was strongly related to downstaging of the
tumor at the time of cystectomy: 38% of patients who received MVAC had no evidence of cancer at the time of cystectomy, in comparison to 15% in the cystectomy-only group. Of note, one-third of patients who received chemotherapy experienced severe hematologic toxicity, although the trial reported no drug-related fatalities.

A UK-led cooperative trial similarly assessed the efficacy of neoadjuvant cisplatin, methotrexate, and vinblastine in patients who subsequently underwent definitive radiotherapy or radical cystectomy for clinically staged MIBC [27]. With a median follow-up of 7.4 years, patients who received chemotherapy had a seven-year survival rate of 43% versus 37% for patients who did not receive neoadjuvant therapy. The long-term results from the BA06 30894 trial demonstrated that neoadjuvant chemotherapy with methotrexate, cisplatin, and vinblastine (MCV) improved overall survival with a benefit of 5%, resulting in a significant 16% reduction in the risk of death [28]. In that trial, the choice of definitive treatment (surgery or radiotherapy) was based on patient or physician choice. There was an overall 23% reduction in the risk of metastases or death (HR: 0.77; 95% CI: 0.66–0.90; p = 0.001) compared to a 13% reduction in the risk of local disease or death (HR: 0.87; 95% CI: 0.75–1.01; p = 0.067) and only 4% reduction in the risk of loco-regional relapse (HR: 0.96; 95% CI: 0.80–1.15; p = 0.632) after MCV. Hence, the benefit of neoadjuvant chemotherapy is mostly on distant, not loco-regional disease. This suggests it may have a complementary benefit to synchronous chemoradiation.

In contrast, RTOG 89-03 examined the utility of neoadjuvant chemotherapy prior to trimodality therapy [17]. Patients with clinically staged MIBC were randomized to two cycles of MCV versus no chemotherapy, followed by definitive radiation with concurrent cisplatin. Tumor response was assessed in both arms after 39.6 Gy pelvic irradiation, and patients manifesting a complete response received an additional 25.2 Gy with one additional dose of cisplatin. Based on cystoscopic and cytologic assessments, neoadjuvant therapy did not increase the rate of complete response. Moreover, the five-year actuarial OS rate was not significantly different between the two arms (48% with neoadjuvant therapy, 49% without). Of note, the study was closed prematurely after 123 eligible patients (71% of the accrual goal) were randomized due to toxicity in the neoadjuvant MCV arm, though a futility analysis at that time indicated no likelihood of a positive result if the study had accured to completion. There was a high rate of neutropenic fever (23%) in the MCV arm, however, this study took place before growth factor support was routinely used with these regimens. Additionally, two cycles of MCV may not be adequate in eradicating micrometastases (the SWOG 8710 [8] and MRC/EORTC BA06 30894 [28] studies, discussed above, administered three cycles of neoadjuvant cisplatin-based combination chemotherapy prior to cystectomy and both reported a survival benefit).

Based on the results of the above trials and given that MIBC is a systemic disease where the cause of relapse after definitive therapy is often attributable to micrometastatic disease at the time of presentation [29], the role of modern neoadjuvant chemotherapy along with trimodality therapy certainly merits further study in MIBC.

Adjuvant chemotherapy has largely been studied in the post-cystectomy setting. A number of phase III adjuvant trials have evaluated various regimens including cisplatin, vinblastine, and methotrexate; cisplatin, doxorubicin, and cyclophosphamide; cisplatin and gemcitabine; methotrexate, vinblastine, epirubicin, and cyclophosphamide (MVEC); and MVAC. Of these, four trials either showed no benefit to adjuvant chemotherapy [30–32] or were underpowered to do so [33], while two suggested improved overall survival with cisplatin, doxorubicin, and cyclophosphamide [34]; MVAC; or MVEC [35]. Unfortunately, each of these trials has been subject to criticism either for methodological issues or low patient accrual [36]. As a result, there remains no clear standard of care with regard to the use of adjuvant chemotherapy following cystectomy for MIBC. In its last three protocols, the RTOG has been studying the tolerability and completion rates of adjuvant chemotherapy (gemcitabine, cisplatin; gemcitabine, cisplatin, paclitaxel) following trimodality therapy in order to potentially better address the concern for undetected micrometastatic disease in MIBC.

**Local failure and salvage cystectomy**

After the completion of trimodality therapy, local disease control in the native bladder remains a concern. Indeed, bladder tumor recurrences have been observed in 24% to 43% of patients after selective bladder-preservation therapy, with failure generally observed at a median of ~2
years after the completion of treatment [4, 5, 7, 17, 37–40]. Among these reports, the rates of muscle-invasive recurrence ranged from 11% to 18.5% with the remainder of local failures comprising non-muscle-invasive disease. In a recent report of 348 MIBC patients treated with tri-modality therapy at the Massachusetts General Hospital from 1986 to 2006, among the 250 patients (72%) having a CR after induction chemoradiation, the ten-year rates of non-invasive, invasive, pelvic, and distant recurrences were 29%, 16%, 11%, and 32%, respectively [4]. In the setting of a muscle-invasive recurrence, salvage cystectomy remains the treatment of choice. This was demonstrated in the BC2001 trial, where the two-year rate of invasive relapse was 18%, with an overall salvage cystectomy rate at two years of 11.4% (95% CI: 7.1–18) [5].

Surgical salvage of a local failure after bladder-sparing therapy is often viewed as challenging. A single institution series of 91 patients who underwent salvage cystectomy at the Massachusetts General Hospital offers long-term data for surgical complications and resultant survival [41]. Patients were followed for a median of 12 years, with 55% (50 of 91) undergoing immediate radical cystectomy for persistent disease after induction chemoradiation (40 Gy) and 45% (41 of 91) undergoing delayed salvage cystectomy for disease recurrence after trimodality therapy with full-dose radiation (64–65 Gy). At 90 days, 16% of patients experienced major complications and the 90-day mortality rate was 2.2%. Significant cardiac and vascular complications (e.g. myocardial infarction, hemorrhage, deep-vein thrombosis, pulmonary embolism, etc.) were more frequent in the group undergoing immediate cystectomy than in the delayed salvage cystectomy group (37% vs. 15%; p = 0.02). Conversely, issues of wound healing (ureteral stricture, infection, wound dehiscence, etc.) were more common in the group undergoing immediate cystectomy than in the delayed salvage cystectomy group (35% vs. 12%; p = 0.05). These rates of surgical morbidity are similar to those seen in patients who undergo primary radical cystectomy alone without chemoradiation [3, 42, 43]. Of note, ten-year disease-free survival for patients undergoing delayed salvage cystectomy in this series was 61%. Another large retrospective series from the Christie Hospital in the UK compared outcomes in 552 patients undergoing cystectomy (313 primary, 239 salvage) [44]. Five-year overall survival was similar in both groups (45% after primary radical cystectomy versus 42% after salvage cystectomy). These studies highlight the fact that a salvage cystectomy can be curative and should be considered in the setting of isolated recurrent invasive disease.

**Quality of life after bladder-sparing therapy**

Several prospective RTOG trials of bladder-sparing therapy were pooled to investigate long-term bowel and bladder toxicity [11]. Of 157 patients with a median follow-up of 5.4 years, 7% experienced late Grade 3 pelvic toxicity (5.7% genitourinary toxicity involving urgency, frequency, or hematuria; 1.9% gastrointestinal toxicity comprising distal obstruction or proctitis). The median time to late Grade 3 pelvic toxicity was 22.1 months and no Grade 4 toxicity was reported. Equally, low toxicity rates were found in similar studies with long-term data [5, 7, 45]. Notably, there were very few (<1%) reports of patients requiring cystectomy due to treatment-related toxicity.

Patient-reported quality of life and bladder function were assessed in a cohort of long-term survivors at the Massachusetts General Hospital [10]. By urodynamic testing, 75% of patients had normal bladder function after bladder-sparing therapy. Reduced bladder compliance was noted in 22% of patients, although only one-third of this group reported distressing bladder symptoms. Overall, 6% of patients reported issues of urinary flow, with 19% noting incontinence and 15% urgency. Of women in the cohort, 11% required pads in the long term. Bowel symptoms arose in 22% of patients, causing distress in 14%. With a median age of 68 years among all men, 36% reported normal erections while 18% noted less-firm erections that were sufficient for intercourse; 54% were capable of orgasm and 50% of ejaculation.

GETUG 97-015 was a phase II trial of definitive radiation (63 Gy) with concurrent cisplatin/5FU for MIBC [46]. A prospective assessment of toxicity showed that in the first year after treatment, urinary symptoms (e.g. frequency, urgency, pain, etc.) actually improved from baseline. Tumor shrinkage was thought to account for this improvement, and favorable urinary function was demonstrated up to two years after treatment.

Taken together, these findings indicate that the patients’ native bladder usually tolerates this treatment and functions well thereafter.
## Outcomes of bladder-sparing therapy

Bladder-sparing studies demonstrate complete response rates to induction chemoradiation of greater than 70%, with less than 30% of patients requiring salvage cystectomy [4, 5, 7, 47]. Five-year overall survival rates range from 48–65%.

A pooled analysis of six RTOG trials included 468 MIBC patients with a median follow-up of 4.3 years among the entire cohort and 7.8 years among survivors. Five-year overall survival after bladder-sparing therapy was 57% (62% for those with clinical T2 disease, and 49% for patients with T3–T4 disease) [47]. Notably, disease-specific survival was comparable between patients younger than 75 years of age and their older counterparts [4, 47], suggesting that this may be an effective treatment approach regardless of patient age.

Importantly, the rates of late invasive recurrence [5, 7] and disease-specific survival [4, 47] do not change significantly beyond five years, suggesting durable disease control in the long term.

There is a paucity of data to directly compare modern bladder-sparing therapy with immediate radical cystectomy for MIBC. Cross-study comparisons are imperfect because of inherent differences in patient selection between candidates for chemoradiation versus surgery. As one might expect, the median age of patients enrolled in cystectomy trials is generally younger than in trials of bladder-sparing therapy. The US Intergroup trial, for example, evaluated cystectomy with or without neoadjuvant chemotherapy and reported a median patient age of 63 years [8]; in contrast, BC2001 evaluated radiation with or without concurrent chemotherapy and had a median age of 72 years [5]. Bearing in mind the generalizability of these data, the median age at diagnosis for bladder cancer is 73 [48].

Moreover, issues of clinical and pathologic staging make it exceedingly difficult to appropriately match patients between the two treatment regimens. Staging in bladder-preserving therapy relies solely on clinical evaluation, which is known to underestimate patients in comparison to cystectomy. To illustrate this point, a retrospective review of patients with bladder cancer who had clinical staging followed by radical cystectomy showed that a significant proportion had more advanced disease than was clinically appreciated [49]. Indeed, 36% of patients who had organ-confined disease by clinical staging were ultimately found to have disease beyond the bladder (≥ pT3). Perhaps more strikingly, 40% of patients with clinically non-muscle-invasive bladder cancer (≤ cT1) were found to have MIBC at the time of cystectomy (≥ pT2). Furthermore, reports have shown that in patients with clinically node-negative MIBC who underwent cystectomy, 19 to 35% were ultimately found to have lymph node involvement on pathologic review [50, 51]. Thus, the discordance between clinical and pathologic staging makes any direct comparison with cystectomy series difficult.

Despite these apparent confounders, long-term outcomes for bladder-sparing therapy appear similar to those of radical cystectomy. In several studies that reported cystectomy outcomes [8, 43, 50, 52, 53], five-year overall survival ranged from 43–59%, well within the range of 48–65% described above with selective bladder-preservation therapy which reserves cystectomy for salvage in non-responders or those with invasive recurrences.

Large registry-based series also report similar outcomes with surgery and radiotherapy. In the UK, many more patients undergo primary radiation therapy, with only a minority having cystectomy as their primary treatment [54]. Despite this, patients undergoing primary radiotherapy had similar five- and ten-year survival rates when compared to those undergoing surgery in this large registry-based study. Similar findings concerning survival were seen in a large Canadian-based registry study where the mode of therapy was not predictive of overall survival [55]. This suggests that the wider use of bladder-sparing techniques, particularly in the older and less fit, could benefit patients either unsuited to or not wishing to undergo radical surgery.

## The role for chemoradiation in non-muscle-invasive disease

Patients with non-muscle-invasive bladder cancer (NMIBC) typically undergo a complete transurethral resection followed by the consideration of intravesical therapy, such as bacillus Calmette-Guérin (BCG) [13]. Although this approach is successful in many patients, nearly half will develop recurrent, BCG-refractory disease requiring a radical cystectomy [56–58]. As in the case of MIBC, many patients present at advanced age or with medical comorbidities and are suboptimal...
Integrating chemotherapy and radiotherapy for bladder cancer

Data are limited regarding bladder-sparing therapy for NMIBC, although a number of institutional reports merit consideration. The University of Erlangen published a retrospective series of 141 patients with high-risk T1 disease who underwent maximal TUR and chemoradiation at the time of initial NMIBC diagnosis and received prompt salvage cystectomy in the event of failure or progression. With this approach, 88% of patients had a complete response and only 19% progressed at five years. Moreover, disease-specific survival was 73% at ten years, a result comparable to patients who undergo immediate radical cystectomy. Of note, however, it is difficult to extrapolate these primary treatment data to patients who fail BCG therapy and, therefore, are considered to have more aggressive disease.

The Massachusetts General Hospital published a series of 18 patients who failed primary BCG therapy for NMIBC and ultimately recurred with MIBC [59]. Combined modality therapy was employed as a second-line approach and at a median follow-up of seven years, 59% of patients were free of any bladder recurrence and disease-specific survival was 70%.

Overall, these early data support using combined-modality therapy for patients with NMIBC who cannot undergo surgery or who otherwise desire bladder preservation. This approach appears to be effective and is currently being studied in a phase II trial of patients with recurrent disease after BCG therapy (RTOG 0926) [60].

Future advances

Although combined modality therapy is curative for many patients with bladder cancer, there remains a cohort for whom recurrence and progression necessitate a radical cystectomy. Recent advances in biomarker research may improve the upfront identification of patients appropriate for bladder preservation. MRE11 is a protein involved in DNA repair and is one such emerging biomarker.

A study from the UK examined pre-treatment tumor specimens for proteins involved in DNA repair and cell-cycle checkpoints [61]; immunohistochemical expression data were then correlated with treatment outcomes. Most significant among the proteins examined, tumor MRE11 overexpression was correlated with higher cause-specific survival for patients who received radiotherapy but not those treated by cystectomy.

Further validation of this finding came by way of 148 patients treated with chemoradiation at Erlangen University [62]. MRE11 overexpression in this cohort was again associated with improved disease-specific survival in patients receiving chemoradiation, but not in those undergoing radical surgery.

Prospective clinical trials are being designed to validate the use of biomarkers to help select the appropriate therapeutic approach.

Conclusion

In an era of increasing emphasis on organ preservation, there is mounting evidence to support the use of chemotherapy and radiation in the treatment of bladder cancer. Decades of study suggest that trimodality therapy has similar durable long-term outcomes to primary cystectomy. Indeed, with appropriate patient selection, it appears that cystectomy can be avoided in most patients without sacrificing local control or survival. The retained native bladder generally functions well and long-term toxicity of bladder-sparing therapy to pelvic organs appears acceptable. These considerations remain especially relevant for elderly or infirm patients who cannot undergo surgery and otherwise have no comparable curative option. Further research will refine our understanding of the optimal candidates for bladder preservation. In the meantime, however, there is ample evidence to suggest that this approach is a safe and effective option for many patients with bladder cancer.

Useful web links


References


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PART IV

Urinary tract reconstruction
CHAPTER 21

Orthotopic neobladder

Eila C. Skinner

Department of Urology, Stanford University School of Medicine, Stanford, CA, USA

KEY POINTS

- Key patient eligibility requirements include normal renal function, available bowel, and negative frozen section urethral margin.
- Patients should be willing and able to do self-catheterization, which is more often required in women than in men.
- Relative contraindications include prior high-dose radiation, urethral stricture disease, and frail general health.
- Careful dissection around the proximal urethra is required for continence preservation in women and men.
- All orthotopic neobladders use detubularized bowel reconfigured into a spherical shape.
- Early post-operative urinary leakage is generally managed with good catheter drainage and percutaneous drainage of any collections. Rarely, bilateral percutaneous diversions are necessary to divert the urine until the leak heals.
- Symptomatic urinary infections are most common in the first three months post-operatively. Chronic bacterial colonization may occur but usually does not require treatment.
- Most common late complications include uretero-ileal stricture and stones, which can occur with any type of neobladder. Pouch rupture and secondary malignancies involving the reservoir are rare events.

Introduction

Urinary diversion is a necessity following radical cystectomy, and has a huge potential impact on patient quality of life going forward. The Bricker ileal conduit has been the standard form of urinary diversion in the United States since 1950 [1]. Besides the need to wear an external appliance, ileal conduit diversion is associated with significant short- and long-term complications [2]. Beginning in the 1970s, Camey, Kock, Skinner, Hautmann, Studer, and others began investigating continent cutaneous and orthotopic alternatives [3–7]. The orthotopic neobladder has now become an accepted form of urinary diversion for both male and female patients and many feel that this should be the diversion of choice for otherwise healthy individuals. In spite of this widespread experience, only 10% of patients undergoing cystectomy in the US today have an orthotopic diversion [8].

Patient selection

The three basic requirements for orthotopic diversion are adequate renal function, the absence of cancer at the urethral margin, and available bowel to construct the diversion. It is estimated that approximately 80 to 90% of males and 75% of females undergoing cystectomy are potential candidates for neobladder construction from a purely medical standpoint [9]. However, there are a number of other factors that should be considered.
Age
Older patients vary tremendously in their physical vigor and overall health. Many men and women over the age of 75 have excellent functional outcomes with orthotopic diversion [10, 11]. However, the frail elderly patient who is mostly sedentary may not benefit from this type of reconstruction.

Renal function
There is absorption of urea and electrolytes when ileum or colon is used for continent diversion that can lead to chronic hyperchloremic acidosis, along with dehydration and bone loss. These complications are typically only seen in patients with compromised renal function. The generally accepted recommended minimum renal function for patients offered continent diversion is an eGFR of 40mL/min [11].

Willingness and ability to do self-catheterization
At least occasional self-catheterization is required for approximately 10–20% of men and up to 60% of women with orthotopic diversion who are followed long term [10, 12]. It is currently impossible to predict which patients may have difficulty emptying, so patients considering orthotopic diversion should be able and willing to potentially self-catheterize. This is most important in women, who may have more difficulty mastering this skill and are at higher risk. It is rare for individuals to be unable to learn this, and is not usually a reason for deciding against orthotopic diversion.

Risk of cancer in the retained urethra
Stein retrospectively evaluated 768 men with a median follow-up of 13 years and showed that prostatic urethral involvement was the main predictor of subsequent diagnosis of cancer in the retained urethra following cystectomy (so-called second primary tumors). Most of these cancers were observed early, at a median of two years. The overall risk was 7% at five years, varying from 5% in those with no prostatic involvement to 12% with CIS of the prostatic urethra and 18% in those with prostatic stromal invasion [13]. The incidence was only 6% if one excludes those with node-positive disease in this latter group [14]. Boorjian et al. found that tumor multifocality was an additional risk factor for urethral cancer [15]. Orthotopic diversion had a protective effect on the risk of urethral cancer in both these series [13, 15].

A number of authors have shown that urethral involvement in women is predicted by disease at the bladder neck or a mass invading into the cervix or vagina preoperatively. Skip lesions appear to be rare. Approximately 70% of women are potential candidates for orthotopic diversion based on the location of the tumor alone [16, 17]. Using these criteria, urethral cancers have been rare in women undergoing orthotopic reconstruction [18, 19]. In both men and women a negative frozen section of the margin is ultimately required prior to construction of a neobladder diversion [11, 13].

Prior pelvic radiation or prostatectomy
Lower doses of radiation < 60 Gy have relatively little impact on the outcome of orthotopic diversion. With higher-dose therapy the degree of damage to the urethra and external sphincter varies depending on the type of radiation (external beam vs. brachytherapy or both) and the field applied. At the University of Southern California, orthotopic reconstruction was performed in 32% of patients undergoing salvage cystectomy [20]. In the series from Ulm, orthotopic diversion was possible in 25% of a similar group of patients [21]. Patient selection criteria include the absence of severe urethral stricture disease, good baseline continence, and relatively healthy-looking urethral tissue at the time of surgery. The final decision must be made at the time of the operation. Patients considering this type of diversion must accept a higher risk of both stricture disease and long-term incontinence [20].

A history of prior radical prostatectomy has recently become an increasingly common clinical scenario for patients undergoing cystectomy. If the patient has good continence prior to cystectomy and care is taken around the apical dissection, then one can expect to have similar results as in patients without such a history [22].

Basic tenets of pouch construction
All orthotopic diversion techniques share the same basic principle of construction, using a detubularized segment of bowel (small or large intestine) that is reconfigured to approximate a spherical shape to establish a compliant reservoir that maintains a consistently low pressure during filling and has a functional capacity of at least 300–500 cc. Differences between techniques primarily involve the segment of
bowel used, the exact folding technique, and whether there is any attempt to prevent reflux.

Dissection of the urethral margin is key to ensure continence. In the male, the techniques that optimize subsequent continence are familiar to most urologists from the experience with radical prostatectomy. Careful dissection around the anterior and lateral urethra is required, avoiding deep sutures into the dorsal venous complex that might injure the underlying nerves [23]. In males, preservation of the neurovascular bundle may improve continence as well as potency after surgery, though there are no prospective series evaluating this question [24].

In females, the urethrovesical junction is well within the pelvis and it is critical to avoid dissection below the endopelvic fascia to avoid damage to the rhabdosphincter. Preservation of the uterus and anterior vaginal wall, whenever possible, may be advantageous if an orthotopic diversion is planned. This can eliminate the risk of vaginal fistula, may improve sexual function, and may decrease the risk of urinary retention [25, 26]. There is some controversy on the importance of preservation of the neurovascular tissue lateral to the vagina, and there are few comparative data to rely on to answer this question [18, 19, 27]. If a hysterectomy is performed or a section of anterior vaginal wall is excised with the bladder specimen, an omental pedicle graft should be laid down between the closed vagina and neobladder to help avoid a fistula. Sacroculpopexy with mesh may be performed in women in whom the uterus is absent or must be removed at surgery.

**Surgical techniques for orthotopic diversion**

There are many techniques for orthotopic neobladder construction, described in detail elsewhere. Urodynamic studies have suggested that reservoirs made from ileum have better compliance, lower pressures, and less mucous than those made from colon [28–30]. Currently the two most popular ileal neobladder techniques are the Hautmann and Studer ileal neobladders, which vary primarily in terms of the folding of the detubularized segment.

There is controversy about whether it is advantageous to prevent reflux of urine from the neobladder up to the kidneys [31]. Since patients void by Valsalva maneuver rather than with contraction of the reservoir, true high-pressure reflux is unlikely with any neobladder [32] The addition of an anti-reflux mechanism has been associated with an increased risk of upper tract obstruction [9, 33–36] A prospective randomized study comparing the Studer and T-pouch failed to show any difference in renal function or infection at three years, suggesting that there may not be a significant advantage of preventing reflux, at least in the intermediate term [36].

The use of surgical staples has been advocated to shorten the duration of the operation and especially to facilitate robotic-assisted intracorporeal neobladder construction [37, 38]. Recently, robotic surgeons have advocated using the standard GIA stapling device with metal staples. The disadvantages of this technique are that the pouch is a U rather than double-folded, and the staples will become a potential nidus for stone formation. The prior experience with the Kock pouch demonstrated a very high rate of stone formation after many years, and early experience with stapled pouches suggests the same [38].

**Studer ileal pouch**

This pouch is made from approximately 56 cm of distal ileum [7, 39]. The proximal 12–15 cm is left intact, and the remainder formed into a spherical reservoir using the Kock double-fold technique (Figure 21.1). This pouch has the advantage of simplicity of construction and also allows the potential to use a longer afferent limb in the case of shortened ureteral length. Studer’s group reported on 480 of these procedures performed from 1985 through 2005 with excellent long-term results in terms of continence, preservation of renal function, and less than 3% uretero-ileal stricture rate.

**T-pouch modification**

Stein and Skinner developed the T-pouch to provide an anti-reflux mechanism but avoid the potential long-term complications seen with the Kock nipple valve. An 8–10 cm segment of ileum for the afferent limb is separated from the proximal portion of the reservoir and then advanced and anchored into a serosal-lined tunnel that acts as a Mitrofanoff-type flap valve when completed (Figure 21.2). An initial description involved tapering the T-limb but that was subsequently abandoned because it appeared to contribute to late stenosis of that segment. The ureters are implanted into the afferent limb and the pouch is subsequently closed.
using the same double-folded technique as used in the Kock and Studer pouch.

**Ileal neobladder (Hautmann pouch)**

This neobladder is constructed from 60–70 cm of distal ileum that is folded in a “W” formation. The limbs are opened along the anti-mesenteric border and sewn together in a spherical shape (Figure 21.3). The site for the urethra is identified before opening the segment so that a small flap can be made to allow for an opening for the urethra. In the classic pouch, the ureters are implanted directly into the reservoir. However, the two ends of the “W” can be left intact and made longer if necessary to accommodate shorter ureters [41, 42].

This pouch has a larger initial capacity than the Studer pouch, which may assist with earlier continence. However, it may also result in an increased incidence of late urinary retention and increased electrolyte reabsorption from the pouch. Hautmann has reported excellent results over 25 years with more than 1000 patients treated with this type of neobladder [9].

**Colon pouches**

Colon pouches have been made using an ileocolic segment, right colon, and sigmoid colon [43–47]. All involve detubularizing the segments used and folding to approximate a spherical shape. Ureters can be anastomosed in a tunneled anti-reflux manner if desired. Sigmoid neobladders may have less risk of retention but long-term continence may be less than for ileal neobladders as well.

**Results**

**Perioperative complications**

The rates of perioperative complications are similar in patients undergoing ileal conduit and orthotopic neobladder [11, 48, 49]. Problems related to the diversion...
Orthotopic neobladder

include urinary leak, catheter problems, and upper tract obstruction. Gastrointestinal complications including ileus, obstruction, and bowel leak are also common after cystectomy and are at least partially related to the need for a bowel anastomosis, which is common to all types of diversion [50].

Urine leak from a neobladder is somewhat more common than from an ileal conduit, but is generally easily managed. It is key to maintain adequate drainage of the neobladder. A large-bore catheter and ureteral stents are generally recommended. A drain is routinely placed near the neobladder, and should be left in place until the drainage is minimal and/or the Foley catheter is removed. Early leaks will usually resolve spontaneously with good catheter drainage; they are only a real problem if a urinoma develops or drainage out of the wound occurs. In such a case, a new drain may need to be placed percutaneously, or occasionally bilateral percutaneous nephrostomy tubes are necessary to divert the urine. Reoperation for a leak should be avoided, since primary repair is unlikely to be successful in inflamed tissue.

Urinary infections are quite common in the early post-operative period [51]. Other common infections include wound infections, pelvic abscess, pneumonia, and Clostridium difficile colitis. Urinary tract infections are most common during the perioperative period and fall off rapidly after three months [9]. Unfortunately, resistant organisms are common during the initial period related to hospital exposure and the presence of catheters.

Approximately 20% of patients undergoing cystectomy in recent years have required readmission after discharge [51]. The most common reasons for readmission are gastrointestinal problems, dehydration, and fever. Aggressive outpatient management with hydration and nursing visits may be helpful to mitigate these problems, though prospective studies are not available. Early recovery (ERAS) programs have been described which have successfully reduced hospital stay without increasing readmissions [52].

Continence and retention

The two primary long-term outcomes of interest to both patients and physicians are the achievement of acceptable continence and the incidence of urinary retention requiring regular self-catheterization. These outcomes vary depending on the age and gender of patients, prior treatments such as radiation or prostatectomy, the length of follow-up, surgical techniques, and the experience of the individual surgeon. Outcomes vary depending on how the information is collected – whether by anonymous validated questionnaire, chart review, or telephone interview. Only a few reports have used the “gold standard” of a validated patient-completed questionnaire [10, 12]. Thus, care must be used in comparing outcomes from one series to another.

Most patients undergoing orthotopic diversion will experience initial urinary incontinence, with a gradual period of improvement of daytime continence over the first few months. The majority of both men and women will achieve acceptable continence in the daytime, approximately 80–90%, by one year [53]. Older patients may take longer to improve and have a higher risk of persistent daytime incontinence than younger patients.
(both male and female). Other identified factors contributing to improved continence include nerve-sparing in men, preservation of the uterus in women, and the absence of diabetes [24, 54]. Although most patients achieve good control, the majority will wear a pad at least some of the time for protection [10, 12, 24, 53, 54].

Night time continence tends to recover more slowly and a significant percentage of patients will have persistent night time accidents, especially if they do not get up regularly to void. This is partly due to sphincter relaxation with sleep, but there is also obligate water loss at night due to secretion by the bowel mucosa that results in high night time urine volume. This improves over one to two years as the mucosa changes with exposure to the urine [55].

Urinary retention (also referred to as “hypercontinence”) has varied considerably between reports, and appears to be much more common in women than men. In studies of patients undergoing Studer or T-pouch ileal neobladder reconstruction using anonymous patient questionnaires, 60% of women but less than 10% of men required self-catheterization at least sometimes [10, 12]. The risk of retention is higher when larger segments of bowel are used and if all or part of the prostate is preserved. Retention in women may be due to prolapse of the pouch into the posterior pelvis, causing a kink at the urethral anastomosis. Techniques to provide posterior support such as sacroculpopexy and omental transposition have been suggested to try to prevent this [35, 56]. Preservation of the uterus and its support structures may be the most effective when possible, but only small series with short follow-up have been reported to date [57].

Patients with poor emptying present with recurrent urinary tract infections, new onset of overflow incontinence at night, or even hydronephrosis or a palpable suprapubic mass on exam. It may develop early but often is a late event. Patients should be screened for proper emptying during follow-up visits.

Management of urinary incontinence and retention
Patients should all be instructed in Kegel exercises postoperatively and also taught the importance of relaxation of the sphincter prior to Valsalva voiding. Some patients may benefit from physical therapy assistance with biofeedback to help them isolate and strengthen the pelvic floor muscles. Patients should be advised to slowly increase their voiding interval during the first few months to increase the pouch capacity. Often, significant coaching is necessary to help patients understand the function of the new bladder.

The evaluation of incontinence should be delayed at least a few months to allow the patient to recover from surgery and the reservoir to expand appropriately. The exception is in women, who should be screened for a possible vesicovaginal fistula early if they are experiencing total incontinence. Pouch-vaginal fistula has been described in up to 5–10% of women and is more common if a portion of the vaginal wall has to be removed during the cystectomy and in irradiated patients. These fistulas do not usually close with conservative management, but can sometimes be repaired primarily through a vaginal approach. They can be quite refractory and may ultimately require transabdominal exploration or even conversion to a cutaneous form of diversion [57, 58].

Fluorourodynamic evaluation may be helpful for patients with persistent incontinence to ensure that the reservoir has reasonable volume and good compliance, especially if the colon has been used for the neobladder. Anticholinergics are generally not helpful. Treatment options for persistent incontinence include periurethral bulking agents, artificial sphincter, and urethral sling. Only small series of each of these treatment options have been reported [59–61].

Evaluation of urinary retention should include a cystoscopy and rectal/vaginal exam to rule out tumor recurrence or stricture. Actual stricture of the neobladder-urethral anastomosis is quite rare, occurring in only about 1% of patients in the absence of tumor recurrence [9]. Distal urethral strictures can occur in some men as well. Patients with prior radiation are at higher risk of these complications.

Urethral dilation is not helpful in either men or women in the absence of an actual stricture. Some have suggested that most patients with urinary retention can be treated successfully by identification and incision of mucosal folds that occur with Valsalva voiding, but others have not found this to be a common cause of retention [62, 63]. Intermittent self-catheterization is the mainstay of treatment to avoid symptomatic complications such as incontinence and infection.

Management of other late post-operative complications
Abdominal wall incisional hernia has been observed in 4% of patients by five years and 6% by ten years, and may be even higher [9, 34]. These hernias may make it
difficult for the patient to generate the increased abdominal pressure required to empty the pouch. Although they may be managed with an elastic support, they are best repaired surgically, usually with mesh.

Complications related to the diversion include uretero-ileal stricture, which is common to all urinary diversion. The rate of these strictures with a standard Bricker–Ledbetter anastomosis should be 3–6% [9, 64]. Ureters that are anastomosed with tunneling or other anti-reflux techniques have a higher stricture rate. Strictures when they occur can cause upper tract obstruction that may be silent and can result in loss of renal function. They can often be managed by endoscopic techniques when identified early within the first year post-operatively, but may require open revision.

Late obstruction from an anti-reflux mechanism can occur and was seen in up to 10% of patients with the classic Kock nipple valve. This will lead to bilateral hydronephrosis, and will often be misinterpreted by radiologists unfamiliar with the anatomy. Diagnosis is facilitated by antegrade nephrostogram, and the problem can usually be managed by endoscopic incision of the valve [65]. Pouch stones can occur in any type of continent diversion. They are most common when metal surgical staples are used in the construction of the diversion and in patients with incomplete emptying [9, 39]. Stones can cause bleeding, infection, or occasionally pain, but are often asymptomatic. They should be removed endoscopically when first identified. Open procedures are most efficient for management of very large stones.

Late symptomatic infections are rare in neobladder patients in the absence of obstruction, retention, or stones. In the series from Ulm with long-term follow-up, symptomatic infections were only seen in 3.4% of patients who emptied well and were not on intermittent catheterization [9]. No difference in the rate of febrile infections was seen in patients with or without an anti-reflux mechanism in the pouch [36]. Colonization of the pouch with bacteria is not uncommon, and routine urinalysis will usually show white and red blood cells at most times [66]. Many patients receive unnecessary antibiotic treatment in the absence of any symptoms.

Pouch perforation is a rare but potentially life-threatening complication of continent diversion. The risk is increased in patients with prior radiation. Patients typically present with acute abdominal pain and distention, often with signs of sepsis, and misdiagnosis by the emergency physicians and general surgeons is common. A CT urogram is diagnostic. These patients usually should be managed with open surgical repair with irrigation because of the high risk of peritonitis. A short attempt at conservative management with catheter drainage may be tried in a patient who is not acutely ill [67].

Finally, recurrence of urothelial cancer in the pelvis is not uncommon in patients following cystectomy. Although most such masses do not cause problems for the orthotopic diversion, occasionally a patient will have bleeding or obstruction that requires intervention. Secondary malignancies arising in the neobladder have been described but these are extraordinarily rare. These are usually managed surgically and may require cutaneous diversion.

**Conclusion**

Orthotopic neobladder provides an excellent alternative to cutaneous diversion for many patients, and should be offered when there is no contraindication. Short- and long-term outcomes in general are very good and although the types of complications differ, the rates of such complications are similar to standard ileal conduit diversion.

**Useful web links**


**References**


Continent cutaneous urinary diversion, orthotopic bladder substitution, and continent anal urinary diversion are different types of continent urinary diversion for patients after cystectomy. The main indication is radical cystectomy for treatment of bladder cancer. Continent cutaneous urinary diversion is usually chosen when favored by the patient or when orthotopic bladder substitution is not possible. This is the case if the previously diagnosed urothelial cancer extends into the prostate or beyond the bladder neck (in females) or if frozen sections from the urethra at the time of cystectomy reveal positive surgical margins for cancer, so that urethrectomy is indicated. Other reasons not to choose an orthotopic urinary diversion are pre-existing irreparable sphincteric incontinence or neurogenic sphincter dysfunction. It is reported that, post-operatively, up to 50% of females will require intermittent catheterization for emptying their neobladder. Hence, transurethral self-catheterization should be initiated pre-operatively in women, since some of them may detect that they

KEY POINTS

- The patient has to be carefully assessed for motivation and capability to perform self-catheterization.
- In patients > 75 years or in patients with a lack manual dexterity (hemiplegics, tetraplegics) to perform transumbilical self-catheterization, an incontinent type of urinary diversion might be preferable.
- Renal function must be reviewed carefully in patients selected for continent urinary diversion (creatinine levels should be < 2.0 mg/dL or age-adjusted GFR > 50%). If the renal reserve is critically reduced, a zero-pressure diversion (i.e. conduit) should be preferred.
- Various techniques exist to construct a pouch – in general following the principle of detubularization and spherical reconfiguration – depending on the bowel segments which are utilized for construction of the pouch: ileum only, ileocecum, or colon only.
- Pre-operative studies should include imaging of the colon by conventional retrograde double-contrast colonography, colonoscopy, or, preferably, CT colonography, if any large bowel segment is used for constructing the pouch.
- The type of ureteral implantation depends on the bowel segments which are used to construct the pouch.
- Several techniques exist to construct a continence mechanism: appendiceal tunneling is the simplest to perform and achieves the highest continence rates, although higher stoma stenosis rates have been reported.
- Neappendiceal conduits fashioned from ileum or right colon are adaptable for right colon pouches. In right colon pouches, tapered and/or imbricated terminal ileum and the ileocecal valve can also be utilized as a continence mechanism.
- Another important technique in providing a continence mechanism is the ileum intussusception nipple.
- The performing surgeon must be able to perform different types of continent cutaneous urinary diversion, as the definitive decision on which type of diversion is employed has to be taken during the individual surgical situation.
prefer catheterization through the umbilicus rather than through the urethra.

Although continent cutaneous urinary diversion provides advantages for the body image of the patient, conduit diversion with an external urinary collecting device is more commonly used. This is due to the fact that continent procedures are technically more challenging and associated with higher complication rates as compared to incontinent ileum or colon conduit urinary diversion [1, 2]. Although operating times have been reduced significantly, the procedure itself remains still more complex and more time consuming than conduit urinary diversion. Higher economic pressures and reimbursement issues disfavor the continent approach and have led to a higher incidence of “quick diversions” with external collecting devices. However, with growing experience over the past 30 years, complication rates of continent cutaneous urinary diversion have decreased significantly. Consequently, this alternative should be offered to motivated and appropriately selected patients.

One would expect that any continent diversion should be associated with an improved quality of life as compared to incontinent diversion. However, there is a large body of literature suggesting that there are no significant differences in quality of life issues between incontinent and continent urinary diversion, although most of these studies include only small patient cohorts and were retrospective[3]. It has been shown in two prospective studies that orthotopic neobladders achieve higher quality of life scores when compared to incontinent diversion. Nevertheless, in the end, subjective quality of life depends mainly on the patient’s pre-operative expectations. Continent urinary diversion may provide a higher quality of life as long as no complications occur.

Therefore, patient selection is crucial for the success of a continent urinary diversion. The counseling physician has to make sure that the patient has the motivation and is able to perform clean intermittent self-catheterization (CISC). Patients with neurogenic deficits such as hemi- or tetraplegia or mental impairment (as well as advanced age, i.e. > 75 years) are mostly better served by incontinent urinary diversion, as they would always be dependent for catheterization of their reservoir.

To avoid unexpected pathology in bowel segments which are to be used for construction of the continent reservoir, patients who receive a procedure utilizing large bowel segments should have pre-operative imaging studies with colonoscopy, conventional retrograde double-contrast colonography, or CT-colonography. Polyps or adenomas should be removed before the anticipated procedure to exclude any pre-existing malignant process of the colon. Diverticula of the ascending colon or caecum are rare and are not a contraindication for the use of the segments for continent cutaneous urinary diversion. Additionally, renal and hepatic function has to be assessed pre-operatively to avoid long-term complications. The pouch (French word for “bag”) will reabsorb urinary constitutes, which are metabolized by the liver and/or excreted by the kidneys. For any continent urinary diversion, the kidney function should be close to normal prior to operation with a maximum creatinine level of 2.0 mg/dL (age-adjusted GFR > 50%). If there is any doubt, a pre-operative creatinine clearance should be performed (>60 mL/min). In the case of bilateral dilation of the upper urinary tract with impaired renal function, one should consider placing nephrostomies for a couple of weeks and re-evaluating kidney function before making the decision on a continent diversion. This can help to avoid the need for a secondary conversion to a “zero-pressure” diversion.

The surgeon undertaking the operation should be able to perform more than one type of continent reservoir and continence mechanism, as unexpected circumstances might occur and necessitate modifications of the continence mechanism or the bowel segments used for construction of the reservoir. Any patient planned for continent urinary diversion should be informed about the possibility that an incontinent diversion (i.e. ileum conduit) might be necessary instead at intraoperative discretion.

The afternoon or evening before surgery, every patient is required to have liquids only, and 2–3 liters of oral hyperosmotic non-absorbable (e.g. macrogol) solution are administered to cleanse the bowel. For continent diversion, the stoma location should preferably be the umbilicus [4]. In all other cases, a skin button matching the diameter of the utilized efferent segment is circumcised. The umbilicus is cosmetically superior, has a lower incidence of stoma stenosis, and provides the best accessibility for catheterization in wheelchair-bound patients [5]. This fact favors the umbilicus compared to stoma positions in the lower abdominal quadrants. The umbilical skin has to be separated from the fascia, which is incised in a cruciate fashion.


After alignment of the tissues, the catheterizable outlet is sutured to the fascia, the umbilical skin, and the peritoneum, avoiding any angulation.

Different techniques for performing cystectomy are described in previous chapters. However, for any continent diversion it is important to preserve maximal length of the ureters, which may be shortened to the final length only before implantation into the pouch. A small portion of each distal ureter is sent for frozen section histologies to ensure tumor-free margins. After mobilizing of the sigmoid and descending colon, the left ureter is mobilized up to the renal pelvis/lower pole of the kidney and a tunnel for pull-through to the right peritoneum is performed by blunt dissection (about two fingers in diameter) ventral of the aorta, caudal to the duodenum, and cranial to the inferior mesenteric artery (IMA), especially if the left ureter needs to be shortened due to oncologic reasons or poor vascularization. The left ureter is passed through this tunnel into the right retroperitoneal space, which has been previously dissected in a similar fashion. Many surgeons dissect the sigmoid mesentery up to the level of the IMA and pass the left ureter to the right side at this level.

The reservoir for continent cutaneous urinary diversion can be constructed from different bowel segments utilizing ileum only (Kock pouch, T-pouch), colon only (Transverse colon pouch, i.e. Mainz pouch III), or a combination of ileum and colon from the ileocecal segment (Mainz pouch I, Indiana pouch). The critical part for any type of continent cutaneous diversion is the catheterizable continence mechanism. Several techniques have been described for constructing this mechanism. The submucosal tunneling technique of the appendix is straightforward. Similarly, a short segment of bowel which is opened on the anti-mesenteric side and transversally re-tubularized (Yang–Monti) can be re-implanted in a comparable submucosal tunnel technique. Furthermore, the terminal ileum may be tapered and can serve, together with the imbricated ileocecal valve, as a continence mechanism (Indiana pouch). The intussuscepted nipple valve, as first described by Kock, and the serosal lined flap valve by Stein et al. [6] are technically demanding procedures associated with high complication and re-operation rates. The complications of an intussuscepted nipple comprise failure by gliding, prolapse of the nipple, or ischemic atrophy. In the latter case, a new nipple valve has to be constructed from a new segment of bowel [7]. The continence principle, which applies for all of these techniques, is passive compression of the efferent segment by increasing filling pressures of the reservoir. From the patients’ side, the most important prerequisites for receiving a continent cutaneous urinary diversion are motivation, the manual dexterity to catheterize the pouch, and the availability of catheters in the specific country.

General considerations about the choice of the type of continent urinary diversion

As mentioned above, continent urinary diversion can be performed by using ileum only or colonic segments only or by using a combination of ileal and colonic segments. Functional and anatomical considerations should lead to the right choice of bowel segments. In general, constructing a pouch from intestinal segments means transforming a cylinder into a sphere. The diameter of bowel which is used to create the reservoir determines the length of bowel which needs to be excluded from the intestinal continuity. The volume formula for a cylinder is \( V = \pi r^2 \times l \), which means that the radius determines the volume by its second power, implying that utilizing bowel of a larger diameter reduces the total length of bowel exclusion. Biliary acids, vitamins (i.e. vitamin B12), and folic acid are absorbed from all ileum, not from colon. Post-operative incidence of malabsorption syndromes is dependent on the length of ileum excluded from bowel continuity. Forty centimeters of ileum exclusion is a critical length for the development of malabsorption syndromes. On the other hand, colon is less distensible than ileum as the tenia limit the longitudinal expansion of large bowel [8]. This might, at first sight, be considered a disadvantage, but in the long term the longitudinal teniae of large bowel segments prevent excessive distension and megapouch formation. Distension is a normal phenomenon for all kinds of reservoirs over time, starting after surgery with an initial volume which is determined by geometry, as described above. Ileum reservoirs are at risk of distending into a megapouch when not regularly catheterized. Moreover, large bowel offers the advantage of anti-refluxing ureteral implantation into the reservoir. Another advantage is the availability of the appendix for in situ tunneling as a continent catheterizable outlet, or the availability of the ileocecal valve for anchoring an ileum intussusception nipple if the appendix is absent or
not usable. Disadvantages of using cecum or colon (i.e. most urologists are reluctant to perform large bowel surgery) have to be weighed against low malabsorption risk, reliable anti-refluxing techniques, available continence mechanisms for the outlet, and a large capacity without tendency of overdistension into a mega reservoir. Another disadvantage might be the fact that diversions using the ileocecal region require resection of the ileocecal valve. Retrograde colonization of the ileum can be an issue, although it is rarely reported in the literature, if no reconstruction of the ileocecal valve is performed when re-establishing the continuity of the bowel.

The same principles of detubularization and spherical reconfiguration are common to all the different techniques of constructing a urinary reservoir, no matter which segment of bowel is utilized. However, if using large bowel segments one should consider that intraluminal pressures are increasing from proximal (cecum) to distal segments of colon (recto-sigmoid) while physiological capacity and compliance are decreasing. This implies that ileocecal reservoirs like the Mainz I pouch have a higher capacity and lower pressures than pure colonic reservoirs. In the following paragraphs, this technique will be described in detail as an example for a composite pouch, and the most important alternatives will be mentioned briefly. In general, it is important that surgeons performing urinary diversion need to be capable of performing several surgical techniques to adjust the pouch to the specific requirements of the individual.

**Surgical techniques**

**Kock pouch (continent ileal reservoir)**

Historically, this technique is very important as it resurrected interest in continent urinary diversion. It was first described by Kock et al. in 1982 [9]. This procedure and the T-pouch are the only procedures which use only ileum segments. Kock’s technique was the first using reconfigured bowel providing a low-pressure urinary pouch with reasonable technical steps to prevent reflux into the upper urinary tract and to secure continence. Skinner and associates refined the technique over the years and made it reproducible [5, 10, 11]. The procedure has been abandoned from the armamentarium of most surgeons due to high complication rates and technical difficulties.

**Double T-pouch**

Abol-Enein and Ghoneim described a technique using ileum for creating an extramural serosa-lined tunnel, in which the ureters were implanted to prevent reflux [12, 13]. Stein and associates first described the use of tapered ileum, which was implanted through a serosa-lined tunnel into an ileum neobladder as an anti-reflux mechanism [6]. They adapted this technique in 1999 to an ileo-anal reservoir and reported their first results with a double T-pouch in the same year at the American Urological Association meeting as a replacement for the Kock pouch [14].

For this procedure, 70 cm of terminal ileum is needed, and this is excluded from the bowel continuity about 15–20 cm above the ileocecal valve. The proximal and distal 12-cm and 15-cm segments are isolated: the proximal segment will serve as an anti-reflux mechanism in an isoperistaltic fashion; the distal segment will serve as a cutaneous continence mechanism after rotation in an anti-peristaltic fashion. The length of the segments can vary according to the length to the ureters and the thickness of the abdominal wall. The medial segment (44 cm) is folded into a “W” with four segments of equal length. At the afferent segment, windows between the vascular arcades are created over a distance of 3–4 cm, through which the segment is sutured with 3/0 silk to the serosa of one U of the W (Figure 22.1); at the efferent segment, windows between the vascular arcades are created over a distance of 7–8 cm and sutured likewise to the serosa of the other U of the W. The afferent segment is then tapered over a 30 French catheter; the efferent segment is gradually tapered over a 16 French catheter (to avoid curling of the catheter in a so-called false cul-de-sac during CISC) using a GIA stapler and preventing any contact of metal staples with urine. Afterwards, the bowel of the W is incised along its antimesenteric border so that it can overlay the two tunnels (T). The orifices of the two valve segments are fixed to the ileum wall with interrupted absorbable sutures (3-0 polyglycolic acid = PGA). Afterwards, the flaps of the ileum are closed over the valves with running 3-0 PGA absorbable sutures. The ureters are implanted in an end-to-side (Leadbetter) technique into the proximal segment and are stented. Eventually, the pouch is closed with two layers of 3-0 PGA absorbable sutures in a side-to-side fashion and the efferent segment/catheterizable conduit is sutured to the umbilicus with single stitches (absorbable), with additional anchor stitches to the fascia to avoid tension or slipping.
The Mainz pouch I procedure has been used in Mainz for continent urinary diversion and also for orthotopic bladder substitution since the early 1980s [7, 18–20]. It uses the ileocecal segment and has undergone some modifications over the years, specifically with respect to the continence mechanism. Originally, it was described with an ileal intussusception nipple as the standard continence mechanism [18–20]. Since 1990, the submucosally tunneled appendix has become the standard efferent continence mechanism when available and usable [21] and the intussusception nipple remains a reserve technique if needed. The Mainz pouch offers a low-pressure reservoir with a good capacity [22] and to
date, more than 1500 procedures have been performed at our institution with good long-term results.

First of all, the appendix must be checked to make a decision as to whether a catheterizable continent appendix outlet is feasible. This is performed by cutting the tip of the appendix, then calibrating and dilating the appendix to assess its usability. A continent catheterizable appendix should allow at least 5 cm of submucosal tunnel length (total appendix length 7–8 cm) and accommodate, after dilation, a minimum size of 14 F (children) to 16 F (adults) catheter. Only afterwards can the length of bowel which has to be resected for the construction of the pouch be decided. Even a normal-looking appendix might reveal an internal obliteration. The submucosal appendix provides excellent continence results but has slightly higher stoma stenosis rates when compared to the ileal intussusception nipple. If the appendix is used, bowel resection requires 20–24 cm of terminal ileum and 10–12 cm of cecum (Figure 22.2). If planning an intussusception nipple, another 12 cm of proximal ileum are needed, which adds up to about 35 cm of ileum (Figure 22.3). After resection of these segments, the bowel anastomosis is performed, either in a single-row, dual-layer (seromuscularis) running end-to-end technique after anti-mesenteric spatulation of the ileum for adjustment of the different bowel diameters or as a stapled end-to-side anastomosis (ileum to ascending colon) using EEA and TA-55 staplers.

Except for the proximal 12-cm segment of the ileum, which is needed for the intussusception nipple, the bowel segments are opened anti-mesenterically for the spherical reconfiguration and pouch formation. This is performed by running all-layer 4/0 polydioxanone monofilament absorbable sutures on a straight 60-mm needle.

The ureters are implanted in an anti-refluxing fashion by creating a 3–4 cm submucosal tunnel from the margin of the transected ascending colon in an “open-end technique”. The ureteric orifices are anchored with two 5/0 glyconate absorbable sutures each at the distal end and completed with 6/0 polyglyconate absorbable monofilament uretero-mucosal sutures.

If the appendix is used as the continence mechanism, the seromuscularis of the anterior tenia of the lower cecal pole is incised down to the mucosa over a length of about 5 cm to establish a submucosal tunnel. If the mucosa is damaged, it should be closed with 6-0 absorbable monofilament sutures. Afterwards, windows between the arcades of the appendix mesentery are created and, after intubation with a Foley balloon catheter (16 or 18 French), the appendix is flipped into the mucosal bed. The seromuscularis of the cecum is closed with non-absorbable monofilament polypropylene 4-0 sutures which tie the appendix down through the windows. The pouch is closed with several running 4/0 polydioxanone monofilament absorbable sutures. Notably, around the ureter entrances, single interrupted sutures are placed to avoid any compression.

If an ileum intussusception nipple is planned as the continence mechanism, the spared proximal 12 cm of ileum have to be prepared for invagination by dissecting the mesentery over a length of about 5 cm beyond the first arcade to ease the intussusception. The intact ileum is grasped in the middle from the mucosal side with two Allis clamps, which are inserted through the ileocecal valve, to establish the isoperistaltic intussusception.

After pulling the nipple through the ileocecal valve, it is stabilized and fixed by three rows of TA-55 staples, two rows of which are applied from inside the pouch and one further row from outside. Three metal staples at the tip of the nipple are removed from the stapler magazine as these are not required for stabilization but would be at risk of exposition to the urine. The pinhole of the stapler application is closed with a single Z-suture to avoid fistula formation and the tip of the nipple is fixed to the ileocecal valve with single 4/0 polyglyconate absorbable monofilament sutures. Finally, the pouch is closed in a similar fashion to that described above.

The efferent segment is pulled through the fascia incision and secured with several 2-0 polyglycolic acid braided absorbable sutures. After pulling the earlier inserted Foley catheter through the umbilical skin (in the case of an appendix nipple), the skin of the umbilicus and the efferent segment are anastomosed with 3/0 polydioxanone uncolored monofilament absorbable sutures. In the case of an intussusception nipple, a new Foley catheter may be inserted from outside into the pouch before anastomosing the efferent segment to the skin.

Indiana pouch

The Indiana pouch also utilizes the ileocecal region. It is probably the most widely used technique for continent cutaneous urinary diversion nowadays. This is mainly for two reasons: it is among the easiest to construct and has few short-term and long-term complications. The technique was first described in 1987 by Rowland and colleagues from Indiana University [24]. They reported
For an ileocecal pouch with appendix stoma, 10–12 cm of cecum and ascending colon and 20–24 cm of distal ileum are separated. The ileum and ascending colon are opened anti-mesenterically, the cecum remains intact to embed the appendix for the continence mechanism. After ureteral implantation into a submucosal tunnel, the seromuscularis of the anterior tenia of the lower cecal pole is incised to create a submucosal tunnel for the appendix. The appendix is flipped over and embedded after creating windows between the arcades of the appendical mesentery and fixed through these by several 4/0 polypropylene non-absorbable monofilament sutures. Source: Thüroff et al., BJU Int. 2010; 106(11): 1830–1854 [23]. Adapted with permission from Wiley.
Figure 22.3 Mainz pouch I with ileum intussusception nipple. a) In comparison to the procedures with appendix, nipple bowel resection has to comprise 12 more centimeters of ileum proximally for constructing the intussusception nipple. b) The proximal 12 cm of ileum in continuity to the pouch remain intact for construction of the intussusception nipple. After exclusion of the mesenterium beyond the first arcade, the isoperistaltic intussusception nipple is constructed by inserting two Allis clamps through the ileocecal valve into the proximal segment of ileum and grasping the ileal wall from inside. c) Two stapler rows are applied from inside, the pinholes at the end of the stapler are closed with monofilament absorbable sutures, the third row is applied from outside to fix the nipple against the wall. d) The tip of the nipple is secured to the ileocecal valve by several monofilament absorbable sutures and the mesenterial slit of the intussusception nipple is closed by several 3/0 monofilament non-absorbable sutures. Source: Thüroff et al., BJU Int. 2010; 106(11): 1830–1854 [23]. Reproduced with permission from Wiley.
similar continence levels of ~93% to the Mainz group [2] with an imbrication of the ileocecal valve as the continence mechanism and tapering/imbrication of the terminal ileum.

In its present form, the Indiana pouch includes about 10 cm of terminal ileum and the entire ascending colon and the right colonic flexure (in total 30 cm of colon) (Figure 22.4). The appendix is resected, as for any kind of pouch which does not use it as the efferent segment. The colonic segment is opened along its anti-mesenteric border and the ureters are implanted into the teniae. The ileocecal valve is imbricated with 3 × 0 silk sutures and the terminal ileum is imbricated with two rows of interrupted sutures over a distance of 3–4 cm over a 12–14 French Foley catheter or tapered with a GIA-stapler. The imbrication should be performed with the pouch still open to control all steps carefully. The ureteral stents and the pouchostomy catheter (suprapubic type of catheter to drain the pouch) are brought out through the pouch wall and the pouch is closed in a Heineke–Mikulicz fashion with running absorbable sutures. The pouch is rotated and the catheterizable ileal conduit is brought out as continent stoma, typically through the rectus muscle or umbilicus. The group reported excellent results with only 3.7% of early pouch-related complications [25].

Figure 22.4 Indiana pouch with imbricated ileum nipple. Isolation of a segment of terminal ileum about 10 cm along and the entire right colon. a) Appendectomy is performed, and the fat pad covering the inferior margin of the ileocecal junction is removed by cauterity. b) Opening of the right colon along its anti-mesenteric border. c) Interrupted sutures are performed over a short distance (3 to 4 cm) in two rows for the double imbrication of the ileocecal valve. d) Opposing sutures on each side of the terminal ileum. Source: Parts a)–c) Wein et al., 2007 [5]. Reproduced with permission from Elsevier; part d) Olsson, 1989 [16]. Reproduced with permission from Advanstar Communications, Inc.
Mainz pouch III
The Mainz pouch III is a continent cutaneous urinary diversion utilizing transverse colonic segments only. The rationale is to avoid early and late complications which are associated with pelvic and abdominal radiotherapy and other causes of ischemic damage to ureters and/or bowel [26]. This pouch may also be used for patients who require complete exenteration of the pelvis with colostomy, as in these cases it avoids a second bowel anastomosis.

After mobilization of small and large bowel, the ureters are resected up to a level at which capillary bleeding occurs, indicating the absence of radiation damage. Selection of 30–40 cm of transverse colon (either including the right or left colonic flexure) is required depending on the individual length of the left and right ureter and the availability of unirradiated bowel. The greater omentum must be separated from the transverse colon. The anastomosis (colo-colostomy) is performed using running seromuscular 4-0 monofilament (polyglycol) sutures. Except for 5 cm of the oral or aboral end, which is needed for the efferent segment, the colon is anti-mesenterically detubularized (Figure 22.5). The efferent segment is created by tapering the end over an 18 French Foley catheter. The mucosa is sutured with a running monofilament polyglycol suture and the seromuscularis with a non-absorbable running suture. After creation of the pouch plate with running 4-0 monofilament polyglycol sutures with a straight needle, the ureters are implanted either in a refluxing or anti-refluxing technique. For the refluxing ureterointestinal anastomosis, which we only recommend for adults, 1 cm of the bowel mucosa is excised on the rear side of the pouch plate. The seromuscular layer is then incised in a cross shape. The ureter is pulled through and anchored to the mucosa of the pouch with two stitches at 5 and 7 o’clock. Afterwards, the anastomosis is completed with interrupted 5-0 monofilament sutures. The ureteric adventitia is externally fixed at the seromuscularis of the pouch wall. The second ureter is implanted 2 cm lateral at the other side of the suture line of the back plate of the pouch. If a non-refluxive implantation is intended, the ureters are anastomosed in a similar fashion to that described above for the Mainz pouch I using submucosal tunnels, which are created from the colonic resection margins. Ureters are intubated with stents, a pouchostomy is placed as described above, the pouch is closed, and the efferent segment is embedded into the anterior suture line of the pouch wall. After creation of windows between the arcades of the tapered colon, the efferent segment is fixed with a few interrupted non-absorbable sutures. Finally, the efferent segment is anastomosed to the umbilical skin, as described previously, and the pouch is fixed with a few interrupted sutures to the abdominal wall. Other techniques creating the efferent segment from a tapered non-irradiated small bowel segment or a full-thickness colonic tube can be used alternatively [27, 28].

Ureteral implantation
A variety of different implantation techniques have been mentioned above in combination with the various types of urinary diversion. We want to point out a few general considerations regarding the choice of the ureteral implantation technique (Figure 22.6). The implantation can be performed in a refluxing and/or anti-refluxing technique, which is dependent on the segment of bowel used for the diversion and the surgeon’s preference. For ileocecal and colonic reservoirs, anti-refluxing ureteral implantation is still the method of choice, with the concept to protect the upper urinary tract from retrograde pressure transmission and ascending bacteriuria, although the currently utilized heterotopic diversions are low-pressure reservoirs. However, this concept has been questioned for orthotopic bladder substitution, since overfilling of the neo-bladder/pouch is not an issue in orthotopic bladder substitution due to the “natural pop-off valve” of urethral leakage and since there is a low incidence of contaminated urine. Circumstances are different in continent cutaneous diversion. The contamination rates are higher due to intermittent catheterization and overfilling of the pouch may occur, since most continence mechanisms provide absolute continence without a pop-off mechanism. The most important anti-refluxing techniques are the Le Duc procedure, in which the ureter is placed into a groove created in the ileal mucosa [29], the submucosal tunnel, as described for the Mainz pouch I [18], and the serosa-lined tunnel [13], which is advantageous for dilated ureters. All these techniques follow the “flap-valve” principle. An oblique entry of the ureter into the reservoir is created with a “tunnel” that allows the transmission of increasing reservoir pressures to the ureter against the outer wall of the pouch (i.e. seromuscularis). Refluxing techniques are the end-to-side anastomosis (Nesbit and Leadbetter) and the spatulated end-to-end anastomosis.

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These are generally used in orthotopic urinary diversion when an afferent ileal segment is used for ureteral implantation (as in the technique of the orthotopic Mainz pouch where the ileocecal valve serves as the anti-reflux mechanism). Another refluxing ureter implantation technique for colon diversions [30] has been described with the Mainz pouch III procedure. Data on ureter stricture

Figure 22.5 Mainz pouch III. a) Transverse colon with either the right or the left colic flexure is opened anti-mesenterically, leaving 5–6 cm of the oral or aboral end intact for creating the efferent segment. b) The efferent segment is tapered over an 18 F silicone catheter. The mucosa is sutured with an absorbable and the seromuscular layer with a non-absorbable running suture. c) Ureters are implanted by a refluxing oblique ureteral anastomosis. d) After closing of the pouch, the neoappendix is embedded onto the suture line and fixed with non-absorbable monofilament sutures through windows in the mesentery of the tapered segment of colon. Source: Leissner et al., 2006 [33]. Reproduced with permission from Wiley.
rates comparing different techniques of ureteral implantation (refluxing vs anti-refluxing) are sparse, there are only a few retrospective studies reporting outcomes of different types of ureter implantation. Pantuck et al. reported no difference of pyelonephritis in ileum neo-bladders between refluxing and anti-refluxing ureter implantation, but a significantly higher risk for uretero-ileal strictures, with 1.7% and 13%, respectively [31]. Hassan and colleagues confirmed these results in 120 patients with 9.7% strictures after anti-refluxing ureter implantation vs 0% after refluxing ureter implantation. However, the risk of post-operative reflux was significantly higher in renal units with pre-operatively dilated ureters after a refluxing implantation technique, with 40% vs 16.7% [32].

Whichever technique is utilized, the ureters are usually stented with 6 or 8 French stents, which are brought out through the wall of the pouch, as is a 10 French pouchostomy catheter. Depending on the efferent segment, silicon balloon catheters (16 – 20 French) are placed when constructing the continent stoma.

The stents are removed ten days after surgery; the indwelling Foley catheters mostly after 21 days to make sure that the continence mechanism is stable for catheterization. Most surgeons perform imaging studies like IVP and a pouchogram to prove the absence of extravasation before dismissing the patient.

Complications

Apart from general surgical complications like bleeding, infection, and anastomotic leakage, a few typical aspects of continent cutaneous urinary diversion have to be mentioned.
In the early post-operative months, non-peristaltic bowel contractions occur but usually subside spontaneously with increasing capacity of the reservoir. Supportive medication with anti-muscarinics may be used.

In approximately 60% of patients, asymptomatic metabolic acidosis can be detected post-operatively by blood gas analysis (i.e. base excess \( \leq 2.5 \text{ mmol/L} \)), which should be prophylactically balanced with alkali substitution (i.e. sodium or potassium citrate or bicarbonate).

Follow-up examinations must include ultrasound of the upper urinary tract or intravenous pyelogram, blood gas analysis, and serum creatinine and urea levels. A risk of secondary malignancy is imminent, yet only cases of urethelial recurrence at the ureter implantation site have been described in the literature. Nevertheless, starting from the fifth post-operative year, annual pouchoscopy and evaluation of serum cobalamin is recommended.

**Summary**

In conclusion, continent cutaneous urinary diversion has been proven to be safe and feasible for patients in whom an orthotopic diversion is oncologically or functionally not advisable. There are various surgical techniques to create a continent, non-refluxing pouch. Important outcome criteria are function and preservation of the upper urinary tract, continence, and the cosmetic result (quality of life) for the patient. Continence rates of about 93% have been reported in long-term studies from different groups for ileocecal reservoirs.

**Useful web links**


**References**


CHAPTER 23

Non-continent urinary diversion

Michael Rink¹, Fredrik Liedberg², and Margit Fisch¹

¹Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
²Department of Urology, Lund University, Malmö, Sweden

KEY POINTS

• Non-continent urinary diversion represents a simple and robust technique for lower urinary tract reconstruction, when temporary or permanent urinary diversion is indicated and continent urinary diversion is contraindicated.

• Non-continent urinary diversion is indicated in advanced/inoperable urothelial carcinoma of the bladder or pelvic malignancies affecting the bladder, simultaneous urethrectomy, comprised renal function (creatinine level > 1.5 mg/dL), severe hepatic dysfunction, as well as advanced age.

• The ileal conduit is the gold standard non-continent urinary diversion.

• The transverse colon conduit represents the optimal bowel segment in patients after pelvic or bowel irradiation.

• The most common general complications after non-continent urinary diversion are metabolic changes, particularly: hyperchloremic metabolic acidosis, stone formation, and renal deterioration.

• Renal deterioration after non-continent diversions during the long-term follow-up predominantly seems to be caused by a lack of ureteral motility, infection, or stone formation.

• Specific complications encompass stomal and peristomal complications, parastomal hernia, and conduit stenosis.

• In general, non-continent urinary diversion seems to be associated with a reasonable quality of life and high patient acceptance.

Introduction

Non-continent urinary diversion remains the most commonly used method for reconstructing the lower urinary tract in conjunction with radical cystectomy. The reported rates of non-continent urinary diversion in cystectomy patients range between 30% and 92%. During the last decade these rates have increased, especially in population-based series [1, 2]. Several reasons may contribute to these findings, with patients’ age at time of cystectomy probably being the most important factor. When considering urothelial carcinoma as the main cause of radical cystectomy, this malignancy can occur at any age. However, the median age at diagnosis is approximately 70 years and thus it is primarily considered a disease of elderly people [3, 4]. With increasing age in the Western world, the rate of cystectomies in elderly patients has increased over the past decades. A general “frailty” in the elderly along with comorbid conditions and a decreased physiological reserve with compromised recoverability, challenge treatments in these patients [4]. It is also our impression that elderly patients are, in general, less interested in continent reconstruction.
although there are exceptions. The majority of patients are searching for a simple system which is easy to handle, with low risk of early and late complications and a short hospital stay. In addition, non-continent urinary diversion is usually associated with a shorter operation time compared to continent reservoirs, which may reduce the risk for post-operative complications or a prolongation of hospital stay. We think that 80 years of age is an arbitrary upper limit for recommending continent urinary diversion and, in fact, many patients above the age of 70 settle for an ileal conduit at the final counseling after informed consent about the pros and cons, reading lay-oriented literature, and, whenever possible, having met patients with different types of reconstruction. Another reason contributing to a high incidence of non-continent diversions is the substantial number of patients with advanced disease at the time of radical cystectomy [5]. Moreover, a considerable number of cystectomies are performed outside of major centers, where patients are less likely to receive continent diversions [6]. In addition, the increasing numbers of robot-assisted cystectomies in the past decade may have also raised the number of non-continent urinary diversions [7].

**Patient preparation**

Finding the best localization of the stoma is an integral part of the pre-operative preparation and is of critical importance in order to avoid post-operative difficulties with the stoma appliance, thus improving the patient’s quality of life. Marking the site of the stoma should be done in close cooperation between urologists and stoma therapists. To achieve the best results, the stoma should be placed in an area free of scars or skin folds. Most often it will be slightly below a line between the umbilicus and the anterior superior iliac spine. The adhesive portion of the appliance is usually a quadrant with a diameter of 7–8 cm, which will influence position with regard to the umbilicus and the iliac spine (Figure 23.1). Prior to surgery the patient should wear the stoma bag for several hours up to a day, in order to identify potential difficulties with the marked and designated location (Figure 23.1).

The benefit of pre-operative bowel preparation before radical cystectomy is debatable. Historically, the most common type of bowel preparation seemed to be intake of polyethylene glycol. However, evidence is emerging to support surgery without formal bowel preparation, at least in ileal diversion [8]. When a

**Figure 23.1** a) Ileal conduit. b) Patient with ileal conduit diversion.
colon conduit is anticipated, bowel imaging with water-soluble contrast media should be performed pre-operatively to exclude polyps or diverticula. Pre-operatively, broad-spectrum antibiotics including broad-spectrum cephalosporins, often in combination with metronidazole, are usually given.

**Surgical techniques**

**Cutaneous ureterostomy**

The cutaneous ureterostomy is the simplest version of a non-continent urinary diversion. Using this technique, one or both ureters are directly implanted to the abdominal skin. This method of diversion is infrequently used today and there are only few reports in the literature during the past 15 years. There are four common types of cutaneous ureterostomies:

1. The single ureterostomy brings only one ureter to the surface of the abdomen.
2. The bilateral ureterostomy brings the two ureters to the surface of the abdomen, with each side separated.
3. Using a double-barrel ureterostomy, both ureters are brought to the same side of the abdomen and channeled to the skin.
4. A transuretero-ureterostomy (TUU) brings both ureters to the same side of the abdomen, channeled through the same stoma.

The main indication for this type of urinary diversion is palliation in advanced stages of bladder cancer, although the majority of diversions in these cases today are performed as percutaneous diversions instead. Cutaneous ureterostomy is associated with less risk of early complications than conduit diversions. Martinez-Pineiro et al. reported an incidence of such complications after cystectomy of 7%, while complication rates were three times higher creating a conduit [9]. The most frequent complication in cutaneous ureterostomy is stomal stenosis, especially in non-dilated ureters due to ureteral ischemia with stricture formation. The rate of stenosis varies from 14% to 67%, according to different reports, with the lower figures reported in more modern series [10, 11]. In these patients, subsequent pyelonephritis due to urine obstruction is a crucial problem [10]. However, high patency rates have been reported following primary plasty of the uretero-cutaneous junction [12, 13]. Urine passage seems to be the most important factor for urinary tract infections in patients with tubeless cutaneous ureterostomy and insignificant bacteriuria becomes significant when urine passage is impaired [10]. Nevertheless, often cutaneous ureterostomies are (protectively) intubated with single-J stents continuously, with the need for a periodic change of the stent every 8 to 12 weeks. New materials allow single-J stents to be left much longer and make them less prone to infection.

In selected cases, cutaneous ureterostomy can be combined with a transuretero-ureterostomy with acceptable results. However, this procedure harbors the risk that urine is shuttling from one ureter to the other – the “yo-yo phenomenon” – due to disrupted ureteric peristalsis. To diminish the risk, the recipient ureter should be mobilized only to the level where the anastomosis will be performed [14]. The end of the non-dilated donor ureter is cut obliquely and sutured without tension end-to-side to the recipient ureter, which is usually dilated.

**Conduit diversion**

Conduits can be constructed from stomach, jejunum, ileum, and colon and there are specific indications for all of them.

**Ileal conduit**

This is the most common form of urinary diversion in conjunction with radical cystectomy. The technique has a low degree of complexity and decades of experience. This diversion type is associated with a short operation time and the fewest intraoperative and immediate post-operative complications.

A 10–20 cm long terminal ileal segment is isolated and the ureters implanted in the proximal end, most usually with a refluxing technique. For ureteral implantation, an end-to-side technique, as described by several authors including Nesbit (Figure 23.2) and Leadbetter [15], or a “double barrel” Wallace technique can be used. The ureter should be spatulated prior to anastomosing to the ileum. The stoma is usually placed below and to the right of the umbilicus through the rectus muscle.

Although already described by the beginning of the 1930s, the technique did not attain clinical popularity until 20 years later, after the publications by Eugene Bricker [16–18]. It quickly replaced uretero-sigmoidostomy as the preferred method for urinary diversion with a lower incidence of metabolic disturbances, the most common being hyperchloremic acidosis.
Contraindications for the use of ileum as a conduit are patients with a short bowel syndrome, inflammatory small bowel disease, and in those whose ileum has been exposed to extensive irradiation due to prior radiation therapy for a pelvic malignant neoplasm.

One important question is whether radical cystectomy is associated with fewer complications when combined with an ileal conduit compared to continent urinary diversion. While some studies found reduced complication rates, some other studies failed to show such differences when stratifying according to comorbidity index [19–22]. Interestingly, recent population-based studies with long-term follow-up demonstrated increased re-operation rate after continent urinary diversion (29%) as compared to ileal conduit (22%), as well as increased risk of in-hospital complications [23, 24]. Newer reports have also suggested an association between hospital volume and surgeon case load with the complication rates. The challenge of optimal care for elderly patients with comorbidities, however, is best mastered at a high-volume hospital by a high-volume surgeon [3, 25].

**Jejunal conduit**

The jejunum has the largest diameter of the small bowel and the longest mesentry. However, jejunal conduits are rarely used today. The jejunal conduit received a bad reputation because of several reports in the 1970s of “jejunal conduit syndrome”, characterized by severe electrolyte deterioration (including hypochloremia, hyperkalemia, and hyponatremia) leading to metabolic acidosis, caused by the inherent absorptive characteristics of the jejunum. The clinical signs are dehydration and lethargy and treatment is intravenous sodium chloride solutions, which often has to be followed by oral salt supplementation for some period of time [26, 27]. However, a more recent report expressed satisfaction with this type of diversion and found a low incidence of electrolyte abnormalities [28]. The authors suggested that a short conduit should be used. The procedure is similar to that for an ileal conduit and a 10- to 15-cm segment of jejunum is isolated. Indications for this type of urinary diversion include the impracticability of distal ileum use, e.g., due to radiation enteritis. Contraindications for the use of this segment include severe bowel nutritional disorders and the presence of another acceptable segment.

**Gastric conduit**

The gastric conduit can be used in exceptional cases. The good blood supply, relatively poorly absorbing mucosa, and acidification of urine have been considered advantageous [29]. In general, there is little experience regarding this type of urinary diversion and information is mainly derived from case series reports. Professor Wiking
Mansson reported his experience from four cases, three of which had severely reduced renal function and needed diversion (personal communication). The conduit was created from the gastric antrum using a GIA instrument and there have been no early or late complications. However, ulcer formation with perforation and subsequent death have been described [30].

**Colonic conduit**

In 1952, Richard Übelhör described the use of a colonic segment for incontinent urinary diversion [31]. There are three regions of colon that are used for conduits: sigmoid, transverse, and ileocecal.

Today, the sigmoid colon conduit is mainly used as an intermediary diversion in children. In contrast, the transverse colonic conduit, initially described in 1969 [32], has been utilized more frequently in patients with urological or gynecological malignancies treated with radiation therapy [33–36]. With its cranial position outside the irradiation field, it fulfills the criteria for use of non-irradiated bowel. The long mesentery enables individual adaptation regarding stoma placement. Ureteral re-implantation can be done using an anti-reflux or refluxing technique [32, 37, 38] and is less prone to stoma stenosis compared to the ileum. A direct anastomosis of the conduit to the renal pelvis represents an additional option (pyelotransverse-pyelocutaneostomy) in patients with total damage to the ureters by irradiation or retroperitoneal fibrosis and in patients with recurrent urothelial tumors in a solitary kidney [35].

The advantage of the ileocecal segment for a conduit is the availability of a long segment of ileum when long segments of ureter need replacement in combination with the advantages of providing colon for the stoma. It is also used in situations in which free reflux of urine from the conduit to the upper tracts is thought to be undesirable [39].

Contraindications to the use of colonic bowel segments include the presence of inflammatory large bowel disease and chronic diarrhea.

**Anatomic and technical considerations for abdominal stomas**

The vast number of stoma complications result from technical errors in their construction and thus some technical issues have to be considered. For any type of stoma it is of critical importance to preserve a portion of the mesentery along the entire length of the bowel. In general, two types of abdominal stomas can be distinguished: those that protrude and those that are flush with the skin. For non-continent urinary diversions, only protruding stomas should be established, as a properly protruding stoma worn with an appliance results in a lower incidence of stomal stenosis and a better appliance fit with fewer peristomal skin problems [39]. Basically there are two types of protruding ileal stomas: the ileal end stoma and the loop end ileostomy.

**The ileal end stoma (“Nipple stoma”; “Rosebud stoma”)**

To create this stoma, 5–6 cm of intestine is brought through the abdominal wall with approximately 2 cm of bowel serving as the nipple, which is everted and fixed to the skin. For accurate fixation, four single-knot sutures are placed through the seromuscular layer and fascia. Especially in obese patients, a more secure nipple may be made by performing multiple myotomies through the seromuscular layer of the bowel above the skin line before construction of the nipple. The myotomies adhere serosa to serosa and reduce the risk of stomal retraction [39].

**The loop end ileostomy (“Turnbull loop stoma”)**

The loop end ileostomy has the advantage of overcoming some problems that may occur in obese patients who often have a thick abdominal wall and a thick, short ileal mesentery. For creation of this type of stoma, the distal end of the ileum is closed and a loop is brought up through the belly of the rectus muscle and onto the anterior abdominal wall. The distal portion of the bowel is brought through the skin and abdominal wall opening such that the closed end lies cephalad to the body of the segment and the non-functional opening is sutured directly to the skin [39]. The distal end of the de-functionalized limb should lie within the abdominal cavity just underneath the posterior rectus sheath. Due to the usually wider diameter of the stoma, compared to the end ileostomy, the Turnbull loop stoma has a lower incidence of stomal stenosis. However, in older reports, an increased incidence of parastomal hernias has been reported [40].

**Considerations for colonic stomas**

The technique for construction of colonic stomas is similar to that of end stomas for the ileum.

For the sigmoid colon conduit, a 12–15 cm long segment is isolated respecting the blood supply. Bowel
continuity is restored using a one-layer seromuscular single suture. The ureters can be implanted directly (Nesbit technique) or using a submucosal tunnel in the open end of the conduit or using a “button hole” technique.

A more extensive bowel mobilization including the right and left colon flexure is required for the transverse colonic conduit. The omentum has to be dissected off the transverse colon. Subsequently, the chosen segment is isolated (Figure 23.3). Ureteral implantation is identical to the sigmoid colon conduit. For the direct anastomosis of the renal pelves to the colon (pyelotransverse-pyelocutaneostomy) the ureters are cut at the uretero-pelvic junction and the renal pelvis is longitudinally spatulated. The right renal pelvis is anastomosed end-to-end to the proximal end of the conduit, the left renal pelvis end-to-side.

For the ileocecal colon conduit, it is important to notice that it is based on the terminal branches of the superior mesenteric artery (i.e., the ileocolic artery). The segment is placed caudad, and an ileum-ascending colon anastomosis is performed. The ileocecal valve may be reinforced to ensure prevention of reflux. The stoma is placed in the right lower quadrant [39].

Complications

Long-term follow-up results are available for all non-continent urinary diversions, giving good insights into common and specific complications after urinary tract reconstruction. The best documentation is available for ileal conduit, followed by colon conduits and cutaneous ureterostomy. Indeed, the incidence of complications correlates with the length of follow-up [41]. Long-term follow-up conduit-related complications include metabolic dysfunction and infections, urolithiasis, as well as conduit, bowel, stoma, and renal dysfunction [42, 43].

General complications

Although significantly less frequent than in continent urinary diversions, general complications in non-continent diversions comprise metabolic changes, particularly including hyperchloremic metabolic acidosis. Hypokalemia and total body depletion of potassium may be seen with ileal and colonic urinary intestinal diversion, although more frequently with the latter, as ileal segments absorb more potassium. In addition, hypocalcemia and/or hypomagnesemia severe enough to cause symptoms do occur, but these are infrequent complications of urinary intestinal diversion [10]. Some of these complications may be triggered by urinary tract infections, which may be associated with pyelonephritis. To rule out complications from electrolyte deterioration, electrolyte levels should be regularly checked, especially in the early post-operative period.

Vitamin B12 deficiency is generally believed to be less frequent in non-continent compared to continent urinary diversion as a longer intestinal segment is used; however, B12 deficiency has also been reported more frequently after ileal conduits as compared to continent urinary diversions [44]. Chronic vitamin B12 deficiency is insidious and may result in irreversible neurologic and hematologic sequelae. A blood check for vitamin B12 levels should be performed at least after three years, as depletion of body stores of vitamin B12 takes three to five years from baseline levels [10].

Urinary tract infections (UTI) are observed early and late after non-continent urinary diversions and are the most common complication, with a bacteriuria incidence reported in virtually all ileal conduit patients [45]. The longer a patient survives after urinary diversion, the greater are the chances for subsequent urinary infection [46]. Differences between intubated and
tubeless non-continent urinary diversions have been noted. In patients with intubated cutaneous ureterostomy, UTI is inevitable, and bacteria are very similar to those detected in complicated UTI. Pyelonephritis may occur in these patients, especially when urine passage is impaired. Therefore, a periodic change of the stent is needed; the chances of impaired urinary drainage increase with longer intervals between stent changes. In patients with tubeless cutaneous ureterostomies or conduits, bacteriuria is very common \[45, 47\]. However, bacteriuria is clinically insignificant in most of these patients without any need for intervention or treatment. Indeed, insignificant bacteriuria can become significant when urine passage is impaired. Insufficient drainage from the stoma may cause pyelonephritis and/or urosepsis, which have been reported in up to 15% of ileal conduit patients [43, 45]. In patients with clinical UTI symptoms, administration of appropriate antibiotics and potentially drainage of the upper urinary tract is indicated. Urodynamic evaluation may be recommended in patients with ileal conduits who have recurrent UTI [10, 25]. In addition, when evaluating hydronephrosis, a loopogram is used to rule out uretero-ileal anastomotic stricture. It is important to notice that recurrent, symptomatic UTIs in non-continent diversions might be associated with abnormalities in the diversion (e.g. elongation of the segment due to stoma stenosis) or surgical imperfection. For example, a too-long bowel segment often causes a syphon with urinary stasis, which is the basis for UTIs.

**Specific complications**

Specific long-term follow-up complications of ileal conduit diversion are frequent, the most common being stomal/peristomal problems, ureterointestinal and stomal stenosis, parastomal hernia, conduit stenosis, and upper tract deterioration.

**Peristomal complications**

These include erythematous/erosive, pseudoverrucous skin lesions, fungal infections, and stenosis and retraction of the stoma. The skin lesions are often a consequence of an inappropriate stoma, such as a flush stoma. Other causative factors may be an allergic reaction to or poor fit of appliances and alkaline urine. These complications jeopardize adherence of the plate of the appliance to the skin and thus entail risk of urine leakage. One should remember that the stoma is the only part of the diversion that the patient can see and actively take care of. A spout at least 2 cm in length should be fashioned, which will decrease the risk of parastomal complications. The spout should protrude into the appliance bag. The appliance will fit much better and there will be less risk of urine leakage.

Studies show that stomal and peristomal problems are common, being reported in up to 65% [43, 48–50]. Such complications may secondarily affect the patient’s lifestyle and also cause emotional and psychosocial problems, aspects that have increasingly attracted interest. The quality of life issue is covered in Chapter 34.

**Stomal stenosis**

Today, stomal stenosis is a rare complication in patients with non-continent urinary diversions. Historically, stomal stenosis has been reported in 20–25% of ileal conduits and 10–20% of colon conduits. In more contemporary series, the overall stenosis rates appear to be lower and range from 3 to 8.5% [39, 51]. Due to their wider diameter, colonic conduits are less prone to this complication (2%). Stomal stenosis may be a late manifestation of technical error at the time of the initial surgery. The typical stenosis location is the level of fascial attachment. The reasons for stomal stenosis are multifactorial, with ischemia, fascial constriction, and improperly placed stomas in a depression or crease contributing to this complication. Additionally, poorly fitting appliances that allow for local skin irritation can lead to ulceration and hyperkeratosis [51]. Once a stomal stenosis develops, the majority of patients require surgical intervention. Due to the impaired urinary excretion, other complications such as obstruction of the conduit, UTI, and renal damage can subsequently occur.

**Ureterointestinal stricture**

In the literature, the post radical cystectomy incidence of ureterointestinal stenosis in non-continent urinary diversions is 2–17% [39]. For ileal conduits, rising stenosis rates are reported, with increasing follow-up duration (early: 2%; late 6%). Anti-refluxing ureteral implantations are suggested to be associated with a higher risk of anastomotic stenosis. In addition, ischemia secondary to ureteral mobilization is a likely cause of stricture formation. A contemporary study found a running anastomosis and post-operative UTI may be associated with uretero-intestinal anastomotic stricture [52]. There are mixed reports as to whether
the risk for uretero-intestinal anastomotic strictures are increased with previous pelvic radiation [53]. For endoscopic treatment, percutaneous and open techniques are used [54].

**Parastomal hernia**
Parastomal hernia is seen in 5–31% [43, 49], with higher incidences reported when a conduit is performed for a benign indication. The hernias are rather large and although the majority of patients are asymptomatic, some need surgery; however, high recurrence rates (21%) requiring another operation have been reported [55]. For first-time parastomal hernia repairs, stoma relocation used to be considered superior to fascial repair [56]. With the increasing use of synthetic, low-weight meshes in a sub-fascial position, and evidence from randomized trials with long-term follow-up that even a prophylactic use of such a technique reduces parastomal hernia incidence after colorectal surgery [57], the use of a light-weight, synthetic mesh can be considered for first-time parastomal hernia repairs. The use of composite meshes with an inner expanded polytetrafluoroethylene layer to prevent intestinal adhesions has also been reported when extraperitoneal repair is not unfeasible [58]. Other techniques with the incision placed lateral and far away from the stoma, with closure of the fascial defect, and using mesh material as onlay have also been reported to give good results [59, 60]. Since the use of synthetic mesh in parastomal hernia repair has been employed, infections with erosions and fistulas due to the artificial material have been reported in this context. Currently, prophylactic implantation of a mesh in the sublay position at the time of urinary diversion is prospectively being evaluated in a Swedish randomized multi-center study.

**Conduit stenosis**
This seems to be unique for ileal conduits. This condition has never been described in colonic conduits. The whole, or part, of the conduit is transformed into a thick-walled tube without peristaltic activity. The pathogenesis of this disorder, which manifests late after diversion, is obscure. Chronic inflammation and/or vascular insufficiency have been suggested. The clinical picture is colicky flank pain and/or fever and is produced by upper urinary tract obstruction. Treatment is by removal of the conduit or partial resection with or without ureteric re-implantation [61].

**Upper urinary tract deterioration**
Numerous retrospective deterioration studies during the 1970s and 1980s revealed a high incidence (13–41%) of renal deterioration associated with a refluxing ileal conduit [62–64]. These figures are not substantially different to recent long-term follow-up reports [43, 49, 65], although one small study in patients with jejunal conduits reported more favorable results [28]. The generally dismal results provided the background for the recommendation of non-refluxing ureterointestinal anastomosis and a more favorable result was reported in non-refluxing ileal conduit diversion [66]. It is, however, difficult to evaluate these different studies in relation to each other, as they are all retrospective. Also, differences regarding age, follow-up, underlying conditions such as diabetes and hypertension with increased risk for renal deterioration [42], and pre- and post-operative techniques and routines might affect study outcomes. Another problem relates to the methods of measuring renal function after urinary diversion. Most reports have relied upon serum creatinine and intravenous pyelography (IVP), but both are imprecise for the purpose. In a prospective randomized study evaluating the type of conduit (ileal versus colonic) and the method of ureteric implantation (refluxing versus anti-refluxing), total and separate GFR was assessed using 51Cr-EDTA [67] and renal scarring was assessed using renal scintigraphy [68]. No statistically significant differences were found with regard to symptomatic urinary tract infection, number of ureterointestinal anastomotic strictures, and incidence of GFR deterioration. At a mean follow-up of ten years, mean GFR dropped from 88 to 71 mL/min in ileal conduit patients and from 88 mL/min to 65 mL/min in colonic conduit patients. Corresponding figures for patients with continent diversion were 100 mL/min and 85 mL/min, respectively. Scarring was more common in refluxing units than in anti-refluxing units, supporting the role of reflux from the conduit in which pressure is not intermittently high [69].

**Quality of life (QoL)**
This topic will also be discussed in Chapter 34, however, we will give a brief overview here.

In short, there are no studies analyzing the quality of life between different types of non-continent urinary diversions. In contrast, several retrospective and some
prospective studies compared the quality of life from patients with conduit diversions compared to continent cutaneous and orthotopic neobladders, respectively [10, 70]. However, it is evident that there is a lack of high-quality data. The majority of QoL studies are retrospective and used inappropriate questionnaires. Although some are validated, they were not designed to evaluate specific urologic aspects.

In comparison to continent cutaneous urinary diversion, patients with conduit diversion were found to have a high global satisfaction in a prospective study by Hardt et al. [71]. It was also noted that most patients would choose the same method again. Similar results without differences in the quality of life were reported in different retrospective studies comparing conduits and cutaneous continent diversions [72–74].

In addition, there are several studies comparing the QoL of patients with conduit diversion versus orthotopic neobladders, but all of them are retrospective [75–79]. Except for one study [78], the type of urinary diversion was not associated with QoL. Even after adjustment for age, there was no significant difference in most QoL indices. However, some studies reported a better body image and physical function, including a more active lifestyle, in patients with orthotopic neobladders [79]. However, this has to be judged carefully with regards to age and comorbidities in patients who are candidates for non-continent urinary diversion. Randomized controlled trials comparing types of urinary diversion using validated, disease-specific QoL instruments are needed.

In summary, non-continent urinary diversions are associated with good global satisfaction and tolerance, and the QoL is apparently comparable with continent diversion types.

Follow-up of patients with conduit diversion

Due to the increasing incidence of complications seen the longer the follow-up, it is necessary that patients after urinary diversion be subjected to indefinite follow-up. However, the optimal follow-up schedule after urinary diversion is not yet defined, due to a lack of high-quality data [80]. Besides the medical follow-up, the schedule should also include regular visits to the stomal therapist. Since the majority of radical cystectomies with urinary diversion are attributable to bladder cancer, follow-up strategies should consider the risk of disease recurrence. As most relapses occur within five years and the median time to local and distant recurrence is 12–24 months after radical cystectomy, follow-up should be intensive for the first five years, particularly for the first two years [80, 81]. Patients with extravesical and lymph node metastasis at radical cystectomy have the highest risk of disease recurrence. The follow-up for bladder cancer patients is discussed in Chapter 11.

Follow-up should comprise blood tests and, in addition to the regular blood tests, vitamin B12 should be checked at least after three to five years following urinary diversions including the terminal ileum. However, the recommendation to start vitamin B12 screening three to five years after cystectomy emanates from the era prior to the introduction of neoadjuvant chemotherapy. The authors’ clinical experience is that B12 substitution has become more common at an earlier time point nowadays with the use of neoadjuvant chemotherapy. Therefore, the authors suggest that B12 screening should commence at the latest after three years in patients treated with neoadjuvant chemotherapy prior to radical surgery.

Ultrasonography is a simple method to check the upper urinary tract for dilatation and therefore could be performed at every visit or at least yearly. In most cases, serum creatinine can be used to follow the patient. As tubular damage precedes glomerular damage from post-renal causes, estimation of alpha-1-microglobulin in urine can be a suitable additional marker for tubular dysfunction [82]. In addition to these rather common follow-up suggestions, the authors also recommend periodic renographic studies for upper urinary tract evaluation. Ultrasonography alone can never be a substitute for IVP, as obstruction can be present without gross dilatation and vice versa. In addition, ultrasonography is user-dependent.

Conclusions

Incontinent urinary diversion has a crucial and consolidated place among the different types of available urinary diversions. Non-continent urinary diversion techniques have, in general, low complication rates, faster rehabilitation compared to continent urinary diversions, and reasonable quality of life. The advancing
age of patients with increasing numbers of comorbidities underscores the need for these simple and robust techniques in the future.

**Useful Web links**

1. [http://www.uroweb.org/guidelines/online-guidelines](http://www.uroweb.org/guidelines/online-guidelines)
2. [http://www.nccn.org/professionals/physician_gls/1_guidelines.asp#site](http://www.nccn.org/professionals/physician_gls/1_guidelines.asp#site)

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PART V

Treatment of regionally advanced and metastatic bladder cancer
CHAPTER 24

Molecular determinants of chemotherapy response

Matthew I. Milowsky1, Peter H. O’Donnell2, Thomas W. Flaig3,5, and Dan Theodorescu4,5

1 Department of Medicine, Division of Hematology/Oncology, University of North Carolina at Chapel Hill, and Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA
2 Department of Medicine, Section of Hematology/Oncology, The University of Chicago, Chicago, IL, USA
3 Department of Medicine, Division of Medical Oncology, University of Colorado Denver, Aurora, CO, USA
4 Department of Surgery, Urology Division, University of Colorado Denver, Aurora, CO, USA
5 University of Colorado Cancer Center, Aurora, CO, USA

KEY POINTS

• Urothelial cancer is a chemosensitive malignancy with a survival benefit seen with cisplatin-based chemotherapy in the metastatic and localized disease (neoadjuvant) settings.

• Cisplatin-based chemotherapy may be associated with significant toxicity in this older patient population with co-existing medical problems.

• Molecular determinants of chemotherapy response would allow for the treatment of patients most likely to benefit and spare patients from the toxicity of treatment when unlikely to benefit.

• DNA repair enzymes including ERCC1 and BRCA1 repair cisplatin-induced double-strand DNA breaks leading to the cisplatin resistance phenotype with low levels predicting improved outcomes with cisplatin-based chemotherapy.

• Drug efflux proteins such as MDR1 reduce intracellular accumulation of cytotoxic agents, with low levels associated with an improvement in outcomes.

• Pharmacogenomic approaches including germline polymorphisms have been associated with response or toxicity to platinum agents with known activity in urothelial cancer.

• Gene expression models including COXEN (COeXpression ExtrapolatioN) have demonstrated the ability to predict chemosensitivity in urothelial cancer.

• Ongoing prospective validation studies of predictive markers for chemosensitivity will be needed to integrate molecular determinants of chemotherapy response into clinical practice.

Introduction

Chemotherapy is a critical component of the multimodality management of patients with urothelial cancer (UC). The demonstration that multi-agent chemotherapy with a cisplatin backbone leads to a response rate of approximately 50% as well as an improvement in survival for patients with advanced/metastatic disease has proven that UC is a chemosensitive malignancy [1]. This improvement in outcome in patients with advanced disease ultimately translated into a survival benefit for perioperative cisplatin-based combination chemotherapy in patients with localized muscle-invasive disease [2]. In spite of the chemosensitive nature of UC, not all patients benefit from...
chemotherapy. Both the median survival of 15 months for patients with metastatic disease and the observation that only 30–40% of patients treated with neoadjuvant chemotherapy achieve a pathological complete response provide a clear rationale for the need for molecular determinants of chemotherapy response [1, 3]. In addition, as the cornerstone for chemotherapy in UC, cisplatin is not without significant toxicity and thus a better ability to predict benefit would allow for the avoidance of toxicity in many patients.

The recent explosion in genomic technologies has led to a better understanding of both tumor and host biology with the identification of many novel pathways involved in tumorigenesis. This technology has become a springboard for the elucidation of potential tumor and host factors that may predict response to treatment. This chapter will focus on the current state of molecular determinants of response to chemotherapy in UC.

**Potential biomarkers predicting response to chemotherapy – DNA repair enzymes, drug efflux proteins, and p53**

In spite of level 1 evidence supporting a survival benefit for the use of neoadjuvant cisplatin-based combination chemotherapy in muscle-invasive UC with a combined hazard ratio of 0.86 (95% CI:0.77–0.95, \( p = 0.003 \)) translating to a 14% reduction in the risk of death and a 5% absolute survival benefit at five years, utilization of neoadjuvant chemotherapy remains dismal [4]. Given the modest improvement in survival outcome, concerns persist regarding treatment-related toxicity as well as delays in definitive therapy [5]. The ability to predict response to neoadjuvant chemotherapy would allay these concerns and provide an opportunity to truly weigh the risks and benefits of cisplatin in many patients who fall into a “gray zone” for treatment. This “gray zone” is not an uncommon scenario for patients with UC who are most often older with co-existing medical problems [6].

The ability to repair cisplatin-induced double-strand DNA breaks leads to the cisplatin resistance phenotype and has led to the investigation of the status of several DNA repair enzymes in a variety of malignancies treated with platinum-based chemotherapy (Table 24.1). One such study has evaluated the breast cancer susceptibility gene 1 (BRCA1) and outcome of neoadjuvant cisplatin-based chemotherapy in bladder cancer [7]. The BRCA1 gene encodes a 220-kDa nuclear protein that plays a major role in responding to DNA damage through DNA repair mechanisms including nucleotide excision repair of DNA adducts, homologous recombination repair, and non-homologous end joining of double-stranded DNA breaks [8]. Both preclinical and clinical studies have demonstrated that loss of BRCA1 function is associated with sensitivity to DNA-damaging agents [8]. More specifically, low expression levels of BRCA1 have been associated with improved outcomes to cisplatin-based chemotherapy in non-small cell lung cancer (NSCLC) and ovarian cancer [9, 10]. In a study of 57 patients with locally advanced bladder cancer treated with neoadjuvant cisplatin-based chemotherapy, BRCA1 mRNA expression was assessed in pre-treatment tumor samples obtained by transurethral resection [7]. The BRCA1 expression levels were correlated with pathological response and survival. BRCA1 levels were divided into tertiles and low/intermediate versus high was associated with an improvement in pathological response (pT0–pT1) rate (66% versus 22%, \( p = 0.01 \)). Median survival was also significantly improved in the low/intermediate versus high BRCA1 level group (168 months versus 34 months, \( p = 0.002 \)). Although BRCA1 expression level represents a potential determinant of response to neoadjuvant cisplatin-based chemotherapy, additional studies including prospective validation are most certainly needed.

The excision repair cross-complementation 1 (ERCC1) enzyme plays a major role in nucleotide excision repair and ERCC1 mRNA expression has been associated with resistance to platinum-based chemotherapy in both preclinical and clinical studies in many malignancies including bladder cancer [11–13]. In a study of 57 advanced and metastatic bladder cancer patients treated with either gemcitabine/cisplatin (GC) or gemcitabine/ cisplatin/paclitaxel, mRNA expression levels of ERCC1 determined by real-time reverse transcriptase PCR (RT-PCR) in tumor DNA were correlated with outcome [13]. Low ERCC1 levels were associated with a significant improvement in median survival (25.4 months versus 15.4 months, \( p = 0.03 \)) and on multivariate analysis, ERCC1 was an independent predictive factor for survival. Additional markers analyzed including BRCA1, ribonucleotide reductase subunit M1 (RRM1), and caveolin-1 were not associated with chemotherapy response. In a
study of ERCC1 expression by immunohistochemistry in 38 patients with muscle-invasive bladder cancer who received neoadjuvant platinum-based chemotherapy, pathologic complete response rates were similar between patients with low and high ERCC1 expression, however, low as compared to high ERCC1 expression was associated with an improvement in median disease-free and median overall survival (OS) (20.5 months versus 9.3 months, \( p = 0.186 \), and 26.7 months versus 9.3 months, \( p = 0.058 \), respectively) [14]. In a meta-analysis of ERCC1 expression levels as measured by immunohistochemistry or RT-PCR in 356 patients with advanced bladder cancer treated with platinum-based chemotherapy from six studies, the median OS and median time to progression-free survival (PFS) were significantly prolonged in ERCC1 low/negative expression as compared to ERCC1 high/positive expression (HR = 0.69, 95% CI: 0.54–0.84, \( p = 0.004 \), and HR = 0.76, 95% CI: 0.66–0.89, \( p = 0.000 \), respectively) [15]. The methodology used to determine ERCC1 expression is important to consider based on recently reported data demonstrating that the predicted effect of immunostaining for ERCC1 protein is problematic based on the inability of currently available ERCC1 antibodies to detect the unique functional ERCC1 isoform capable of nucleotide excision repair and cisplatin resistance [16]. Although ERCC1 may represent a potential marker of sensitivity to platinum-based chemotherapy in patients with bladder cancer, larger confirmatory studies are needed.

Drug efflux proteins, including multidrug resistance gene 1 (MDR1), represent another class of potential biomarkers to predict response to chemotherapy in patients with bladder cancer. Multidrug resistance gene 1 encodes a membrane-associated and ATP-dependent drug efflux pump that has been shown to reduce intracellular concentrations of many cytotoxic agents. In a study evaluating formalin-fixed paraffin-embedded tumor samples from 108 patients with locally advanced bladder cancer treated on a phase III trial randomizing patients to adjuvant chemotherapy with cisplatin and methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin (MVEC), MDR1 expression was assessed using quantitative RT-PCR and correlated with clinical outcome [17]. Low as compared to high MDR1

### Table 24.1 Select studies of potential biomarkers for prediction of response to cisplatin-based chemotherapy in UC.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Detection level</th>
<th>Detection method</th>
<th>Sample population</th>
<th>Endpoint evaluated</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>mRNA</td>
<td>RT-PCR</td>
<td>Locally advanced/neoadjuvant chemotherapy (( n = 57 ))</td>
<td>PR (pT0–pT1)</td>
<td>Low/intermediate vs. high – 66% vs. 22% (( p = 0.01 ))</td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS</td>
<td>Low/intermediate vs. high – 168 mo vs. 34 mo (( p = 0.002 ))</td>
<td></td>
</tr>
<tr>
<td>ERCC1</td>
<td>mRNA</td>
<td>RT-PCR</td>
<td>Advanced/ Metastatic (( n = 57 ))</td>
<td>OS</td>
<td>Low vs. high – 25.4 mo vs. 15.4 mo (( p = 0.03 ))</td>
<td>[13]</td>
</tr>
<tr>
<td>ERCC1</td>
<td>Protein</td>
<td>IHC</td>
<td>MIBC/ neoadjuvant chemotherapy (( n = 38 ))</td>
<td>DFS</td>
<td>Low vs. high – 20.5 mo vs. 9.3 mo (( p = 0.186 ))</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>Protein and mRNA</td>
<td>RT-PCR and IHC</td>
<td>Meta-analysis in advanced bladder cancer (( n = 356 ))</td>
<td>OS</td>
<td>Low/negative vs. high/positive – HR = 0.69, 95% CI: 0.54–0.84 (( p = 0.004 ))</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td>mRNA</td>
<td>RT-PCR</td>
<td>Locally advanced/ Adjuvant chemotherapy (( n = 108 ))</td>
<td>OS</td>
<td>Low vs. high – HR = 0.28, 95% CI: 0.13–0.62 (( p = 0.002 ))</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFS</td>
<td>Low vs. high – HR = 0.25, 95% CI: 0.11–0.55 (( p = 0.0006 ))</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PR, pathological response; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival, IHC, immunohistochemistry; RT-PCR, real-time quantitative polymerase chain reaction.
expression was associated with improved PFS and overall OS (HR = 0.28, 95% CI: 0.13–0.62, p = 0.002, and HR = 0.25, 95% CI: 0.11–0.55, p = 0.0006) with a two-year progression rate of 25% versus 65% and a five-year survival rate of 62% versus 23%. Prospective studies are needed to further define the role for MDR1 in predicting response to chemotherapy in UC.

Alterations of the tumor suppressor gene, p53, are one of the most common genetic events in invasive bladder cancer and have been associated with a poor prognosis and potential chemosensitivity [18–22]. More recent data suggest that p53 alone is not an ideal prognostic biomarker and incorporation of p53 into a panel of biomarkers may provide more accurate prognostic information [23, 24]. The role of p53 inactivation in predicting a benefit from DNA-damaging agents has been more controversial. In a retrospective analysis of patients with bladder cancer treated on an adjuvant cisplatin-based chemotherapy trial, the benefit of therapy was confined to patients with p53 inactivation [25]. A study was subsequently designed to test the hypothesis that p53 inactivation was associated with a clinical benefit from DNA-damaging agents [26]. This phase III trial of adjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) was performed in patients with p53-altered T1/T2-N0 UC of the bladder. Patients with tumors demonstrating ≥ 10% nuclear reactivity on immunohistochemistry for p53 were offered random assignment to adjuvant MVAC for three cycles or observation, and p53-negative patients were observed. Although 499 of 521 registered patients underwent p53 assessment, with 272 (55%) positive cases, only 114 (42%) were randomly assigned. The trial was halted based on a futility analysis with an overall five-year probability of recurring of 0.20 (95% CI: 0.16–0.24) with no difference based on p53 status in the randomly assigned patients (HR = 0.78, 95% CI: 0.29–2.08, p = 0.62). Of those patients randomly assigned to MVAC, only 67% received three cycles and 12 received no treatment. Unfortunately, neither the prognostic nor the predictive value of p53 could be confirmed, related to the lower than predicted event rate, the failure to receive the assigned therapy, and the high patient refusal rate.

Additional confirmatory studies to evaluate the DNA-repair enzymes including ERCC1 and BRCA1 as well as the drug efflux protein, MDR1, are needed before any definitive conclusions can be drawn regarding their role in predicting chemosensitivity. With respect to p53 and other individual genetic markers, the ability to rapidly and more extensively probe the genome of individual tumors using next generation sequencing and other novel technologies will undoubtedly lead to more robust genetic signatures and predictive models for chemosensitivity in patients with bladder cancer.

**Germline pharmacogenomics**

Pharmacogenomics is the study of genetic factors determining drug response or toxicity. While the field now encompasses information from the host and tumor genomes including germline single nucleotide polymorphisms (SNPs), gene copy number alterations, and acquired (tumor) mutations [27, 28], this section will focus on germline pharmacogenomic markers, in particular SNPs.

The concept of applying germline pharmacogenomic biomarkers to the treatment of UC follows that of other cancers wherein drug response or toxicity has been shown to be predictable, in part, through knowledge of inherited variation [29].

Drug–toxicity relationships exemplify the original, classic examples of pharmacogenomic associations, perhaps for the obvious reason that systemic drug disposition is often tightly correlated with toxicity risk. The well-described pharmacogenomic relationship between irinotecan and UGT1A1 for risk stratification of neutropenia predisposition among patients receiving this drug for colon cancer represents one such example [30]. More recently, however, accumulating data also suggest that germline polymorphisms likely affect disease response outcomes as well [31–34].

Taken in combination, the laudable ideal for germline pharmacogenomics is that one could identify the patients most (or least) likely to benefit from chemotherapy while simultaneously considering risk of toxicity. Patients with the greatest prediction for benefit and persons with low risk of toxicity could be treated using the standard regimen. Those with a low likelihood of benefit and at high risk of toxicity from a particular agent might reasonably be considered for an alternative therapy.

Since platinum-based chemotherapy represents the only available standard for locally advanced and metastatic UC, the discussion of pharmacogenomic associations for
cisplatin and carboplatin is most relevant and will be the focus of the majority of this section.

The pharmacogenomics of platinum agents has been an area of particularly active interest since discovery of the role of ERCC1, a gene involved in the nucleotide excision DNA-repair pathway [35]. As previously discussed, ERCC1 has been correlated with both susceptibility to cisplatin toxicity and overall anti-tumor response to cisplatin in various cancers [36], however, its role as a germline pharmacogenomic marker has been limited, in part because germline SNPs in ERCC1 and other related DNA excision-repair genes have failed to consistently replicate across studies [37].

ERCC1 represents a candidate gene – a gene known to be involved in the platinum pharmacodynamic pathway. Most pharmacogenetic analyses have taken a candidate gene approach that utilizes biological data to guide the selection of drug response genes in a pathway. In the case of drug response phenotypes, such candidate gene studies have mostly focused on drug metabolizing enzymes, drug transporters, and genes believed to be involved in the mechanistic pathway of the drug being studied. This approach is limited by our knowledge of the drug phenotype, and thus inherently limits the chance of discovering causal SNPs not involved in mediating drug levels or in a known purported mechanistic pathway [38, 39]. Additionally, it is unlikely that single genes, even candidate genes, entirely explain an individual’s drug susceptibility risk, meaning that chemotherapeutic sensitivity is likely a multi-genic trait.

Genome-wide approaches permit this possibility and approach identification of pharmacogenomic markers in an unbiased fashion. In contrast to candidate gene studies, genome-wide association studies (GWAS) and gene-sequencing efforts collect polymorphism data across the entire human genome and have significant power to detect variants that confer a modest risk for a complex phenotype [40]. Genome-wide association studies capitalize on the large number of (typically common) SNPs that have been localized and validated across the genome. Whole-genome sequencing takes genome-wide approaches even further and has the ability to interrogate the entire genome, rather than only common, pre-selected SNPs. Technological advances have made genome-wide association studies relatively common and technically easy to perform. Advances in whole-genome sequencing proficiency are similarly making this technology readily available and affordable.

Regarding platinum drugs, two well-performed recent studies have used GWAS approaches to identify novel, interesting variants which may govern response to platinum-based chemotherapy. While the findings from both studies require further examination in broader populations (and notably, neither study included patients with UC), these studies importantly included independent replication populations in which testing confirmed a SNP association found in an original discovery set. These studies therefore illustrate the point that replication (and, if possible, functional validation) are critical steps for evaluation of pharmacogenomic biomarkers.

The first study [32] identified a novel platinum SNP by first using a previously refined genome-wide discovery approach in well-genotyped lymphoblastoid cell lines [41, 42]. The SNP (rs1649942, in the gene NRG3) was replicated for association in an independent set of cell lines, and then also replicated clinically by its independent, highly statistically significant association with both PFS and OS (p per allele = 0.009) in a large study of ovarian cancer patients receiving carboplatin-based chemotherapy [32]. However, this SNP was not significant in a second, more heterogeneous clinical validation analysis of > 1000 patients from numerous ovarian cancer cohorts. Ongoing work is examining whether this SNP has applicability for only carboplatin and whether it might replicate in other populations.

The second study utilized a genome-wide analysis to identify germline SNPs as prognostic factors in small-cell lung cancer patients treated with platinum (either cisplatin or carboplatin) and etoposide [33]. Of 26 SNPs nominally associated in a discovery set of 245 patients, 2 SNPs (rs10895256 and rs716274) were confirmed to be significantly associated with OS in a replication cohort of 305 patients after adjusting for covariates (both p < 0.002 after correction for multiple testing). rs1820453 (a SNP in complete linkage disequilibrium with rs10895256) is of particular interest. Located in the promoter region of the YAP1 gene on chromosome 11, a gene encoding a transcriptional activator implicated in P73-dependent apoptosis, the authors found that the T/G polymorphism at rs1820453 forms a transcriptional factor binding site in the promoter of YAP1, resulting in considerably decreased expression of YAP1 in target lung tissues. The functional significance of the rs1820453 SNP conferring poorer survival could thus be explained by downregulation of YAP1 in patients with the G allele, resulting in suppressed function of P73-dependent
apoptosis, and thereby potentially causing poorer responsiveness to chemotherapy-induced apoptotic cell death [33]. While this study included only patients of Han Chinese ethnicity, the identified SNP is also prevalent in other ethnic populations, increasing the potential generalizability of the findings. These results also await additional confirmatory studies, and testing in UC (a disease which also has particular sensitivity to platinum-based therapies) would be desirable.

Germline polymorphisms associating with response or toxicity to other agents with known activity in UC are currently being studied as well, including SNPs associated with gemcitabine [43], methotrexate [31], and doxorubicin and vinblastine [44], although replication and validation of these markers still remains necessary. Continued development of germline preclinical models to identify novel polymorphisms of interest for the drugs used against UC also remains of interest [45, 46].

In summary, it is likely that there will soon be a number of replicated germline pharmacogenomic biomarkers relevant to being prospectively or functionally tested and applied within UC. Validated markers could then be considered for clinical implementation to further the mission of personalized oncologic care within UC.

Gene expression models in urothelial cancer

Over the past 15 years, the evaluation of genome-wide gene expression has provided a high-throughput “snapshot” of genomic programs operating in a cell or tissue type of interest. More recently, next generation sequencing has begun to identify the mutations in UC [47]. The role of these as tools for developing predictive markers for UC prognosis is very promising. In addition, data from tumor characterization using these tools have also revealed the limitations of traditional, histologically-based evaluations of cancer for the purposes of determining optimal systemic therapy. Looking ahead, it is likely that the selection of the most appropriate systemic anti-cancer medical therapy for an individual patient may become more dependent on the identification of the activation/deactivation of specific molecular pathways as opposed to simply knowing the origin of the neoplastic tissue.

Along these lines, the use of gene expression models (GEM) has been integrated into the care of multiple tumor types and has the ability to identify “driver” molecular pathways, which may inform the prognosis or even predict the efficacy of a specific treatment for an individual tumor [48, 49]. In bladder cancer, there are no GEMs currently utilized in standard clinical practice, but work in this area has been reported. Gene expression analysis has also been used to predict the response to chemotherapy in order to distinguish patients who are going to benefit from this additional therapy. One early study has shown that gene expression can be used to build predictive models of the response to a single drug, as well as to combination regimens [50]. In this study, baseline gene expression profiles from a panel of 40 bladder cancer cell lines were used to develop chemotherapy response prediction models, which showed highly significant concordance with empirically assessed responses. In another study by Takata and colleagues, gene expression was measured in 27 invasive bladder cancer biopsies prior to treatment with neoadjuvant MVAC chemotherapy [51]. The authors identified a set of 50 genes that significantly differed between fourteen responders and thirteen non-responders. The same investigators have subsequently validated their predictive signature on 22 additional patients [52], showing that their gene expression signature could correctly predict MVAC response in 19 out of 22 cases, with approximately 100% sensitivity and 73% specificity. Als and colleagues analyzed gene expression in 30 patients with locally advanced or metastatic bladder cancer [53], identifying 55 genes that proved to be expressed at lower levels in patients with longer survival. In this study, the authors failed to observe any difference in terms of gene expression between patients treated with different chemotherapy regimens. Two of the genes that discriminate patients by their survival – emmprin and survivin – were further investigated by immunostaining, showing that they were significantly associated with overall survival \( p \leq 0.001 \). The investigators also documented different response rates to chemotherapy based on survivin and emmprin staining, with double-positive tumors exhibiting a response rate of 27%, and double-negative tumors exhibiting a response rate of 82%, with an odds ratio in double-negative tumors of 11.9 (95% CI: 3.2–42.3) [53].

The use of molecular profiles to predict treatment outcomes requires a training dataset to identify the profile and a second, independent clinical trial to validate it. This strategy is promising but is time-consuming
and expensive and is not amenable to the rapid development of biomarkers to regimens that include new drugs before clinical studies are carried out. A new strategy was recently proposed that extrapolates in vitro drug response data to make in vivo predictions based on the gene-expression profiles that are common to both. This approach, called COXEN (COEexpression Extrapolation), uses expression microarray data as a “Rosetta Stone” for translating between drug activities in a cancer cell line panel to drug activities in a set of clinical tumors. This approach represents a “correlation of correlations”, bridging in vitro cell sensitivity data with the relevant gene expression of a particular patient population [54]. The COXEN algorithm proceeds through six discrete steps [55] (Table 24.2). In developing GEMs for the most commonly used chemotherapy regimens in bladder cancer, the first two COXEN steps were accomplished using the NCI-60 cell panel. These 60 cell lines represent a variety of tumor types and have been molecularly profiled and treated with tens of thousands of compounds, thus serving as a rich resource for in vitro drug response data [56]. Once a “gene signature” for in vitro chemotherapy response is identified in the NCI-60, these genes are then compared to a second gene set which is relevant to the final target population (e.g. advanced bladder cancer patients), thus identifying a new set of concordant genes to be included in the final GEM. In this way, the COXEN algorithm translates the in silico NCI-60 cell line drug sensitivity data into a relevant GEM by correlating it with an appropriate human gene-expression dataset, in a way humanizing the initial cell-based gene set. COXEN may be differentiated from other, more commonly utilized a posteriori approaches for the development of predictive GEMs in that COXEN provides an a priori GEM, which has the advantage of accelerating the application of such GEMs clinically. COXEN does not rely on or require existing, treated clinical samples to derive its GEM (traditional training set), but is able to derive a GEM from the NCI-60 data and gene expression in relevant (untreated) human tissues (Figure 24.1). In addition to the identification of predictive GEMs, COXEN is able to identify novel mechanisms of drug activity via the gene identified through the process [57].

While the COXEN method has been tested across many tissue types including breast and ovarian cancer, specific evaluation of COXEN has been pursued in bladder cancer [58]. In a previously reported study by Als et al., 30 patients with locally advanced or metastatic urothelial carcinoma were treated with GC or MVAC, the two most common combination chemotherapy regimens in current use [53]. The gene expression of the respective tumors was determined in addition to the patient's clinical outcomes to chemotherapy treatment, allowing for the application of the COXEN combination GEMs for GC and MVAC in this dataset. In the MVAC-treated patients, the COXEN GEM scores between responders and non-responders were statistically significantly different ($p = 0.033$), demonstrating evidence of COXEN’s segregation of those benefiting from chemotherapy. Notably, in the COXEN-assigned “responders” group, the three-year survival was 61% in contrast to just 16% in the COXEN non-responders ($p = 0.015$) (Figure 24.2a).

In a second COXEN GEM bladder cancer evaluation, the use of neoadjuvant chemotherapy was studied. This study used the aforementioned Takata et al. dataset from profiled tumors of patients treated pre-operatively with two cycles of MVAC chemotherapy [51]. Pertinent to COXEN’s predictive, as opposed to simply prognostic, value, patients in this series were defined as responders based on tumor response to chemotherapy, via downstaging at the time of surgery – a direct chemotherapy effect. Using the COXEN combination GEM for MVAC, there was a significant difference in the COXEN scores between those with tumor downstaging and those

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**Table 24.2** The COXEN algorithm may be divided into six distinct steps.

| Step 1: Experimentally determine the drug’s pattern of activity in the cells of set 1. |
| Step 2: Experimentally measure molecular characteristics of the cells in set 1. |
| Step 3: Select a subset of those molecular characteristics that most accurately predicts the drug’s activity in cell set 1 (“chemosensitivity signature” selection). |
| Step 4: Experimentally measure the same molecular characteristics of the cells in set 2. |
| Step 5: Among the molecular characteristics selected in step 3, identify a subset that shows a strong pattern of coexpression extrapolation between cell sets 1 and 2. |
| Step 6: Use a multivariate algorithm to predict the drug’s activity in set 2 cells on the basis of the drug’s activity pattern in set 1 and the molecular characteristics of set 2 selected in step 5. |
| The output of the multivariate analysis is a COXEN score. |

Source: Havaleshko et al. [50]. Reproduced with permission from the American Association for Cancer Research.
Assessing survival rates at three years, 81% of the COXEN-selected responders were alive compared to 33% in the COXEN-selected non-responders ($p = 0.002$) (Figure 24.2b) and notably, the COXEN-assigned predictions of response were independent of tumor stage, grade, and gender.

In this study, the 15-gene predictive GEM derived by Takata et al. using the traditional a posteriori method with a training and validation group for MVAC was also applied to the abovementioned Als dataset, to assess the robustness of this GEM across independently treated patient cohorts. In this application, the Takata GEM did not separate out patients based on survival outcomes ($p = 0.73$), although COXEN had successfully accomplished this segregation of subjects, as noted earlier.

Combining the performance of the COXEN combination GEM for MVAC across both the Als and Takata studies for “responders”, a sensitivity of 83% and a specificity of 64% was established, with a positive predictive value of 71% and a negative predictive value of 78% [58].

Predictive GEMs could be used in a variety of clinical settings with very relevant applications in bladder cancer. For example, despite positive phase III clinical trial results and integration into clinical treatment guidelines, neoadjuvant chemotherapy is remarkably underutilized in the United States [4]. While there are several potential reasons for the low level of pre-operative chemotherapy use, a key consideration is the risk for progression of without tumor response [58].
disease during the administration of chemotherapy in a resistant patient. For this reason, some opt to proceed with cystectomy first and then give consideration to adjuvant chemotherapy after surgical staging, despite limited and some contradictory data to support this post-operative chemotherapy approach.

One application of a predictive GEM with clinical relevance in bladder cancer is the assignment of patients’ pre-operative chemotherapy based on the gene expression of the diagnostic tumor biopsy. Since there are several acceptable chemotherapy options available (GC and MVAC), patients could be assigned to the regimen to which they would be most likely responsive. Additionally, if a low level of response was predicted to all available chemotherapy regimens, these select patients could proceed directly to surgery and not delay this potentially curative procedure for three months for likely ineffective pre-operative chemotherapy. SWOG 1314, A Randomized Phase II Study of CO-eXpression ExtrapolationN (COXEN) with Neoadjuvant Chemotherapy for Localized, Muscle-Invasive Bladder Cancer is ongoing via the National Cancer Institute cooperative group mechanism. While this study will specifically test the COXEN combination GEMs for GC and MVAC, it will additionally provide prospectively-gathered clinical outcomes with standardized gene expression data for the entire cohort, which will be useful in any future validation of new GEMs in this clinical setting.

A further refinement of molecularly-driven patient treatment selection approach would be the utilization of an upfront, prognostic GEM to select the intensity of therapy based on the predicted risk (chemotherapy plus surgery versus surgery alone). For example, a 20-gene GEM has been established which predicts for the presence of lymph node metastases from bladder cancer at the time of cystectomy, based on the diagnostic biopsy [54]. Using both frozen and formalin-fixed tissues and selecting genes expressed robustly in both, this GEM was developed using two separate training cohorts, before validation using data from the independent AUO-AB-05/95 phase III trial cohort. With an area under the curve (AUC) of 0.67 (95% CI: 0.60–0.75) for identification of lymph node involvement at surgery, this GEM identifies a high-risk patient group with a relative risk (RR) of lymph node involvement of 1.74 (95% CI: 1.03–2.93) at the time of surgery, compared to an RR of 0.70 (95% CI: 0.51–0.96) in the COXEN-designated low-risk group.

In summary, the use of GEMs in bladder cancer is an area of ongoing investigation and activity. There are specific disease-oriented opportunities for the use of GEMs in bladder cancer, based on the current standard of care using neoadjuvant chemotherapy before definitive local therapy. In an ideal setting, patients with localized, muscle-invasive bladder cancer would first undergo a risk-assessment GEM, such as the 20-gene GEM highlighted here. Those with low-risk disease (at some established level) could be considered for surgery alone and be spared the toxicity of pre-operative chemotherapy. In those deemed at high risk, a second assessment using predictive GEMs would be used for the selection of the most effective chemotherapy regimen, while also directing those patients with a low likelihood of response to any available chemotherapy directly to surgery.

**Conclusion**

Unlike any other time, the current tools for scientific discovery offer a unique opportunity to make tremendous strides in medical research. Novel approaches including the utilization of pharmacogenomics to predict drug sensitivity, resistance, and toxicity, and predictive gene-expression models to select the most effective chemotherapy will most certainly lead to major advances in the management of patients with bladder cancer.

**References**

A Excision repair cross

B Playground for urology scientists?


H In a cell-based approach and analysis of its association with treatment response in childhood acute lymphoblastic leukemia. JAMA 2009; 301(4): 393–403. Epub 2009/01/30.


Molecular determinants of chemotherapy response


CHAPTER 25

Neoadjuvant chemotherapy in the treatment of muscle-invasive bladder cancer

David I. Quinn¹ and Cora N. Sternberg²

¹ University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA
² Department of Oncology, San Camillo Forlanini Hospital, Rome, Italy

KEY POINTS

• Neoadjuvant cisplatin-based chemotherapy given before cystectomy or radiation therapy improves survival in muscle-invasive bladder cancer.

• Many patients with bladder cancer have significant comorbid medical conditions that make administration of chemotherapy and perioperative management a challenge.

• Muscle-invasive bladder cancer is best managed by a multidisciplinary clinical team in a center with significant experience treating the disease.

Introduction

Bladder cancer is the second most common cancer of the genitourinary tract, with some 386,000 new cases worldwide [1, 2], in which approximately 1 in 3 cases are locally invasive or metastatic at presentation. In high-grade cancer there is a very high rate of early systemic dissemination. In patients with locally advanced bladder cancer, defined as extending into muscle, survival is predicated upon pathologic stage and lymph nodal involvement. As the stage increases, especially when there is cancer that extends outside of the bladder wall and/or lymph nodal metastases, the prognosis worsens [3]. Local or metastatic failure is presumably due to occult metastatic disease that was present at the time of initial diagnosis.

Cystectomy and chemoradiation series

Radical cystectomy (RC) is considered to be the “gold standard” of treatment for patients with clinically localized muscle-invasive bladder cancer, although outcomes with bladder preservation using chemoradiation protocols in expert centers are similar [3, 4]. However, despite potentially curative surgery or chemoradiation, approximately one-half of patients with deep, muscle-invasive urothelial carcinoma (UC) (stages T2b–4) develop metastatic disease within two years [5]. At five years, the survival rate after cystectomy is, at best, 65%, ranging from 36% to 48% in large series from the University of Padua, Memorial Sloan-Kettering Cancer Center and the University of Southern California [3, 6–9] depending on the presence of extravesical extension (pT3) and lymph node metastases (N1–N3) (Table 25.1). Both factors are associated with an increased risk for recurrence following cystectomy. In contemporary series, five-year overall survival rates up to 57% have been reported in patients with clinically unsuspected N1 disease, as compared to 0–27% for those with larger volume N2 to N3 disease [3, 10, 11].

In good-performance bladder cancer patients treated with cisplatin-based chemotherapy and definitive radiation in trials from the Radiation Therapy Oncology Group (RTOG), the University of Erlangen, the University
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of Paris, and Massachusetts General Hospital (Table 25.2), the five-year survival ranges from 42–62%, with rates of survival with an intact bladder of 36–46% [4, 12–19].

**Rationale for chemotherapy prior to definitive surgery or chemoradiation therapy**

Neoadjuvant or adjuvant chemotherapy has the potential to eradicate micro metastases and improve survival in patients with muscle-invasive UC. This appears to be particularly important for patients with pathological extravesical and lymph node-positive disease [20].

Administering chemotherapy prior to surgery versus afterwards in the adjuvant setting offers several potential advantages. Patients may be able to tolerate treatment better and the response of the primary tumor to chemotherapy can be assessed [21–25], providing prognostic significance. In an early study of patients treated with neoadjuvant cisplatin-based therapy followed by definitive surgery, 91% of patients who responded to chemotherapy (defined as pathologic stage ≤ T1) were alive at a median follow-up of 25 months, in contrast to 37% of non-responders [24].

Downstaging of the tumor may provide an indication of the activity of neoadjuvant chemotherapy, especially in patients who have a pathologic complete response and in patients who are pT1 stage after therapy. Those patients with residual disease at radical cystectomy (RC) should probably be offered clinical trials evaluating non-cross-resistant alternative agents. A complete response after neoadjuvant therapy at the TURBT may also permit consideration of organ preservation in selected cases where the patient has a major perioperative mortality risk, where there is an isolated lesion in the dome of the bladder, or where the patient absolutely refuses cystectomy. The standard of care, however, is that the majority of patients require and undergo radical cystectomy or radical radiotherapy because of a high risk of residual disease even in those patients with seemingly no evidence of cancer on cystoscopy and biopsy [26]. This is due to the discordance between clinical (TURBT) and pathologic staging (cystectomy).

An important potential disadvantage of neoadjuvant chemotherapy has been highlighted in an early study reported by Scher et al. [21]. Although 57% of patients achieved a clinical and cystoscopic complete response following neoadjuvant MVAC chemotherapy, only 30% had a pathologic complete response at cystectomy. Subsequently, in SWOG S0219, where patients received neoadjuvant carboplatin, gemcitabine, and paclitaxel, more than half the patients assessed to disease-free by cystoscopic evaluation and biopsy had occult cancer deep in muscle in the cystectomy specimen [26].

Another theoretical disadvantage of the neoadjuvant approach is the possibility that some low-stage, low-risk patients may unnecessarily receive neoadjuvant chemotherapy. Conversely, delays in definitive local treatment could potentially be associated with disease progression [27].

The primary disadvantage of the adjuvant (post-operative) chemotherapy paradigm may be that it does not appear feasible in a third of patients within 90 days of cystectomy due to post-operative complications or slow recovery of functional status [28, 29]. In addition, approximately 40% of patients who would be candidates for neoadjuvant chemotherapy may not be candidates for post-operative cisplatin because of a perioperative decline in renal function [30].

Besides all these pros and cons, both approaches are targeting microscopic disease and the question is to know what the best option is for an individual patient. No published trials have directly compared pure populations of neoadjuvant versus adjuvant chemotherapy. Data from the MD Anderson Cancer Center suggest that outcomes for patients getting pre- or post-operative MVAC chemotherapy may be similar [31]. In the absence of a specific randomized trial that has compared optimal neoadjuvant

<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>N</th>
<th>Five-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padua [6, 7]</td>
<td>1999</td>
<td>258</td>
<td>44%</td>
</tr>
<tr>
<td>University of Southern California [3]</td>
<td>2001</td>
<td>633</td>
<td>48%</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Cancer Center [8]</td>
<td>2001</td>
<td>184</td>
<td>36%</td>
</tr>
<tr>
<td>SWOG 8901/Intergroup 0800 [36]</td>
<td>2003</td>
<td>317</td>
<td>49%</td>
</tr>
</tbody>
</table>

**Table 25.1** Series of cystectomy for muscle-invasive bladder cancer.
and adjuvant chemotherapy regimens in association with cystectomy, it is not possible to make a definitive recommendation about the utility of adjuvant chemotherapy as compared to neoadjuvant treatment. This will be discussed further in Chapter 26 on adjuvant chemotherapy.

### Randomized trials of neoadjuvant chemotherapy: data support a survival benefit

Neoadjuvant chemotherapy theoretically should provide a benefit to patients, whether it is given before cystectomy or before RT. In the United States, radical cystectomy is preferred for patients who have a good performance status. In most of Europe, radical cystectomy is also the preferred option, although some institutions consider local radical radiotherapy as an alternative. The recently published regimen using mitomycin-C and 5FU with concurrent radiation therapy produced excellent results in terms of local disease control and a five-year survival rate of 48% in the British BC2001 trial [19]. This regimen can be used in patients with renal impairment, significant comorbidities, and/or neuropathy with acceptable acute and minimal long-term toxicity.

Several randomized trials have explored whether neoadjuvant chemotherapy improves survival in bladder cancer. The results of these randomized trials are presented in Table 25.2 [18, 32, 33]. Some studies suffered from small sample size, suboptimal chemotherapy, premature closure, or inadequate follow-up time [34]. Among these trials, single-agent regimens failed to show a survival benefit from neoadjuvant therapy [35]. However, well-designed multi-agent chemotherapy trials utilizing effective cisplatin-based combination chemotherapeutic regimens have helped to demonstrate an improvement in survival. These trials have shifted the treatment paradigm in muscle-invasive disease, favoring more the use of neoadjuvant chemotherapy [18, 36].

The SWOG 8710-Intergroup Trial 0080 randomized patients with T2–T4a TCC of the bladder to radical cystectomy alone (154 patients) versus three cycles of MVAC followed by radical cystectomy (153 patients) over an 11-year period [36]. The use of neoadjuvant chemotherapy was associated with a higher rate of complete pathologic response (38% versus 15%, \( p < 0.001 \)). At a median follow-up of 8.7 years, improvements in median survival (77 versus 46 months, \( p = 0.06 \)) and five-year survival (57% versus 43%, \( p = 0.06 \)) favored the neoadjuvant MVAC arm. Because of its size, this trial had limited potential to discern a clinically meaningful difference. This trend toward improved survival favoring MVAC-treated patients, with an estimated reduction in the risk of death by 25% (hazard ratio [HR]: 1.33) provides evidence of benefit [36]. There were no treatment-related deaths and neoadjuvant chemotherapy did not adversely impact the ability to

### Table 25.2 Trials of combined chemotherapy and radiotherapy.

<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>N</th>
<th>Chemotherapy</th>
<th>Five-year survival with intact bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation Therapy Oncology Group – study 85-12 [12]</td>
<td>1993</td>
<td>42</td>
<td>DDP</td>
<td>52%</td>
</tr>
<tr>
<td>Radiation Therapy Oncology Group – study 89-03 [14]</td>
<td>1998</td>
<td>123</td>
<td>CMV +RT and DDP</td>
<td>48%</td>
</tr>
<tr>
<td>University of Erlangen [16, 17]</td>
<td>2002</td>
<td>289</td>
<td>DDP, or Carboplatin</td>
<td>51%</td>
</tr>
<tr>
<td>University of Paris [85]</td>
<td>2001</td>
<td>120</td>
<td>DDP/5FU</td>
<td>63%</td>
</tr>
<tr>
<td>Massachusetts General [15, 86]</td>
<td>2002</td>
<td>190</td>
<td>CMV or DDP/5FU</td>
<td>54%</td>
</tr>
<tr>
<td>BC2001 UK [19]</td>
<td>2012</td>
<td>360</td>
<td>MMC/5FU</td>
<td>48%</td>
</tr>
</tbody>
</table>

*Four-year survival data
proceed with radical cystectomy or increase adverse events related to surgery.

Several studies have been published based on retrospective analysis of this trial database. In one such analysis, surgical factors were evaluated in 268 patients with muscle-invasive bladder cancer who underwent radical cystectomy in this intergroup trial [37]. The surgeries were performed by 106 surgeons at 109 different institutions. Half of the patients received neoadjuvant MVAC. The five-year post-cystectomy survival and local recurrence rates in all patients who underwent cystectomy were 54% and 15%, respectively. Surgical variables associated with longer post-cystectomy survival were negative margins (HR: 0.37; \( p = 0.0007 \)) and removal of \( \geq 10 \) nodes (HR: 0.51; \( p = 0.0001 \)). These associations did not differ by treatment arm. Predictors of local recurrence were positive margins (odds ratio [OR]: 11.2; \( p = 0.0001 \)) and removal of < 10 nodes (OR: 5.1; \( p = 0.002 \)). The quality of surgery was an independent prognostic factor for outcome after adjustments were made for pathologic factors and neoadjuvant chemotherapy usage.

Another analysis evaluated the impact of histology when neoadjuvant MVAC was given in this trial. Surprisingly, there was evidence of a survival benefit from chemotherapy in patients with mixed tumors [38]. The presence of squamous or glandular differentiation in locally advanced urothelial carcinoma (UC) of the bladder does not seem to confer resistance to MVAC and, in fact, may be an indication for the use of neoadjuvant chemotherapy before radical cystectomy.

The MRC/EORTC performed a large trial in which 976 patients were enrolled and randomized to neoadjuvant CMV (491 patients) or no neoadjuvant chemotherapy (485 patients) over a 5.5-year period in 106 institutions. This trial was performed contemporaneously to the SWOG 8710 trial. The results of this trial were updated at a median follow-up of approximately seven years [32]. Management of the primary tumor involved cystectomy, radiation therapy, or both and was left to the choice of investigators. An initial 8% improvement in time to progression and a 5.5% difference in absolute three-year survival (HR = 0.85; 95% CI: 0.71–1.02) favoring the neoadjuvant chemotherapy arm was reported. When results were published in 1999, a non-significant trend toward improvement in survival was observed in patients in the CMV arm. In 2011, with a median follow-up of eight years, a statistically significant improvement in survival was observed for patients who received neoadjuvant chemotherapy \( (p = 0.037; \text{HR} = 0.84; 95\% \text{CI}: 0.72–0.99) \). This trial, well powered and with adequate follow-up, demonstrated both a survival benefit and improved loco-regional control with neoadjuvant CMV chemotherapy, however, the predefined end point with an improvement in survival of 10% was, in fact, not reached. Estimated survival at ten years was 36% with CMV and 30% with RT alone [39].

A trial that was almost identical to the SWOG study was performed by the Gruppo Uro-Oncologico Nord Est (GUONE) cooperative group in Italy [40]. Over a 6.5-year period, 206 patients were randomly assigned to neoadjuvant MVAC before cystectomy or to cystectomy alone. No clear differences in survival were demonstrated, as three-year survival was 62% for the MVAC-treated patients and 68% for patients in the cystectomy alone arm.

The Nordic cystectomy I trial evaluated neoadjuvant doxorubicin, cisplatin, and pre-operative RT before cystectomy versus pre-operative RT and cystectomy alone. A 15% survival difference in favor of patients treated with chemo radiotherapy was seen in only a subset analysis of patients with T3 or T4 disease. Investigators were unable to confirm this survival advantage in the subsequent Nordic cystectomy II trial, in which 317 patients were randomly assigned cystectomy or cystectomy preceded by methotrexate and cisplatin (without RT) [41]. However, combining the two trials provided positive results in favor of neoadjuvant chemotherapy [42].

**Meta-analyses**

Because of the uncertainties of the definitive value of neoadjuvant chemotherapy in terms of survival, a meta-analysis of neoadjuvant chemotherapy trials was performed [43]. Data from 2688 patients treated in ten randomized trials evaluating neoadjuvant chemotherapy for invasive UC were reviewed. Of note, this analysis did not include data from the SWOG Intergroup trial. Compared to local treatment alone, neoadjuvant platinum-based combination chemotherapy was associated with a significant benefit in overall survival (HR = 0.87, 95% CI: 0.78–0.98, \( p = 0.016 \)), a 13% decrease in the risk of death, and a 5% absolute survival benefit at
five years (overall survival increased from 45–50%). When trials utilizing single-agent cisplatin were included, the survival benefit did not achieve statistical significance (HR = 0.91, 95% CI: 0.83–1.01, p = 0.084). However, single-agent cisplatin did not show an improvement in survival (p = 0.26) compared with no neoadjuvant therapy. As all platinum-based combination trials were analyzed as a group, it is not possible to discern the best combination for use in neoadjuvant therapy.

A subsequently reported meta-analysis that included individual patient data from 3005 individuals enrolled in 11 randomized trials, including the SWOG data extrapolated from the published report [36], confirmed the survival benefit for neoadjuvant cisplatin-based combination chemotherapy compared to local therapy alone [43, 44].

A very similar meta-analysis of neoadjuvant randomized controlled trials was conducted in Canada [44]. A total of 16 eligible trials that included 3315 patients were identified, and 2605 patients provided data suitable for a meta-analysis of overall survival. The pooled HR was 0.90 (95% CI: 0.82–0.99; p = 0.02). Eight trials used cisplatin-based combination chemotherapy, and the pooled HR was 0.87 (95% CI: 0.78–0.96; p = 0.006), consistent with an absolute overall survival benefit of 6.5% from 50% to 56.5% (95% CI: 2–11%). A major pathologic response was associated with improved overall survival in four trials. Neoadjuvant cisplatin-based chemotherapy improved overall survival in muscle-invasive urothelial carcinoma, but the size of the effect was modest.

The use of perioperative chemotherapy was limited until 2003–2005, when these meta-analyses were published. Among 7161 analyzable patients in the National Cancer Database with stage III bladder cancer diagnosed between 1998 and 2003, perioperative chemotherapy was administered to 11.6% of patients, with 10.4% receiving adjuvant chemotherapy and 1.2% receiving neoadjuvant chemotherapy [45]. After 2003, there has been a slight increase in its use. In a more recent report on 40,388 patients aged 18 to 99 years diagnosed with muscle-invasive (stages II to IV) bladder cancer in 2003 to 2007 from the National Cancer Database, the incidence of those who received chemotherapy increased from 27.0% in 2003 to 34.5% in 2007 due to an increase in neoadjuvant chemotherapy and chemotherapy without surgery [46]. Clinical Practice Guidelines (CPG) may help to increase the implementation of neoadjuvant chemotherapy. A Canadian study [46] has shown that neoadjuvant referral and treatment rates increased after publication of the CPG. However, overall referral and treatment rates remained low [47].

### Barriers to implementation of neoadjuvant chemotherapy for bladder cancer

Based on these observations and despite level I evidence, neoadjuvant cisplatin-based chemotherapy continues to be underutilized, but it is increasing in the management of bladder cancer [48–50]. Many surgeons remain concerned that chemotherapy toxicity will preclude surgery because of toxicity but recent large-scale analyses do not support this [47, 51]. Institutional interdisciplinary tumor boards provide a footing for objective assessment of patients for perioperative chemotherapy that can significantly increase the rate of neoadjuvant chemotherapy usage [52]. The major barrier to perioperative chemotherapy use in the bladder cancer population is renal impairment, with as many as 50% of patients having a glomerular filtration rate (GFR) of < 60 mL/min, making them cisplatin ineligible by many definitions [53, 54]. In addition, in many contemporary series, around one-third of patients have comorbidities apart from or as well as renal impairment that may preclude cisplatin-based treatment [52]. Given that these comorbidities are often factors that predict for poorer cancer and non-cancer outcomes from radical cystectomy, some of these patients might be better treated with non-platinum-containing regimens such as that validated in the BC2001 trial of radiation with or without 5FU and mitomycin chemotherapy, which can be given to patients with a GFR as low as 20 mL/min [19].

### Novel combinations of neoadjuvant therapy for bladder cancer

The promising results from newer combinations such as gemcitabine and cisplatin/carboplatin with or without paclitaxel in patients with metastatic disease have led to their investigation in the neoadjuvant setting. The attainment of pCR (pT0) in the cystectomy specimen is a potential surrogate of progression-free and overall survival and some feel that this makes the neoadjuvant setting in high-grade muscle-invasive bladder cancer an ideal setting to test novel regimens and new agents [36, 55–58]. Although these newer regimens are promising, there
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are no data from randomized trials supporting their use in the neoadjuvant setting [59], limited data from phase II trials, and virtually no data with targeted non-chemotherapy agents despite the stated presence of “actionable targets” in around 50% of recurrent urothelial cancers [60].

In a phase II trial, 68 patients with adequate renal function and clinical T3 or T2 with hydronephrosis, N0, M0 bladder cancer received three cycles of neoadjuvant paclitaxel, carboplatin, and gemcitabine (PCaG) with a primary endpoint of pCR. Patients with T4 or node-positive patients received six cycles of PCaG with an endpoint of resectability [61]. In 22 patients deemed resectable at study entry, 32% of those assessable were pCR at surgery. In the group with locally advanced disease, 24 of 29 (83%) patients were considered resectable after chemotherapy and 21 underwent cystectomy with 5 assessed as achieving a pCR. The major caveat from this study is that this regimen was fairly toxic in a population with moderate baseline renal dysfunction and almost universal neutropenia experienced over six cycles, warranting prophylactic granulocyte growth factors in accordance with guidelines if this regimen were to be used outside of a trial [62, 63].

The SWOG conducted a phase II trial of three cycles of neoadjuvant paclitaxel, gemcitabine, and carboplatin followed by cystoscopic surveillance or immediate RC for patients with T0 at cystoscopy and biopsy status after chemotherapy [26]. Patients with cystoscopically defined T0 status could elect to have immediate RC or to undertake cystoscopic surveillance. There was an acceptably high rate (60%) of persistent cancer in the surgical specimen at immediate RC in patients presumed to have pT0 status, which suggests that RC is a critical component of therapy.

More recently, the University of Michigan completed a clinical trial of three cycles of neoadjuvant nab-paclitaxel, carboplatin, and gemcitabine prior to cystectomy, where the percentage of patients with pathologic complete response (pT0) at cystectomy was the primary endpoint [64]. This trial built upon the prior experience with a triplet regimen (see above) and the activity of nab-paclitaxel in advanced urothelial cancer [62, 65]. Six of 29 patients (27.3%) had no residual cancer at surgery, while 54.5% had no evidence of muscle-invasive disease. Nearly all patients experienced Grade 3–4 neutropenia; 17 patients (58.6%) required growth factor, and 16 patients (55.2%) experienced Grade 3–4 thrombocytopenia, while there was 1 toxicity-related death.

While recently, some important potential benefits have been reported with the use of the triple chemotherapy regimen of cisplatin, gemcitabine, and paclitaxel in the adjuvant setting [66], the Spanish cooperative group study closed early with not enough patients to draw conclusions. Only the MVAC regimen has been extensively evaluated in the neoadjuvant setting. Recent experience with triplet regimens incorporating carboplatin have suggested efficacy but at the cost of considerable myelosuppression and other toxicity. On that basis, MVAC is the standard regimen when neoadjuvant chemotherapy is used. The question as to whether use of a dose-dense or accelerated version of MVAC with granulocyte colony-stimulating factor support [67] might improve outcome has been explored in the phase II neoadjuvant setting. A British study of accelerated MVAC for three or four cycles prior to cystectomy demonstrated feasibility and excellent safety, with 84% of doses delivered on schedule and without reduction in 60 patients, with a complete response rate of 43% [68]. Two similar studies done in North America confirmed the safety of the approach and yielded pCR rates of 26% and 39% [69, 70].

While the gemcitabine/cisplatin (Table 25.3) doublet has not been validated in the perioperative setting, recent retrospective data from the Memorial Sloan-Kettering Cancer Center (MSKCC) show that the GC regimen produces a pCR rate of 35%, similar to MVAC [71]. A pooled analysis of several studies using GC in the neoadjuvant setting reported a pCR rate of 25.6% [72]. In contrast, data from the Cleveland Clinic showed that only 7% of patients achieved a pCR with mostly GC and other non-MVAC-based regimens mainly administered in community oncology practices [59]. In a recently published retrospective series from USC, there was no significant difference between GC and MVAC for response, downstaging, predicted five-year survival, or relapse-free survival. However, patients with lymph node involvement appear to have a much better five-year RFS with MVAC compared to GC (53% versus 0%, log rank p = 0.019) [73]. Response data from another neoadjuvant GC cohort reported that responses were seen in the primary bladder cancer but not in lymph nodes with this regimen [56]. These data require further evaluation in prospective trials.

In the absence of definitive supportive data for GC in the neoadjuvant setting, MVAC remains the preferred regimen.
Bladder Cancer: Diagnosis and Clinical Management

Trials are building upon combinations of GC or dose-dense MVAC (DD-MVAC), with novel biological agents administered in three to four cycles in the neoadjuvant setting and with pCR as a key intermediate endpoint [74] (Table 25.3). This has not proven to be fruitful thus far. A trial of GC combined with sunitinib in the adjuvant setting proved very toxic despite dose reductions and had to be terminated early, with a pCR rate similar to that seen with GC alone [75]. The combination of MVAC with bevacizumab proved to have acceptable toxicity, with a pCR rate of 38% [76].

**Developing personalized neoadjuvant therapy: a paradigm to define risk of relapse and response to systemic therapy**

The ability to predict response to a specific therapy is still a major challenge in oncology. Advances in molecular research have led to the identification of genetic markers that impact upon response to chemotherapy. Based on detailed molecular information for each individual tumor, the clinician will ultimately be able to more accurately select the appropriate therapy for each patient according to individual predicted responses. This customized treatment using chemo sensitivity markers such as intratumoral molecular pharmacology markers (pharmacogenomics and genetics) should aid in improving outcomes [77, 78].

Several reports have outlined a variety of potential predictive markers either in localized disease or in advanced disease. Data remain limited, but it is conceivable that in coming years a marker or a panel of markers may be available that achieve this predictive goal, allowing improved patient selection for chemotherapy. Recent preliminary data suggest that pre-therapy microdosing of platinum drugs in patients coupled to the development of DNA adducts in the blood can predict response or resistance to platinum chemotherapy [79]. This premise is being tested in expanded cohorts of bladder and lung cancer patients.

To identify those bladder cancer patients that will derive the most benefit from neoadjuvant chemotherapy, studies to date are limited. At present, many of the published results of gene-expression profiling are preliminary, based on small sample sizes, and it is not possible to make a definitive statement on the role of gene-expression profiling in the molecular prognostication of invasive UC. Work in this area is directed along two concurrent themes: risk stratification and chemotherapy response prediction, and has recently been reviewed [80–84].
Summary

In summary, two large randomized trials and two meta-analyses support the concept that neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer provides a survival benefit greater than with surgery alone. This approach should be considered for patients who are candidates for cisplatin-based combination chemotherapy and radical cystectomy. For patients who are not candidates for this approach, other options include cystectomy alone, chemoradiation with non-platinum drugs, and/or a clinical trial.

Useful web links

3 http://annonc.oxfordjournals.org/content/21/suppl_5/v134.full = European Society for Medical Oncology.

References


48 Porter MP, Kerrigan MC, Donato BM, Ramsey SD: Patterns of use of systemic chemotherapy for Medicare beneficiaries


Introduction

Bladder cancer is the second most common malignancy of the genitourinary tract [1]. In the United States, more than 74,000 new cases of bladder cancer and about 16,000 deaths were estimated in 2015 [2]. Urothelial carcinoma is the most common histologic subtype and accounts for 90% of all bladder cancers. Seventy percent of patients present with non-muscle-invasive tumors at diagnosis and 10–15% of them will develop muscle-invasive bladder cancer (MIBC) within the first year of treatment, portending a poor prognosis [3, 4].

In patients with MIBC, pathologic stage and nodal status are the most important prognostic factors for progression and overall survival (OS) [5]. Radical cystectomy alone is associated with a five-year survival rate of up to 80% for selected patients with organ-confined disease without lymph node metastases. However,
although local treatment can be curative, patients with extravesical disease and patients with lymph node involvement have a five-year survival rate of approximately 40-50% and 15–35%, respectively [6]. Although surgical techniques and imaging exams have improved, the overall mortality for patients with MIBC remains quite stable [7]. Thus, early disease detection and/or integration of new systemic therapies may represent important strategies to improve clinical benefit in patients with MIBC.

As discussed elsewhere in this book, patients with metastatic MIBC are usually treated with multi-agent chemotherapy, achieving high objective response rates and overall survival improvement. However, only 10–20% of patients with clinically evident metastatic bladder cancer treated with platinum-based chemotherapy will be long-term survivors [8]. These rates are similar to those seen in patients with metastatic breast and colorectal cancer, in which the value of chemotherapy in early-stage disease is well established [9, 10]. Based on the survival benefit described in the limited metastatic setting and the benefits of adjuvant chemotherapy observed in other solid tumors, the rationale for the early administration of chemotherapy in MIBC patients with localized or locally advanced MIBC in which a radical cystectomy is planned was developed.

The current National Comprehensive Cancer Network (NCCN) guidelines recommend radical cystectomy as the standard of care for all patients with muscle-invasive non-metastatic disease and sufficient performance status. Neoadjuvant cisplatin-based chemotherapy is strongly recommended based on level 1 evidence showing a survival benefit, although it is still currently being underutilized [11]. The role of adjuvant chemotherapy has remained controversial. However, given the benefit of chemotherapy in the neoadjuvant setting and the poor prognosis of some patients following radical cystectomy, adjuvant chemotherapy is obviously and frequently used in patients with high-risk bladder cancer that have not received neoadjuvant chemotherapy. A multi-institutional study of 4541 patients across 14 academic centers in the United States from 2003 to 2008 found that only 12% of patients received neoadjuvant chemotherapy (NAC) and 22% received adjuvant chemotherapy [12]. A recent nationally representative report from the National Cancer Database (NCDB) highlights a gradual increase in the utilization of NAC from 7.6% in 2006 to 20.9% in 2010 [13].

**Adjuvant treatment**

Micro-metastases may be present at the time of diagnosis and most of the subsequent deaths arise from metastatic disease clinically unrecognized at diagnosis [14]. Failure rates after radical cystectomy are around 30–45%, supporting the rationale for perioperative use of systemic treatment strategies [15].

The approach of administering chemotherapy after local treatment has led to increased survival in patients with several other malignancies [9]. Because of this, adjuvant chemotherapy has been widely studied in MIBC for the last three decades and several randomized and non-randomized clinical trials have evaluated the role of this therapeutic strategy after local therapy (Table 26.1). However, results are not unequivocal and only a few trials have shown a survival benefit for adjuvant chemotherapy. The majority of randomized clinical trials designed to evaluate adjuvant treatment in MIBC suffer from several methodological problems: small sample size, early stopping of accrual, variability in chemotherapy regimens, number of cycles and dose received, which contribute to the confusion on data interpretation.

**Advantages**

The major advantage of adjuvant treatment versus NAC is the accuracy of patient selection. The pathological staging allows the selection of patients most likely to benefit from this treatment according to the risk of recurrence (e.g. T3, T4, and N+), reducing the risk of overtreatment [11]. In a large retrospective cohort of 3166 patients designed to evaluate discrepancies in clinical and pathologic stage and their effect on outcome, clinical understaging was identified in about half of the patients undergoing radical cystectomy for MIBC. On the other hand, pathologic downstaging occurred in 18% of patients [16]. In addition, pre-cystectomy nomograms for prediction of advanced bladder cancer fail to add relevant information to clinical staging alone [17].

Moreover, with adjuvant chemotherapy, the local surgical treatment is performed immediately and no time is wasted in those patients who would not respond to a specific chemotherapy agent and/or would not benefit from this therapeutic strategy in terms of overall survival. In addition, physicians are sometimes reluctant to delay the local treatment because they fear that it may increase the incidence of perioperative morbidity
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<th>Overall survival (HR, 95% CI)</th>
<th>Significance (Y/N)</th>
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<td>T4: 37</td>
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<td>48.1 vs. 60.7</td>
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<td>26</td>
<td>23</td>
<td>35.1 (24.5–45.6)</td>
<td>76.9 vs. 87</td>
<td>0.57 (0.31–1.05)</td>
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<td>46</td>
<td>45</td>
<td>69 (36–96)</td>
<td>50 vs. 48.9</td>
<td>1.02 (0.57–1.84)</td>
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<td>T0–1: 16</td>
<td>58</td>
<td>Methotrexate</td>
<td>64.8 (61.2–70.8)</td>
<td>20.7 vs. 16.1</td>
<td>1.11 (0.45–2.72)</td>
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<td>T0–1: 1</td>
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<td>35 (15–57)</td>
<td>45.1 vs. 41.3</td>
<td>1.29 (0.84–1.99)</td>
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<td>Cisplatin 70 mg/m²</td>
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<td>(Randomized 1:1 to receive this either on Day 2 or 15)</td>
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<td>45.1 vs. 41.3</td>
<td>1.29 (0.84–1.99)</td>
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<td>T3N0: 20</td>
<td>68</td>
<td>Paclitaxel 80 mg/m²</td>
<td>29.8 (1–95)</td>
<td>35.3 vs. 60.8</td>
<td>0.38 (0.22–0.65)</td>
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*Mean or median follow-up time (in months) as reported by each study during time of publication. Types of range reported include minimum to maximum, inter-quartile range, and 95% confidence intervals.

†Based on number of events in treatment/control arm vs. ITT population randomized to treatment/control.
Adjuvant chemotherapy for invasive bladder cancer

with neoadjuvant strategies [18]; this is increasingly being refuted with contemporary data [19]. When neoadjuvant chemotherapy was compared to adjuvant chemotherapy, there were no differences in perioperative morbidity [20]. Also, some limited time delay on time to surgery – up to three months – does not seem to have a huge impact on the overall outcome [21, 22], and may, in fact, practically represent the length of time sometimes seen on the waitlist of a high-volume, fellowship-trained busy urologic oncology center.

Disadvantages
The improvements in surgical techniques resulting in decreased morbidity and the advent of orthotopic bladder substitutions have increased the tendency of urologists to perform radical cystectomy and then consider adjuvant chemotherapy based on pathological stage. On the other hand, a major disadvantage of this approach is that the bladder cannot be considered for potential bladder preservation and the start of the systemic therapy to treat occult metastasis is delayed while the treatment of the primary tumor is being performed. Furthermore, the pathologic downstaging and the pathologic response induced by the neoadjuvant chemotherapy administration provide prognostic information [23]. With adjuvant chemotherapy, the only way to assess treatment benefit is to rule out disease progression during follow-up.

An additional potential disadvantage is the difficulty in administering chemotherapy to patients after cystectomy, because of the consequent decline in performance status (prolonged surgical recovery due to post-surgical complications) and the renal function decline, limiting the ability to administer cisplatin-based chemotherapy [24].

Evidence summary

Retrospective studies
A large retrospective multi-center study evaluated the association of adjuvant chemotherapy with overall survival [25]. In this study, 3947 patients from 11 centers who underwent radical cystectomy without neoadjuvant treatment were identified. 932 (23.6%) received adjuvant chemotherapy and it was independently associated with improved OS (HR: 0.83; 95% CI: 0.72–0.97; \( p = 0.017 \)). In particular, there was a significant improvement in survival in a subgroup of patients who predominantly presented both pT3 stage and lymph node–positive disease (HR: 0.75; 95% CI: 0.62–0.90; \( p = 0.002 \)). This group exhibited a 32.8% five-year probability of cancer-specific survival. The retrospective nature of this analysis and the potential selection bias impose limitations on the interpretability of these results [25].

Prospective non-randomized studies
One of the first studies addressing the impact of adjuvant chemotherapy was conducted by Logothetis and colleagues in 1989 [26]. In this study, 71 patients at high risk for relapse based on pathologic criteria (pT3b, pT4, N1, and vascular or lymphatic invasion) were treated with cisplatin, cyclophosphamide, and adriamycin. Patients who received adjuvant chemotherapy showed a five-year survival rate of 70%, compared with 37% for those 62 patients who did not (as part of a historical control). Clearly, this large difference could be explained by patient selection bias. However, a benefit with treatment was clearly suggested [26]. Similar results were found in another study in 1998 in which 35 patients received a median of four courses of cisplatin, methotrexate, and vinblastine (\( n = 23 \)) or the same drugs with doxorubicin (\( n = 12 \)). Despite toxicity, patients at high risk appeared to present better long-term survival rates with adjuvant treatment [27].

Randomized clinical trials
A study with adjuvant cisplatin mono-chemotherapy after cystectomy was conducted by Studer et al. Seventy-seven patients with non-metastatic MIBC were stratified after radical cystectomy based on nodal status (stage pN0 versus pN1–2) and were randomly assigned to observation or post-operative cisplatin mono-chemotherapy. In this study, no survival differences between the observation and the cisplatin group were found, even in the high-risk group, which suggests that mono-chemotherapy is an inadequate strategy [28].

Skinner and colleagues assigned 91 patients with T3–4 or N+ MIBC to two groups, one of which received adjuvant cisplatin, doxorubicin and cyclophosphamide, the other of which was just observed after radical cystectomy. Patients who received adjuvant chemotherapy had a significant increase in time to progression and overall survival. Of note, this study has been criticized for several methodological problems, as discussed later on [29]. In addition, another study in
Germany randomized patients to receive adjuvant chemotherapy (MVAC or MVEC) or observation. This study reported a benefit in overall survival and progression-free survival with adjuvant chemotherapy [30]. This phase III study was prematurely closed because of suggested striking benefits of adjuvant chemotherapy, and a small number of patients were included in the final analysis because of premature closure. Furthermore, a highly questioned procedure was conducted: patients assigned to the control arm did not receive any further treatment at the time of recurrence. Another small German series which evaluated adjuvant MVEC versus observation reported no statistically significant differences in overall survival [31].

In another mixed randomized trial, 140 patients were assigned to receive two neoadjuvant cycles followed by three adjuvant cycles after surgery compared to five adjuvant cycles of MVAC. This study was unable to demonstrate a survival difference, but there was a suggestion that neoadjuvant may be more feasible than adjuvant chemotherapy. Only 54 of 70 patients (77%) received two or more cycles of MVAC after surgery, whereas 68 of 70 (97%) received at least two cycles when assigned to initial neoadjuvant MVAC [20].

More recent trials using cisplatin/gemcitabine (GC)-based regimens in the adjuvant setting have also failed to provide definitive supportive evidence for routinely recommending chemotherapy, mainly due to poor accrual. The prospective Italian Multicenter Trial of 194 patients was underpowered to demonstrate a survival difference in patients receiving four cycles of adjuvant GC (HR: 1.29; 95% CI: 0.84–1.99, p = 0.24) [32], but again, this trial closed prematurely due to poor accrual, limiting the interpretability of the results.

The Spanish Oncology Genitourinary Group (SOGUG) trial was designed to randomize 340 patients with T3–T4 or node-positive disease to treatment using four cycles of paclitaxel, gemcitabine, and cisplatin (PCG) or observation. Here again, the trial was prematurely closed after only 142 patients were enrolled. At a median follow-up of 51 months, adjuvant PCG resulted in a significant increase in OS compared to no chemotherapy (60% versus 30%, HR: 0.44) [33].

The third contemporary study of adjuvant chemotherapy was designed by the EORTC to compare deferred therapy at the time of recurrence with adjuvant therapy according to physician choice of GC, MVAC, or DD-MVAC. This trial had an initial goal of 660 patients but further amendment reduced the design to 360. Despite the amendment, the trial was also closed after enrollment of only 242 patients due to slow accrual. Results will be presented at ASCO 2014.

An innovative biomarker-driven trial in patients with organ-confined disease (including patients with pT1 and pT2, N0M0) randomized patients by altered p53 levels to three cycles of MVAC versus observation. There was no difference in relapse-free survival and no impact on any of the outcome measures based on p53 status [34]. This was the first trial to select patients for systemic treatment based on molecular markers. Again, this trial suffered from the poor accrual paradigm.

Meta-analysis
Because of limitations on interpretability of single trials, several meta-analyses have been conducted and recently updated. The Advanced Bladder Cancer Meta-Analysis Collaboration conducted a meta-analysis in 2005, subsequently published as a Cochrane review [35]. Individual patient data were obtained from 491 patients in six trials. Finally, 66% of patients from eligible trials (90% randomized to cisplatin-based combination chemotherapy) were included in the Cochrane study. This meta-analysis found a 25% overall relative reduction in the risk of death for patients receiving adjuvant chemotherapy. Limitations cited in this meta-analysis included four of six trials stopping early, few deaths (283 of 491), and the failure of patients assigned to the control arm to receive standard of care at relapse [35].

Since this meta-analysis, several trials, previously described, were reported to evaluate adjuvant cisplatin-based regimens for MIBC. Recently, an updated meta-analysis of nine randomized trials including 945 patients reported a disease-free survival (HR: 0.66; 95% CI: 0.45–0.91, p = 0.014) and overall survival benefit (HR: 0.78; 95% CI: 0.61–0.99; p = 0.044) in MIBC patients who received adjuvant cisplatin-based chemotherapy after radical cystectomy compared with those who underwent surgery alone [36]. Additionally, lymph node-positive patients appear to have a greater disease-free survival benefit than lymph node-negative patients on meta-regression, however this has been criticized as being a “post-hoc analysis of unplanned stratification” [37], therefore cautious interpretation has been suggested until an eagerly anticipated updated individual patient data meta-analysis [38, 39].
Ongoing clinical trials

Alternative regimens have been investigated in the adjuvant setting in patients who are not eligible to receive cisplatin-based neoadjuvant treatment. A phase III German clinical trial focusing on this group of patients was recently closed due to slow accrual. This study was designed to evaluate gemcitabine alone in patients who were not eligible to receive cisplatin-based chemotherapy (NCT00146276). Again, with several limitations on trial conduct, the results did not support its use. Another study is testing a Her2-targeting autologous antigen-presenting cell-based vaccine in patients who express Her2 in the specimen after radical cystectomy (even if prior neoadjuvant chemotherapy has been given) (NCT01353222). Finally, the MAGNOLIA study is a placebo-controlled phase II clinical trial to evaluate the safety and effects of recMAGE-A3 plus AS15 cancer immunotherapeutic product in subjects with MAGE-A3 expression (NCT01435356). This trial is accruing in the Research Foundation of the European Association of Urology (EAURF) Group.

Molecular biology and targeted therapies

Bladder cancer is a heterogeneous disease. In the genomic era, understanding the molecular pathophysiology of MIBC may lead to improvements in therapeutics. The Cancer Genome Atlas (TCGA) has allowed the molecular characterization of a large number of tumors. Recently, the TCGA of bladder cancer identified potential therapeutic targets in 69% of the 131 tumors evaluated [40]. Chromatin-modifying genes were identified as being altered in high frequencies, indicating the future possibility of targeted therapy for these chromatin abnormalities.

The identification of driving genomic alterations as mutations, even if occurring in only a small subset of bladder cancer patients, may help us to identify new targets for therapeutic interventions and biomarkers that can predict response to therapies. Recently described mutations in the TSC1 gene have predicted response to mTOR inhibitors like everolimus [41–43]. Another example is the PIK3CA gene, mutated in up to 26% of cases in the series by Ross and colleagues that may predict sensitivity to PIK3CA/mTOR inhibitors [44]. This may substantially increase the survival benefits that have already been observed in MIBC treatment. So far, no molecularly targeted agents have been tested besides Her2 vaccine in this disease, and whether these concepts would be applied in the adjuvant setting still needs to be addressed.

Moreover, a 20-gene expression profile to predict the pathological node status suggests that molecular biologic techniques may be useful in selecting high-risk patients. However, this will require prospective validation [45]. Therefore, patient selection for current and future available therapeutic strategies will allow more effective use of perioperative chemotherapy for high-risk patients.

Conclusions and future directions

The use of neoadjuvant chemotherapy and an adequate pelvic lymph node dissection are now the standard of care and are widely recognized as two important factors influencing improved long-term survival [46]. However, due to the low rates of adoption of neoadjuvant chemotherapy, clinicians are often faced with the decision of whether or not to recommend adjuvant chemotherapy for many moderate- to high-risk patients [15]. Although with the recent meta-analysis this has improved, there is still insufficient evidence to support the routine use of adjuvant chemotherapy, and the use of neoadjuvant chemotherapy should be reinforced. Nonetheless, outside clinical trials, adjuvant treatment appears to be a reasonable option for patients with pathologic extravesical and/ or node-positive disease and who are eligible to receive cisplatin-based combination therapy and have not received chemotherapy before the radical cystectomy.

Useful web links

1 http://www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines/Urogenital-Cancers
2 http://www.uroweb.org/guidelines/online-guidelines/
3 http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

References


CHAPTER 27

Treatment of metastatic bladder cancer

Gopa Iyer1, Fabio Calabrò2, and Dean F. Bajorin3

1 Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
2 Department of Medical Oncology, San Camillo Forlanini Hospitals, Rome, Italy
3 Weill Cornell Medical College, New York, NY, USA

KEY POINTS

• The standard of care for first-line treatment of metastatic urothelial carcinoma is cisplatin-based combination chemotherapy with either MVAC or GC.
• No standard treatment exists for patients ineligible for cisplatin-based chemotherapy, although carboplatin-based regimens are active in this setting.
• At this time, no standard of care exists for the treatment of recurrent urothelial carcinoma and patients should be encouraged to participate in clinical trials whenever possible.
• Targeted therapies to date have not shown a significant improvement in survival over standard chemotherapy in metastatic UC, although genetic pre-selection of patients whose tumors harbor biomarkers of response to such agents will hopefully improve upon current treatment paradigms.

In 2013, an estimated 72,570 new cases of urinary bladder cancer were diagnosed in the United States, with 15,210 deaths [1] While the majority of these cancers were superficial and treated with local therapy, including transurethral resection with the possible addition of intravesical treatment, up to 70% of these patients will recur and 20% of such recurrences are muscle-invasive, requiring perioperative chemotherapy with cystectomy as the standard of care [2]. Approximately 5% of patients present with metastatic disease which, in the vast majority of cases, is incurable.

The initial treatment for metastatic bladder cancer evolved from a number of phase II studies investigating the efficacy of single-agent therapy with cisplatin, methotrexate, vinblastine, and doxorubicin. These early studies established overall response rates (ORR) for each agent ranging from 17–30% while trials combining two or three drugs resulted in improved response rates. Based upon these results, the four drug combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) was tested in 25 patients with metastatic UC, with an impressive ORR of 71% (50% complete response (CR) rate) and a median survival of 13 months [3]. Hematologic toxicity was commonly observed with this regimen, with neutropenic sepsis in 16% of treated patients.

Further trials confirmed the efficacy of MVAC compared to other single-agent and combination regimens. Cisplatin, cyclophosphamide, and doxorubicin (CISCA) and MVAC were compared in a phase III trial in 110 patients with metastatic UC [4]. The CR and partial response (PR) rates were superior in the MVAC cohort with an ORR of 65% vs. 46% (p = 0.05) for MVAC and CISCA, respectively, while the median survival was also better with MVAC (48.3 weeks vs. 36.1 weeks). Toxicities were comparable, including febrile neutropenia rates of 14% vs. 5% in the CISCA and MVAC regimens, respectively. In a phase III Intergroup randomized controlled trial of 269 patients comparing single-agent cisplatin to MVAC, response
rate (RR) was significantly improved with the combination regimen (39% vs. 12%, \( p < 0.001 \)), as were progression-free survival (PFS, 10 vs. 4.3 months) and overall survival (OS, 12.5 months vs. 8.2 months, \( p = 0.0002 \)) [5]. Unsurprisingly, the MVAC regimen was associated with worse toxicities, including neutropenic sepsis, Grade 3/4 mucositis, nausea, and vomiting, as well as five drug-related deaths versus none with single-agent cisplatin. A long-term follow-up of the Intergroup study displayed the persistent superiority of MVAC over cisplatin at six years in terms of OS (\( p = 0.00015 \)) [6]. Notably, however, disease-specific survival was poor in both treatment arms, with 3.7% of patients who received MVAC alive without disease and 1.6% of cisplatin-treated patients, underscoring the need for new treatments that could improve long-term survival in this disease. Pre-treatment prognostic factors significantly impacted median survival in this patient population: Karnofsky performance status (KPS) \( \geq 90\% \), the absence of weight loss, and the absence of liver, lung, or bone metastases were associated with a median OS of 18.2 months versus 4.4 months for patients with all of these risk factors in the MVAC treatment arm. Notably, the same difference in OS was observed in patients receiving cisplatin alone, suggesting that these prognostic indicators are independent of treatment. In the long-term follow-up of this study, KPS \( \geq 80\% \), transitional cell histology and the absence of liver and bone metastases were associated with improved survival. Bamias et al. performed a randomized phase III study through the Hellenic Cooperative Oncology Group comparing the combination of docetaxel plus cisplatin (DC) to MVAC in 200 patients with metastatic urothelial carcinoma (UC) [7]. As with the studies described above, this trial also detected better efficacy for MVAC versus DC, with a RR of 54.2% vs. 37.4% (\( p = 0.017 \)), a median time to progression of 9.4 months vs. 6.1 months (\( p = 0.003 \)), and a median survival of 14.2 months vs. 9.3 months (\( p = 0.026 \)). Furthermore, MVAC resulted in higher rates of Grade 3/4 neutropenia (35.4% vs. 19.2%, \( p = 0.006 \)) and neutropenic sepsis (11.6% vs. 3.8%, \( p = 0.001 \)) as well as thrombocytopenia (5.7% vs. 0.9%, \( p = 0.046 \)). In this trial, colony-stimulating factor support was administered with every cycle with a concomitant improvement in delivery of MVAC and a decreased rate of neutropenic sepsis and neutropenia compared to other studies. Of note, in this trial there was no stratification according to performance status, one of the major prognostic indicators in patients with advanced UC, and there was a higher proportion of patients with poor performance status in the DC arm, which may have contributed to the poor outcomes in this arm. See Table 27.1 for a summary of phase III studies of cisplatin-based chemotherapy.

While these trials established the efficacy of MVAC in the metastatic setting, the significant toxicities of myelosuppression and mucositis associated with this regimen stimulated efforts to define a new cisplatin-based drug combination with equivalent efficacy but improved tolerability. Based upon promising phase II data for gemcitabine plus cisplatin (GC), a phase III randomized study comparing MVAC to GC was performed in 405 patients with locally advanced or metastatic UC [8]. The study was designed to detect a four-month survival difference in favor of GC. The median OS was similar between both study arms (13.8 months for GC vs. 14.8 months for MVAC, \( p = 0.75 \)), and overall response rate in patients who received at least one cycle of treatment was 49.4% for GC and 45.7% for MVAC (\( p = 0.51 \)). In contrast, toxicity profiles were dissimilar between the two regimens: MVAC was associated with neutropenia and febrile neutropenia as well as a neutropenic sepsis rate of 12% vs. 1% in the GC arm (\( p < 0.001 \)), while patients who received GC had a higher incidence of Grade 3/4 anemia (27% vs. 18%). In terms of non-hematologic toxicities, the rates of Grade 3/4 mucositis were significantly higher with the MVAC regimen. The toxic death rate was 3% with MVAC and 1% with GC. Although this trial was not designed as an equivalency trial, these results defined both the better safety profile of GC compared to MVAC and the similar efficacy of both regimens, providing an alternative to MVAC therapy in the treatment of patients with metastatic UC. Notably, a long-term analysis of this phase III study at five years revealed continued equivalent survival rates between GC and MVAC: median OS of 14 months vs. 15.2 months, five-year overall survival rates of 13% and 15.3%, and median PFS of 7.7 months vs. 8.3 months [9]. Prognostic factors indicative of improved survival included KPS > 70%, low/normal alkaline phosphatase level, number of disease sites, and the absence of visceral metastatic disease. However, these results also underscore the consistent observation that, although patients with metastatic UC experience initial robust responses to platinum-based chemotherapy, relapses are frequent and mortality from recurrent disease is high. The limited
long-term effectiveness of cisplatin-based combination chemotherapy drives a need for novel therapeutics in the metastatic setting.

A number of studies have investigated the utility of alternative platinum-based regimens and treatment schedules in an attempt to improve upon the long-term outcomes for metastatic disease. In the phase III EORTC Intergroup Study 30987, 626 patients with locally advanced or metastatic UC were randomized to receive either GC or the triplet regimen of paclitaxel, gemcitabine, and cisplatin (PCG) [10]. Median OS was similar between the two treatment arms (15.8 months with PCG vs. 12.7 months with GC, \( p = 0.075 \)); however, a non-preplanned subset analysis of those patients with bladder primary tumors displayed a statistically significant superior OS with PCG (15.9 vs. 11.9 months, HR 0.80, 95% CI: 0.66–0.97; \( p = 0.027 \)), as did a similar analysis that removed the 8% of patients who were ineligible for study. Additionally, the ORR for patients on the PCG arm was significantly higher than those patients receiving GC (55.5% vs. 43.6%, \( p = 0.0031 \)). While Grade 4 neutropenia and febrile neutropenia were more commonly observed in the PCG arm (13% vs. 4%), no increased rate of neutropenic sepsis was noted between the two arms; Grade 4 thrombocytopenia was more common with GC therapy (11.4% vs. 6.8%). Although this trial did not reach the predefined endpoint of a four-month improvement in median OS with PCG (instead showing a 3.1-month improvement in the intent to treat patient subset), a statistically significant improvement was observed when only including eligible patients or those patients with bladder primaries. These results infer that, despite morphologic similarities, there may be genetic and/or epigenetic differences between urothelial carcinoma of the upper and the lower urinary tracts that affect clinical outcomes.

A phase II study was performed of the combination of ifosfamide, paclitaxel, and cisplatin (ITP) in 30 patients with metastatic UC, spurred by promising phase II results of ifosfamide in this disease [11]. Of 29 evaluable patients, the major response rate (CR+PR) was 79%, with a disease-free survival of 31% at 17.9 months and a median survival of 18.3 months. CRs were observed in a subset of patients with T4 nodal disease who subsequently underwent consolidation cystectomy. Febrile neutropenia was present in 17% of patients, renal insufficiency in 13%, and neuropathy in 10%. The response rates and survival seen with ITP compare favorably with MVAC; however, the improved tolerance

### Table 27.1 Phase III cisplatin-based trials in metastatic UC.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Regimens</th>
<th>N</th>
<th>ORR</th>
<th>Median survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logothetis et al</td>
<td>MVAC vs. CISCA</td>
<td>110</td>
<td>65% vs. 46% (( p = 0.05 ))</td>
<td>48.3 wks vs. 36.1 wks</td>
<td>First-line metastatic setting</td>
</tr>
<tr>
<td>Cooperative Group Study</td>
<td>MVAC vs. Cisplatin</td>
<td>269</td>
<td>39% vs. 12% (( p &lt; 0.001 ))</td>
<td>12.5 mo vs. 8.2 mo (( p = 0.0002 ))</td>
<td>First-line metastatic setting; increased toxicity with MVAC</td>
</tr>
<tr>
<td>HCOG</td>
<td>MVAC vs. DC</td>
<td>200</td>
<td>54.2% vs. 37.4% (( p = 0.017 ))</td>
<td>14.2 mo vs. 9.3 mo (( p = 0.026 ))</td>
<td>G-CSF administration reduced neutropenic sepsis rates</td>
</tr>
<tr>
<td>von der Maase</td>
<td>MVAC vs. GC</td>
<td>405</td>
<td>45.7% vs. 49.4% (( p = 0.51 ))</td>
<td>14.8 mo vs. 13.8 mo (( p = 0.75 ))</td>
<td>Neutropenic sepsis, mucositis with MVAC; anemia with GC</td>
</tr>
<tr>
<td>EORTC 30987</td>
<td>PCG vs. GC</td>
<td>626</td>
<td>55.5% vs. 43.6% (( p = 0.0031 ))</td>
<td>15.8 mo vs. 12.7 mo (( p = 0.075 ))</td>
<td>First-line locally advanced or metastatic setting</td>
</tr>
<tr>
<td>EORTC 30924</td>
<td>HD-MVAC vs. MVAC</td>
<td>263</td>
<td>62% vs. 50% (( p = 0.06 ))</td>
<td>15.5 mo vs. 14.1 mo (( p = 0.122 ))</td>
<td>PFS, CR rates, and OS superior with HD-MVAC</td>
</tr>
<tr>
<td>HCOG</td>
<td>DD-MVAC vs. DD-GC</td>
<td>130</td>
<td>60% vs. 65.3% (( p = 0.06 ))</td>
<td>18 mo vs. 19 mo</td>
<td>DD-GC with lower neutropenic infections, better tolerated</td>
</tr>
</tbody>
</table>

\( N \): Total number of patients enrolled; ORR: objective response rate; MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; CISCA: cisplatin, cyclophosphamide, doxorubicin; DC: docetaxel, cisplatin; GC: gemcitabine, cisplatin; PCG: paclitaxel, cisplatin, gemcitabine; HD-MVAC: high-dose MVAC; DD-MVAC: dose-dense MVAC; DD-GC: dose-dense GC; EORTC: European Organisation for Research and Treatment of Cancer; HCOG: Hellenic Cooperative Oncology Group; PFS: progression-free survival; OS: overall survival; CR: complete response; G-CSF: granulocyte-colony stimulating factor; wks: weeks; mo: months
Treatment of metastatic bladder cancer

with GC has precluded widespread use of ITP in the metastatic UC population.

The benefit of higher doses of chemotherapeutic agents delivered more frequently (dose-dense therapy) has been tested in metastatic UC in a number of trials in which a dose-intense MVAC regimen was administered with either GM-CSF or G-CSF. A phase I/II ECOG study delivered escalating doses of MVAC every four weeks to 35 patients with metastatic UC in the first-line setting [12]. The ORR was 60%, with 28 patients developing Grade 3/4 leukopenia and 8 deaths (23%) during the study. Unfortunately, in several trials toxicity was also significantly increased. Based upon these results, dose escalation of MVAC was not recommended in the United States. Subsequently, a phase III EORTC study (30924) randomized 263 patients with locally advanced or metastatic UC to receive either standard-dose MVAC or high-dose MVAC (HD-MVAC), with the latter regimen consisting of 14-day cycles of all four drugs as compared to the four-week cycles which comprise the traditional MVAC regimen, allowing for twice the dose of cisplatin and doxorubicin to be administered in half the time [13]. Growth factor support was provided for patients randomized to HD-MVAC. While the primary endpoint of OS was similar between the two arms, PFS was significantly prolonged with HD-MVAC as compared to standard MVAC (9.1 months vs. 8.2 months, \( p = 0.037 \), HR 0.75, 95% CI: 0.58–0.98). The ORR was higher with HD-MVAC although not reaching statistical significance (62% vs. 50%, \( p = 0.06 \)) and significantly more CRs were observed with high-dose therapy. Notably, leukopenia and febrile neutropenia were more commonly seen with standard MVAC, likely due to the use of G-CSF in 94% of patients receiving high-dose treatment as compared to 19% for patients on the MVAC arm. Mucositis was also more common with standard MVAC, while the rates of toxic death were similar between both arms. A long-term analysis at 7.3 years median follow-up showed that the median PFS was 9.5 months for high-dose therapy vs. 8.1 months for standard-dose MVAC (\( p = 0.017 \)) and OS was 15.1 months vs. 14.9 months (HR 0.76, 95% CI: 0.58–0.99) [14]. The ORR was significantly better with HD-MVAC vs. MVAC (72% vs. 58%, 2-sided \( p = 0.016 \)), again also showing a superior CR rate with high-dose treatment (25% vs. 11%, 2-sided \( p = 0.006 \); however, 81% of all patients on the study had died by the time of long-term follow-up, with a cancer-specific death rate of 64.9% with HD-MVAC and 76% with MVAC, implying a persistently high relapse rate following an initial robust response to chemotherapy with both regimens.

A phase III study through the Hellenic Cooperative Oncology Group compared dose-dense MVAC (DD-MVAC) to dose-dense GC (DD-GC) in locally advanced or first-line metastatic UC patients, with the latter regimen consisting of gemcitabine 2500 mg/m^2 as compared to the standard 1000 mg/m^2 with both agents delivered every 14 days instead of every 21 days with G-CSF support [15]. Of 63 evaluable patients on each arm, the median OS (19 months for DD-GC and 18 months for DD-MVAC) and PFS (8.5 and 7.8 months respectively) were not statistically different, although this study was prematurely closed due to incomplete accrual. Interestingly, patients with an ECOG PS of 1 manifested an improved OS with DD-GC (HR 0.46, 95% CI: 0.24–0.86, \( p = 0.015 \)). The ORR was not significantly different between DD-MVAC (60%) and DD-GC (65.3%), although these response rates are both higher than those observed with standard-dose chemotherapy. Toxicity-related treatment cessation was more common with DD-MVAC than DD-GC (13% vs. 3%) and two toxic deaths were observed with DD-MVAC versus none for DD-GC. The favorable results observed in this study may be, at least in part, due to a selection bias. In fact, more than 90% of the patients had an ECOG PS of 0–1, more than 50% of patients in both arms had no visceral metastases, and 38% had 0 metastatic sites. Administration of non-cross-resistant agents in sequence may improve outcome by targeting tumor cells with different sensitivity profiles. The utility of sequential chemotherapy using different agents was evaluated in metastatic UC in a phase II study of ITP alternating with the combination of doxorubicin plus gemcitabine (AG) [16]. Sixty patients were enrolled onto the study; patients received AG every two weeks for six cycles followed by ITP every 21 days for four cycles. The ORR for this study was 73%, with a CR rate of 35% and a median survival of 16.4 months. Consolidative surgery was feasible in 12 of 28 patients who manifested a significant response to chemotherapy and the median survival for this patient subset was 29.8 months. The survival benefit for AG ITP is slightly better than that seen with MVAC or GC but the 95% CIs for all three studies overlap, making a survival comparison...
across studies impossible. The authors concluded that this sequential regimen was associated with significant toxicity and did not offer a clear benefit as compared to non-sequential cisplatin-based regimens.

In summary, while dose-dense and sequential therapies may improve response rates modestly, the impact upon OS is questionable due to the high relapse rate of UC following initial chemotherapy responses. This consistent finding suggests the need for a better understanding of the biology of UC as well as the incorporation of novel non-chemotherapeutic agents into the treatment of this disease.

**Non-cisplatin-containing chemotherapy regimens**

While cisplatin has historically been the mainstay of chemotherapeutic regimens in UC, several non-cisplatin-based therapies have been studied in the metastatic setting. Carboplatin, a second-generation platinum compound without the nephrotoxic side effects of cisplatin, has been investigated in a number of clinical trials. Phase II studies comparing cisplatin- to carboplatin-containing regimens have shown improved response rates and a higher probability of achieving CRs with cisplatin [17]. A randomized phase II study compared MVAC to the triplet of methotrexate, carboplatin, and vinblastine (M-CAVI) in the advanced UC population, yielding similar ORRs between the four- and three-drug regimens (52% vs. 39%, \( p = 0.3 \)), yet with an improved median disease-specific survival in the MVAC treatment arm (16 months vs. 9 months, \( p = 0.03 \)) [18]. A phase III trial of carboplatin plus paclitaxel vs. MVAC was initiated through the ECOG in patients with metastatic UC but was severely underpowered, ultimately accruing 85 patients of a planned 330, making it difficult to draw definitive conclusions regarding the efficacy of the carboplatin plus paclitaxel regimen [19]. The ORR for the carboplatin doublet was 28.2% vs. 35.9% for MVAC (\( p = 0.63 \)), with a median PFS of 5.2 months vs. 8.7 months (\( p = 0.24 \)) and OS of 13.8 months vs. 15.4 months (\( p = 0.65 \)). More severe toxicities were found with higher frequency in MVAC-treated patients. Non-platinum-containing regimens utilizing taxanes with gemcitabine have also been investigated in metastatic UC. The combination of gemcitabine and paclitaxel was evaluated in the locally advanced or metastatic first-line setting in a phase II study, showing an ORR of 37% with 5 of 54 patients (9.2%) achieving a CR [20]. The preponderance of CRs was observed in patients with locally advanced UC or metastatic disease confined to lymph nodes. The median PFS and OS were 5.8 months and 13.2 months, respectively, with survival favorably linked to better performance status. The most frequent toxicity was myelosuppression, including Grades 3–4 neutropenia (18%) and thrombocytopenia (5%). In a single-arm phase II study, 31 patients with untreated, locally advanced, or metastatic UC received the combination of gemcitabine plus docetaxel [21]. In an intention to treat analysis, the ORR was 51.6%, including 4 (12.9%) patients achieving a CR with a median TTP and OS of 8 months and 15 months, respectively. Grade 3–4 neutropenia was observed in 27.6% of patients, with a febrile neutropenia rate of 6.1%.

The available data on the platinum-free combinations in advanced urothelial carcinoma suggest that, although these combinations are active and tolerable, at the present time, patients who are eligible for cisplatin should be treated with cisplatin-based combination chemotherapy.

**Prognostic and predictive biomarkers in metastatic UC**

Defining prognostic factors in the pre-treatment setting provides a framework to inform drug selection for phase III studies based upon phase II response data by reducing bias related to intrinsic features of the study population. Using patient populations that are balanced for prognostic factors also allows for more meaningful comparisons of the survival outcomes between clinical trials. These factors can also assist in making treatment decisions based upon the number of risk features present; for example, patients with multiple risk factors with a poor overall prognosis may be better suited to receive best supportive care instead of chemotherapy. Prognostic factors that predict survival for patients with metastatic disease were derived from the clinical characteristics and outcomes of 203 patients treated with MVAC chemotherapy across five clinical trials [22]. Univariate and multivariate analyses were performed to select variables with prognostic significance, identifying KPS below 80% and the presence of visceral (lung, liver, or bone) metastases as unfavorable predictors of survival. Patients with zero, one, or two risk factors were found to have distinct
median survivals of 33, 13.4, and 9.3 months, respectively. Similar results were obtained by the Spanish Oncology Genitourinary Group (SOGUG) in a phase I/II study of 56 patients with advanced urothelial tumors treated with the combination of cisplatin, paclitaxel, and gemcitabine. Factors associated with reduced survival were performance status > 0, presence of visceral metastases, and more than one site of disease. The median survival times for patients with zero, one, or two risk factors were 32.8, 17, and 9.6 months, respectively [23]. The results of a phase III study of vinflunine (described below) after failure of platinum-based therapy were analyzed by multivariate analysis and identified hemoglobin < 10 g/dL, the presence of liver metastases, and an ECOG PS ≥ 1 as parameters impacting survival in the second-line setting [24]. Patients with zero, one, two, or three risk factors exhibited median survivals of 14.2, 7.3, 3.8, and 1.7 months, respectively. These same factors were validated using survival data from a phase II single-arm trial of vinflunine.

While numerous clinical trials have shown a benefit to the utility of chemotherapy for advanced UC, the disparity between response rates and long-term survival emphasizes the lack of durability of responses harnessed through chemotherapy. In the first-line metastatic setting, approximately 15% of patients are able to achieve durable responses to cisplatin-based regimens, but prospective identification of such individuals has proven challenging. Cisplatin is the cornerstone of UC-specific chemotherapy regimens and research efforts have sought to identify predictive biomarkers of response to this agent. Analysis of mRNA expression levels of ERCC1, a component of the nucleotide excision repair (NER) pathway, which is utilized to repair the DNA adducts formed by cisplatin, as well as other mediators of DNA repair, was performed in 57 tumors from patients with advanced UC who received either the triplet regimen of PCG or GC [25]. Levels of mRNA transcripts from ERCC1, BRCA1, RRM1, and Caveolin-1 were measured and correlated with multiple clinical parameters, including response to chemotherapy, survival, and time to disease progression. Median survival was found to be significantly improved in patients with low ERCC1 tumor levels (25.47 months vs. 15.4 months, p = 0.03), possibly due to an attenuated ability to repair platinum-mediated DNA damage; however, no association was found between response to chemotherapy and ERCC1 transcript levels. In the neoadjuvant setting, BRCA1 mRNA levels correlate with response to cisplatin chemotherapy: using a cohort of 57 patients treated with neoadjuvant cisplatin-based regimens, BRCA1 mRNA transcripts were measured and classified as low, intermediate, or high [26]. Twenty-four (66%) of 39 patients with low/intermediate BRCA1 transcript levels achieved a major response, defined as pT0/T1 residual disease, while only 4 (22%) of 18 patients with high BRCA1 transcript levels achieved such a response (p = 0.01). Since BRCA1 is involved in DNA repair, lower expression levels may predispose to heightened sensitivity to DNA-damaging agents such as cisplatin, resulting in improved response to platinum agents, a finding that is observed in BRCA1/2 mutant ovarian cancer.

Gene-expression signatures that define response or resistance to chemotherapeutic agents have been investigated in multiple tumor types. A co-expression extrapolation (COXEN) methodology uses gene-expression signatures derived from in vitro drug testing of cell line panels such as the NCI-60 to identify predictive biomarkers of response to standard chemotherapy and targeted agents [27]. These data can then be utilized to predict response to specific therapies. In separate retrospective studies, the COXEN model was able to distinguish between responders and non-responders to both MVAC and GC combination chemotherapy. Consequently, prospective validation of COXEN as a predictive “marker” is planned in an intergroup study led by SWOG. This phase II study will randomize patients with muscle-invasive bladder cancer to either dose-dense MVAC or standard-dose GC as neoadjuvant chemotherapy; the primary endpoint of the study is to validate the COXEN prediction for pathologic response of the primary tumor to each regimen.

**Second-line therapy**

Given the high recurrence rates following platinum-based chemotherapy in metastatic UC, a number of trials have attempted to identify effective agents in the second-line setting. Unfortunately, with the exception of a phase III study of vinflunine, no agent has been shown to display a significant improvement in survival following disease recurrence, with response rates of 15–30% at best in previously treated patient populations and short response durations. No FDA-approved
standard of care currently exists following progression on platinum-based chemotherapy, although the NCCN guidelines suggest the use of pemetrexed or a taxane and to consider participation in a clinical trial when possible.

**Standard agents**

A number of standard chemotherapeutics have been screened in small phase II studies of second-line therapy for metastatic UC. The taxanes, including paclitaxel and docetaxel, stabilize microtubules and prevent depolymerization into tubulin components, leading to mitotic cell cycle arrest. Thirty patients with relapsed or refractory UC following treatment with one cisplatin-containing regimen were treated with docetaxel at 100 mg/m² every three weeks as part of a phase II study in which the primary endpoint was ORR and tolerability [28]. The ORR was 13.3% (95% CI: 3.8–30.7%) and median OS was 9 months (95% CI: 6–12 months). Grade 3/4 neutropenia was observed in 83% of patients and febrile neutropenia in 50%; 60% of patients required a dose reduction for neutropenia. A phase II study of weekly paclitaxel following failure of first-line chemotherapy in the metastatic setting was conducted by Vaughn et al. [29]. Of 31 patients, three patients (10%) achieved a PR, two of whom had responded to prior taxane therapy. The median time to disease progression was 2.2 months, with a median OS of 7.2 months on this study. Common Grade 3 toxicities included anemia (13%) and asthenia (7%). Grade 1/2 neuropathy was observed in 43% and 17% of patients, respectively.

The antifolate analog pemetrexed was tested in multiple phase II studies of patients with metastatic or relapsed UC. Paz-Ares et al. treated patients with relapsed disease and found an ORR of 29% (95% CI: 14–48%) [30]. Two toxic deaths, related to sepsis and renal insufficiency, were observed within the first six patients enrolled onto the trial when using a dose of 600 mg/m², resulting in a dose reduction to 500 mg/m².

A second phase II study conducted by the Hoosier Oncology Group treated 47 patients who had relapsed after prior therapy and found an ORR of 27.7% with 3 CRs and 10 PRs, with a median OS of 9.6 months [31]. Patients received folic acid and B12 supplementation. However, a third study showed an ORR of 8% (95% CI: 0–29%) with 1 PR out of 12 evaluable patients [32]. Although these studies show variable response rates, potentially due to confounding factors such as prior number of therapies and performance status, pemetrexed is a fairly well-tolerated agent that is commonly used in the second-line setting.

**Novel chemotherapeutics and targeted agents**

Tables 27.2 and 27.3 summarize novel and targeted therapeutics investigated in the second-line setting, respectively. The novel Vinca alkaloid vinflunine was approved by the European Medical Agency (EMA) for treatment of metastatic UC following progression after platinum-based therapy based upon a phase III study of 370 patients comparing this agent to best supportive care [33]. Of 357 eligible patients, the median OS was 6.9 months with vinflunine plus best supportive care versus 4.3 months with best supportive care alone \((p = 0.04)\). Furthermore, vinflunine-treated patients exhibited a 23% reduction in the risk of death (HR 0.77; 95% CI: 0.61–0.98). The ORR was 8.3% with treatment versus 0% with best supportive care \((p = 0.002)\). Within the intent to treat population, no statistically significant improvement in OS was noted, likely due to lack of stratification of patients based on pre-treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase/N</th>
<th>RR</th>
<th>OS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixabepilone</td>
<td>II/42</td>
<td>11.9%</td>
<td>8 mo</td>
<td>16 grades 3-4 neutropenia episodes, 1 death from neutropenic sepsis</td>
</tr>
<tr>
<td>Vinflunine</td>
<td>III/357</td>
<td>8.3%</td>
<td>6.9 mo</td>
<td>Compared drug + BSC vs. BSC; no negative drug-related QOL impact</td>
</tr>
<tr>
<td>Eribulin</td>
<td>II/40</td>
<td>38%</td>
<td>9.4 mo</td>
<td>34% RR in patients receiving prior therapies</td>
</tr>
<tr>
<td>(Nab)-paclitaxel</td>
<td>II/47</td>
<td>27.7%</td>
<td>10.8 mo</td>
<td>Phase III trial comparing drug to paclitaxel under way</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>II</td>
<td>Pending</td>
<td>Pending</td>
<td></td>
</tr>
</tbody>
</table>

*Table 27.2 Novel chemotherapeutics in the second-line treatment of metastatic UC.*

\(N\): Number of evaluable patients; RR: response rate; OS: overall survival; BSC: best supportive care; QOL: quality of life
prognostic factors such as performance status and the presence of visceral metastases. Indeed, 10% more patients randomized to the vinflunine plus best supportive care arm had poorer performance status scores. Fifty percent of patients on the vinflunine arm experienced neutropenia, with febrile neutropenia occurring in 6%. Other common Grade 3/4 toxicities included anemia (19%), constipation (16%), and fatigue (19%). Notably, patient quality of life was not significantly impacted by vinflunine therapy as compared to best supportive care. An updated survival analysis performed at a follow-up of 45.4 months found

\[
\text{Table 27.3 Novel targeted therapies in the treatment of metastatic UC.}
\]

<table>
<thead>
<tr>
<th>Anti-angiogenic agents</th>
<th>Phase/N</th>
<th>ORR</th>
<th>OS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab plus GC</td>
<td>II/43</td>
<td>72%</td>
<td>19.1 mo</td>
<td>First-line; 53% PR, 19% CR rates</td>
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<tr>
<td>Bevacizumab plus GC</td>
<td>II/47</td>
<td>49%</td>
<td>13.9 mo</td>
<td>First-line; induction bevacizumab 2 wks prior to therapy</td>
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<tr>
<td>Pazopanib</td>
<td>II/41</td>
<td>51.2%</td>
<td>4.7 mo</td>
<td>Second-line after cisplatin; ORR includes PR+stable disease</td>
</tr>
<tr>
<td>Vandetanib plus D vs. D</td>
<td>11/142</td>
<td>7% vs. 11%</td>
<td>5.85 mo vs. 7.03 mo</td>
<td>Second-line after platinum; diarrhea/rash with vandetanib</td>
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<tr>
<td>Sorafenib</td>
<td>11/142</td>
<td>0%</td>
<td>5.9 mo</td>
<td>First-line; 4 pts with SD; 1 GI perforation</td>
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<tr>
<td>Sunitinib</td>
<td>II/77</td>
<td>A: 7% B: 3%</td>
<td>1A: 7.1 mo vs. B: 6 mo</td>
<td>Second-line after 1-4 prior therapies; intermittent vs. continuous dosing</td>
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<td>Bortezomib</td>
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<td>Everolimus</td>
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\*N: Number of evaluable patients; ORR: objective response rate; OS: overall survival; GC: gemcitabine, cisplatin; GCa: gemcitabine, carboplatin; D: docetaxel; RTK: receptor tyrosine kinase; EGFR: epidermal growth factor receptor; FGFR3: fibroblast growth factor receptor 3; mut: Mutant; PCa: paclitaxel, carboplatin; SAHA: suberoylanilide hydroxamic acid; HDAC: histone deacetylase; PR: partial response; CR: complete response; SD: stable disease; GI: gastrointestinal; FISH: fluorescent in situ hybridization; ECD: extracellular domain; mo: months; wks: weeks; N/A: not applicable

In the phase II sunitinib study, patients in arm A received intermittent dosing and those in arm B received continuous dosing of drug.
a median OS of 6.9 months versus 4.6 months for treatment versus best supportive care, respectively [34]. A multivariate analysis identified vinflunine as being associated with improved survival (HR: 0.719; 95% CI: 0.57–0.906, p = 0.0052), underscoring the persistent effectiveness of the agent in this patient population.

Eribulin, a synthetic analog of the marine macrolide halichondrin B derived from the Japanese sponge Halichondria okadei, inhibits microtubule polymerization. The drug is minimally cleared through the kidney, making it an appealing agent in UC patients, who frequently have pre-existing renal insufficiency. A phase II study of eribulin in 40 patients with advanced UC revealed an ORR of 38% (95% CI: 23–54%) in 37 evaluable patients, with a median PFS of 3.9 months and median OS of 9.4 months. The RR in patients who had received prior perioperative chemotherapy was 34% [35].

Nanoparticle albumin-bound (nab)-paclitaxel has been FDA approved for the first-line treatment of metastatic or relapsed breast cancer in the salvage setting as well as locally advanced or metastatic non-small cell lung cancer (NSCLC) in combination with carboplatin. A multi-center phase II study of nab-paclitaxel was performed in patients with metastatic UC, either in the second-line setting (excluding first-line taxane therapy) or in relapsed disease within one year of receiving perioperative chemotherapy only [36]. Of 47 evaluable patients, 27.7% experienced an objective response, defined as CR plus PR. When stable disease for four months was included, the disease control rate was 49% (95% CI: 36.1–63.9%). Notably, of the 32 patients who had received first-line chemotherapy in the metastatic setting, the disease control rate was 47% vs. 53% in the 15 patients who had received perioperative chemotherapy. Median PFS was 6 months (95% CI: 3.9–8.5 months) and median OS 10.8 months (95% CI: 5.8–16.9 months). Grade 3 or higher toxicities included joint pain (2%), neuropathy (6%), hypertension (6%), fatigue (23%), and disease-related pain (23%). 33.3% of patients required a dose reduction, most commonly due to neuropathy or fatigue, while treatment was stopped in 14.6% of patients due to drug-related toxicities. Finally, PFS and OS were significantly lower in patients with specific pre-treatment prognostic variables, including Hgb < 10, ECOG PS > 1, and time from prior chemotherapy of < 5 months. Based upon these results, a phase III trial sponsored through the National Cancer Institute of Canada Clinical Trials Group is underway, comparing nab-paclitaxel to paclitaxel in the second-line setting.

**Anti-angiogenic therapy**

Preclinical data suggest a potential role for anti-angiogenic therapy in UC: measurement of microvessel density (a reflection of angiogenesis in UC) and VEGF mRNA levels in a cohort of 51 patients who received neoadjuvant MVAC followed by cystectomy revealed that both parameters independently predicted for disease recurrence and metastasis [37]. Furthermore, elevated serum VEGF levels are associated with worse disease-free survival in UC. The Hoosier Oncology Group conducted a phase II study of bevacizumab in combination with GC in the first-line metastatic setting in UC (GU 04-75) [38]. The primary endpoint was a 50% improvement in PFS with the GC-bevacizumab regimen as compared to GC alone. The initial treatment regimen included gemcitabine 1250 mg/m² on days 1 and 8, cisplatin 70 mg/m² on day 1, and bevacizumab 15 mg/kg on day 1 of a 21-day cycle. Chemotherapy was continued for eight cycles while bevacizumab was administered for up to twelve months. Seven out of 17 patients initially enrolled onto the study experienced deep vein thrombosis/pulmonary embolism events, resulting in a dose reduction of gemcitabine to 1000 mg/m² and a subsequent drop in the frequency of such events. Out of 43 evaluable patients, the ORR was 72% (95% CI: 56–85%), including 8 patients (19%) achieving a CR and 23 patients (53%) a PR. Three of the patients who achieved CR underwent consolidation cystectomy with pathologic stages of TisN0, T1N2, and T3N0. The median PFS and OS were 8.2 months (95% CI: 6.8–10.3 months) and 19.1 months (95% CI: 12.4–22.5 months) at a median follow-up of 27.2 months. The most common Grade 3 or higher toxicities observed included neutropenia (35%), DVT/PE (21%, although only 8% incidence was seen after reduction of gemcitabine dosing), and anemia and thrombocytopenia (12% each). Three deaths were related to treatment: sudden cardiac death, CNS hemorrhage, and aortic dissection. Creatinine > 1.1 mg/dL and Hgb > 13 g/dL were associated with reduced OS. When patients were stratified into intermediate and poor risk based upon the presence of visceral metastases and PS > 1, the OS was better in this trial compared to historical survival
rates (intermediate risk: 20.4 months vs. 13.4 months; poor risk: 15.7 months vs. 9.3 months).

A phase II study was performed of gemcitabine and carboplatin plus bevacizumab in cisplatin-ineligible metastatic UC patients, or those patients deemed incurable with cisplatin, in the first-line setting [39]. Eligibility criteria included a creatinine clearance of 30–59 mL/min (Jeliffe), KPS of 60–70%, the presence of visceral metastatic disease, or a single kidney. For this trial, bevacizumab 10 mg/kg was administered two weeks prior to initiation of chemotherapy in an attempt to improve intratumoral chemotherapeutic penetration. Bevacizumab 15 mg/kg was subsequently administered on day 1 of each 21-day cycle and maintained for up to 18 treatments as tolerated in those patients with radiographic response to treatment, while chemotherapy was given for a total of six cycles. Of 47 patients evaluable for outcome, the ORR was 49%, with 3 (6%) patients attaining CR. Median PFS, the primary endpoint of the study, was 6.5 months (95% CI: 4.7–7.8 months). The median OS was 13.9 months (95% CI: 11.9–18.1 months). Although the one-sided lower bound of confidence was 4.77 months, which was less than the predefined PFS of > 4.8 months necessary for additional investigation of this combination, the median OS of 13.9 months is substantially higher than the survival rates for carboplatin-based regimens described above. A 20% rate of Grade 3/4 vascular thrombotic events was noted in this trial, which is comparable to the 17% rate of such events in a cohort of patients treated with gemcitabine plus carboplatin at Memorial Sloan-Kettering Cancer Center, suggesting that the pro-thrombotic effects of platinum therapy may be responsible for the majority of the events observed on study. Additional Grade 3/4 toxicities included myelosuppression, infection, fatigue, and elevated liver function tests. These results suggest a potential role for bevacizumab in improving response rate as well as OS when combined with platinum-based chemotherapy in the metastatic setting. A CALGB multi-center phase III randomized double-blind study of GC vs. GC plus bevacizumab in the first-line metastatic setting has recently completed accrual and is awaiting final analysis.

Pazopanib is an oral multi-targeted tyrosine kinase inhibitor that targets VEGFR-1, -2, and -3, PDGFR alpha and beta, and c-kit. A single-arm phase II study of pazopanib 800 mg once daily was performed in patients with metastatic UC which had progressed after cisplatin-containing therapy [40]. Of 41 patients on study, 21 (51%) had received two or more prior regimens. The percentage of patients deriving clinical benefit, which includes those achieving PR or stable disease, was 51.2 (95% CI: 35.1–67.1%). There were no CRs and 7 PRs (ORR 17.1%). The median PFS and OS were 2.6 months (95% CI: 1.7–3.7 months) and 4.7 months (95% CI: 4.2–7.3 months), respectively. Four (10%) patients were progression-free at 19-month follow-up and remained on drug. The most frequent Grade 3 serious adverse events included fatigue (5%), hypertension (7%), and fistula formation in the GI tract (5%) and vagina (5%). These latter events were observed in the context of shrinking visceral metastases, potentially defining a patient subset at higher risk for such a complication when treated with pazopanib. In this study, interleukin-8 levels were measured at four weeks as a marker of resistance to anti-angiogenic therapy, and elevated levels were found to be associated with worse OS (HR 2.29, 95% CI: 1.35–3.87, \( p = 0.002 \)).

Vandetanib is an oral tyrosine kinase inhibitor targeting VEGFR2, EGFR, and RET. A randomized phase II trial of vandetanib or placebo in combination with docetaxel was performed in metastatic UC patients who had progressed after a platinum-containing regimen [41]. The median PFS in 142 patients was 2.56 months versus 1.52 months in the vandetanib-containing arm versus docetaxel alone, respectively (HR 1.02; 95% CI: 0.69–1.49, \( p = 0.939 \)). The median OS for vandetanib plus docetaxel versus docetaxel was 5.85 months versus 7.03 months (HR 1.21; 95% CI: 0.81–1.79, \( p = 0.347 \)). The ORR was 7% in the combination arm (including one CR) versus 11% with docetaxel alone (\( p = 0.56 \)). Toxicities were more frequent with the addition of vandetanib (66% vs. 44%, \( p = 0.012 \)) and of higher grade (60% vs. 36%, \( p = 0.007 \)). Grade 3/4 diarrhea (7%) and photosensitivity/rash (11%) were only observed with vandetanib plus docetaxel. Thirty-seven patients who progressed on the docetaxel arm crossed over to receive vandetanib plus docetaxel. Thirty-seven patients who progressed on the docetaxel arm crossed over to receive vandetanib plus docetaxel. One patient achieved a PR and five achieved stable disease with single-agent therapy. The Bellmunt prognostic factor model in the second-line setting [24] was validated in this study; additionally, patients who underwent cystectomy were found to have a better OS, possibly related to less aggressive, organ-confined disease at the outset. Overall, single-agent or combination therapy with vandetanib was not found to be effective in platinum-refractory UC, although this trial included a significant number of heavily pre-treated patients.
Sorafenib is a multi-targeted oral receptor tyrosine kinase which inhibits VEGFR1–3, PDGFR, c-KIT, FLT3, and the MAPK pathway. A multi-institutional phase II study of sorafenib dosed at 400 mg once daily in the first-line metastatic setting found no objective responses to therapy [42]. Of 14 evaluable patients, four achieved stable disease by RECIST criteria but only one remained on therapy for more than three months. The median survival was 5.9 months, with time to progression of 1.9 months. Seventeen patients were evaluable for toxicity; Grade 3 or greater adverse events included hand–foot syndrome, abdominal pain, back pain, and bladder infection. One patient experienced a jejunal perforation. Sorafenib 800 mg daily was tested in a phase II ECOG study in metastatic UC patients progressing after one prior line of therapy [43]. No responses were noted in the 22 patients eligible for response evaluation. Three (14%) patients experienced stable disease while fifteen patients experienced progression of disease. Median PFS and OS were 2.2 months and 6.8 months, respectively. Nineteen percent of patients experienced Grade 3 fatigue and hand–foot syndrome.

Sunitinib is a multi-targeted tyrosine kinase inhibitor affecting VEGFR1–3, PDGFR a/b, c-kit, FLT3, and RET. Based upon its efficacy in renal cell carcinoma and preclinical studies showing sensitivity of UC cell lines, a phase II study of sunitinib in advanced UC patients who had progressed after 1–4 prior regimens was conducted [44]. Patients initially received 50 mg daily on a four-week on, two-week off schedule; due to symptoms of tumor progression during the time period off therapy, a continuous daily dosing at 37.5 mg was used. The primary endpoint of the trial was to define response rate, with an ORR of ≥ 20% considered promising. Four PRs were observed, three in the intermittent dosing cohort of 41 evaluable patients (7%) and one in the continuous dosing cohort of 28 evaluable patients (3%). More limited prior chemotherapy and higher KPS were both associated with improved response to sunitinib. The median PFS and OS for intermittent and continuous dosing were 2.4 versus 2.3 months and 7.1 versus 6 months, respectively. Notably, this trial showed evidence that RECIST responses may not be the optimal method of gauging sensitivity to therapy, including an increase in the overall size of tumors but with significant necrotic or hemorrhagic changes, suggesting treatment response.

One patient experienced a cardiac arrest thought to be precipitated by bleeding into hepatic metastases. Fifty-seven patients were observed to have Grade 3/4 toxicities, including fatigue, nausea, and myelosuppression, as well as Grade 3 hematuria in two patients.

In summary, anti-angiogenic agents are an ongoing focus of research in UC and although the biological basis of angiogenesis in urothelial tumors is well known, their influence in the prognosis of this disease has yet to be demonstrated.

Receptor tyrosine kinase inhibitor therapy

Multiple studies have detected overexpression of both EGFR and Her2 in UC. A phase II study of the dual EGFR and Her2 tyrosine kinase inhibitor lapatinib was undertaken in patients with advanced UC following progression on one prior platinum-based regimen [45]. All tumor tissue was stained by IHC for EGFR and Her2 and required ≥ 1+ expression in > 10% of tumor cells above background for enrollment. Patients received 1250 mg orally once daily. The primary endpoint was ORR > 10% and in the intention to treat population, one patient out of 59 experienced a PR, for an ORR of 2%. The clinical benefit of lapatinib, defined as ORR plus stable disease, was 32% (19 patients for ≥ 8 weeks). Notably, 17 of these 19 patients (89%) displayed either 2+ or 3+ EGFR and/or Her2 overexpression. The OS for those patients with overexpression was 30.3 weeks versus 10.6 weeks for those without (p = 0.0001). While the overall response to lapatinib was unimpressive, the majority of responders displayed overexpression of the drug’s targets, EGFR and Her2, suggesting that genetic pre-screening of patients for targeted therapies may result in profound responses.

The EGFR tyrosine kinase inhibitors erlotinib and gefitinib have shown little efficacy in UC. EGFR expression was assessed by IHC in primary and metastatic samples from 20 patients; moderate to strong staining of cell membranes was observed in 65% of metastatic specimens. A phase II SWOG trial investigated monotherapy with gefitinib at a dose of 500 mg daily in UC patients who had progressed on one prior chemotherapy regimen [46]. The trial required IHC staining of EGFR, Her2, and p53, although patients were not pre-selected based upon staining pattern. The median OS was three months, with 81% of patients progressing at first evaluation. Seventeen of 31 enrolled patients had adequate tissue for staining; eight patients...
had 2–3+ EGFR staining, 18% had strong Her2 staining, and 10% had strong staining for both. Common Grade 3/4 toxicities included rash (13%), fatigue (10%), and diarrhea (7%). A phase II CALGB study (90102) of GC plus gefitinib in the first-line metastatic setting was conducted using a daily gefitinib dose of 500 mg followed by maintenance gefitinib in any patient responder [47]. Of 54 evaluable patients, the ORR was 42.6% (95% CI: 29.2–56.8%) with 7 CRs and 16 PRs, median time to progression of 7.4 months (95% CI: 5.6–9.2 months), and OS of 15.1 months (95% CI: 11.1–21.7 months). These response rates and survival times are not substantially different from therapy with GC alone. However, one possible reason for the lack of response to EGFR-targeted drugs may be the absence of activating mutations. In one retrospective study, sequencing of 19 UC bladder tumors revealed no exon 19 deletions or exon 21 L858R mutations, while 2–3+ expression levels by IHC were observed in 10 tumors [48].

The fibroblast growth factor receptor-3 (FGFR3) tyrosine kinase is mutated in an estimated 70% of low-grade bladder tumors, predicting for a more favorable outcome, and 20% of high-grade disease. The majority of such alterations result in modification of a wild-type amino acid residue to a cysteine, leading to aberrant disulfide bond formation and constitutive dimerization of two FGFR3 monomers with downstream activation of multiple pro-mitotic signaling pathways. Several therapies targeting FGFR3 are in development, including monoclonal antibodies and small molecule inhibitors. The tyrosine kinase inhibitor dovitinib was evaluated in a multi-center phase II trial in patients with advanced, progressive UC [49]. Forty-four patients received dovitinib 500 mg daily on a five-day on/two-day off schedule and were classified by FGFR3 mutation status (testing performed using a combination of mass spectrometry and Sanger sequencing). Thirty-one patients were wild-type, 12 were mutant, and one unknown. The ORR for the wild-type and the mutant patients was 0% and 3%, respectively, and the median PFS was 1.8 months and 3 months. The most common side effects included diarrhea, asthenia, and nausea. Given the significant imbalance of patients with wild-type FGFR3 as well as technical challenges with accurate genotyping, it is difficult to define the true efficacy of FGFR3 inhibitory therapy in UC based on these results.

Monoclonal antibody therapy
The combination of paclitaxel, carboplatin, and the anti-Her2/neu monoclonal antibody trastuzumab, was investigated in a phase II clinical trial in the first-line metastatic setting [50]. The rationale for this study included the finding that Her2 overexpression (2–3+) was observed in 28% of a series of 80 bladder cancers managed with cystectomy. In 60 cases, metastatic lesions were also analyzed by IHC: 92% of primary tumors displaying Her2 overexpression had concomitant overexpression in metastatic sites. Overall, 86% of distant metastases and 63% of lymph node metastases harbored overexpression of Her2. These results suggest that Her2 overexpression by IHC occurs in bladder cancer and is preserved in the majority of metastatic deposits arising from overexpressing primary tumors, underscoring the potential utility of anti-Her2 therapy in UC. In this phase II study, eligibility criteria included 2–3+ Her2 overexpression by IHC in primary or metastatic tissue, ERBB2 amplification by fluorescence in situ hybridization (FISH) of 2 or greater from primary or metastatic tissue, or detection of Her2 extracellular domain within serum at a concentration of > 16 ng/mL. The primary endpoint for this study was cardiac toxicity rate, with secondary endpoints including survival, time to progression, and toxicity. Fifty-seven (52%) of 109 patients screened had evidence of Her2 overexpression by one of the three definitions. Of these, 44 patients were treated, with an ORR of 70% (95% CI: 55–83%), including 4 confirmed CRs and 21 confirmed PRs. The median time to progression was 9.3 months with a median OS of 14.1 months. Of the patients with 2+ and 3+ Her2 overexpression by IHC, 67% and 75% exhibited responses, respectively. Eighty-two percent of patients with ERBB2 amplification by FISH responded to treatment versus 67% of patients without evidence of amplification. Two patients died from infectious complications and the rate of febrile neutropenia was 1.4%. Ten (22.7%) of 44 evaluable patients displayed Grade 1–3 cardiac toxicity, including one Grade 3 left ventricular dysfunction. These results suggest that the addition of trastuzumab to triplet chemotherapy is tolerable. Further analysis of the efficacy of trastuzumab therapy in Her2 amplified and/or overexpressing UC is warranted given the high response rates observed in this trial; however, the correlation between genetic amplification and protein overexpression is not as well...
defined in UC as in breast carcinoma, and the optimal method of detection (FISH vs. IHC) is unclear.

A phase II study of the anti-EGFR antibody cetuximab with or without weekly paclitaxel was conducted in patients with advanced UC progressing after one line of chemotherapy. The primary endpoint was two-month PFS for each arm. Nine of 11 patients on the cetuximab arm progressed by eight weeks and, based upon the early stopping rule for this study, this arm closed to further accrual. No objective responses were observed. For the patients who received combination therapy, the ORR was 25%, with 3 CRs and 4 PRs and with a PFS of 16.4 weeks, an improvement from the response rates observed with single-agent paclitaxel [51].

**Epigenetic therapy**

Control of gene expression can occur through multiple processes, including alteration of the packaging of DNA. Specifically, the promoter regions of genes can be tightly packaged into chromatin, denying access to transcription factors. Acetylation of histone particles, the core proteins around which DNA is wound, results in loosening of chromatin and subsequent access to transcription factors. Acetylation is regulated by both histone acetylases and deacetylases. Histone deacetylase (HDAC) inhibitors disrupt transcriptional regulation, resulting in transcriptional upregulation of certain genes, such as TP53 and RB1, and transcriptional suppression of others. Vorinostat (suberoylanilide hydroxamic acid or SAHA) is an HDAC inhibitor that was investigated in the second-line setting for metastatic UC in a phase II trial [52]. Three of 14 patients exhibited stable disease, with eight patients progressing on drug. Median disease-free survival and OS were 1.1 months and 4.3 months, respectively. Five patients experienced Grade 4/5 toxicity while two patients died on study. The study was discontinued due to lack of apparent efficacy.

**Proteasome inhibitor therapy**

The proteasome is a multi-protein intracellular complex that functions to degrade intracellular polypeptides, including cyclins, IκB, and p53, thus regulating the expression of those molecules involved in cell growth and proliferation. Blockade of proteasome function is hypothesized to result in inhibition of anti-apoptotic and pro-mitotic pathways which promote a neoplastic phenotype. Based upon cell line and xenograft experiments indicating sensitivity of UC to the proteasome inhibitor bortezomib, a phase II trial was conducted in patients with advanced UC that had progressed after one prior chemotherapy regimen [53]. No patients achieved an objective response to therapy and the trial was discontinued at an interim analysis. The median time to progression was 1.4 months (95% CI: 1.1–2 months), with a median OS of 5.7 months (95% CI: 3.6–8.4 months). Common Grade 3/4 toxicities included myelosuppression, fatigue, constipation, and sensory neuropathy. Based upon the results of this study, bortezomib monotherapy in the second-line setting was not recommended.

**PI3 kinase (PI3K)/Akt/mTOR targeted therapy**

Alterations within the PI3K/Akt/mTOR pathway are found frequently in bladder cancer. In one study of 97 high-grade bladder tumors, pathway aberrations, consisting of mutations and/or copy number changes, were found in up to 30% [54]. Multiple inhibitors of this pathway are currently undergoing testing in different tumor types, including UC. A phase II study of the mTOR complex 1 inhibitor everolimus in the metastatic second-line setting found that 23 of 45 patients (51%) were progression-free at two months [55]. The median PFS and OS were 2.6 months and 8.3 months, respectively, for all 45 patients. One patient achieved a durable CR, another patient achieved a PR, and 12 patients exhibited stable disease (range of 1–24% reduction in size of target lesions), suggesting that everolimus does have biologic activity in metastatic UC. Whole-genome sequencing of the complete responder detected a nonsense mutation in Tubrous sclerosis 1 (TSC1) and Neurofibromatosis 2 (NF2), tumor suppressor proteins that inhibit activation of mTOR [56]. Loss of both of these proteins is predicted to result in constitutive activation of the mTOR pathway and is likely the genetic basis for sensitivity to everolimus in this patient. Notably, tumors from five patients who exhibited some degree of response were sequenced and four were found to harbor TSC1 alterations; in contrast, only one of nine patients who progressed possessed a TSC1 mutation. The presence of additional co-alterations is hypothesized to modulate the degree of response to everolimus, resulting in the variability of response observed in this study. These results demonstrate the feasibility of using next generation sequencing in the clinical setting in order to identify previously occult biomarkers of drug sensitivity that can aid in the selection of patients most likely to respond to targeted agents.
Useful web links

1 http://www.cancer.gov/cancertopics/pdq/treatment/bladder/HealthProfessional/page9
2 http://www.cancer.gov/clinicaltrials/search/results?protocolsearchid=6393364&vers=2
3 http://www.nccn.org/professionals/physician_gls/I_guidelines.asp#bladder

References


CHAPTER 28

Treatment of poor risk patients

Maria De Santis1 and Matthew D. Galsky2

1 Ludwig Boltzmann Institute for Applied Cancer Research (LBI-ACR VIEnna) and Applied Cancer Research – Institution for Translational Oncology Vienna (ACR-ITR VIEnna) – KFJ Hospital, Vienna, Austria
2 Genitourinary Medical Oncology, Icahn School of Medicine at Mount Sinai, and The Tisch Cancer Institute, New York, NY, USA

KEY POINTS

• Clinical variables can be used to predict the outcome of patients with advanced urothelial cancer.
• Carboplatin-based chemotherapy regimens may be considered for patients ineligible for cisplatin, based on poor renal function or borderline performance status.
• Patients with both poor renal function and borderline performance status or with poor performance status may experience excessive toxicity with conventional combination chemotherapeutic regimens. The optimal treatment approach for such patients remains to be defined.

Introduction

Patients with advanced urothelial cancer (UC) experience heterogeneous outcomes to treatment. While the median survival of patients treated with cisplatin-based combination regimens is approximately 14 months, a small subset of patients are alive at five years while others succumb to much more rapidly progressive disease. Prognostic models have been developed for stratification of clinical trials and for patient counseling. These models have reproducibly demonstrated that both tumor-associated and patient-associated characteristics may be determinants of poor prognosis. Therefore, the term “poor risk”, while not uniformly defined, will be used in the current chapter to refer to patients that suffer from tumors with inherently aggressive biology as well as to patients that are “unfit” to receive standard therapies due to comorbidities and poor performance status.

What is poor risk urothelial cancer?

Clinical prognostic factors – chemotherapy-naïve patients

The development of modern cisplatin-based combination chemotherapy regimens between 1985 and 2000 (particularly, MVAC [methotrexate, vinblastine, doxorubicin, and cisplatin] [1] and GC [gemcitabine and cisplatin] [2]), changed the outlook for patients with advanced UC and such regimens have been adopted as standard first-line therapy. In a pivotal trial, response rates (RR) of 49% versus 46%, time to disease progression of 7.4 months with both regimens, and median survivals of 14.8 versus 13.8 months were achieved with MVAC and GC, respectively. However, patients treated with these regimens demonstrated heterogeneous outcomes, prompting the identification of prognostic models [3, 4].

In a pooled analysis by Bajorin et al. [3], 203 patients with unresectable or metastatic UC treated with MVAC...
in five trials were analyzed for possible prognostic factors. On univariate analysis, several variables were associated with adverse outcomes, including: low hemoglobin level, elevated leukocyte count, elevated platelet count, elevated lactate dehydrogenase level, elevated alkaline phosphatase level, low albumin, low Karnofsky Performance Status (KPS), previous surgery to remove the primary tumor, presence of bone, lung, and/or liver metastases and any visceral metastases. However, on multivariate analysis, only KPS < 80% and the presence of visceral metastases (lungs, liver, bone) remained significant. Combining these variables, three risk groups emerged: zero poor prognostic variables, one poor prognostic variable, and two poor prognostic variables, with significantly different median survivals (33.0, 13.4, and 9.3 months, respectively). The likelihood of surviving five years for risk groups zero, one, and two were 33%, 11%, and 0%, respectively ($p < 0.0001$). Similarly, achieving an objective response to chemotherapy (78%, 74%, and 36%, respectively), or achieving a complete response (CR) (35%, 11%, and 0%, respectively), differed among the three risk groups [3]. These two poor prognostic factors (poor KPS and visceral metastases) were subsequently validated in trials exploring different MVAC schedules [5] and the triplet regimen of cisplatin, paclitaxel, and gemcitabine [6].

**Clinical prognostic factors – cisplatin-ineligible patients**

Patients may also be considered “poor risk” if they are not suitable for standard systemic therapy [10–13]. Despite the lack of adequately designed and powered randomized trials demonstrating that cisplatin-based chemotherapy confers a survival benefit compared with carboplatin-based chemotherapy, a meta-analysis [14] has shown a significantly increased likelihood of achieving an objective response, and complete response, with cisplatin-based therapy. Furthermore, practice guidelines support the notion of the superiority of cisplatin-based, compared with carboplatin-based, regimens in this disease (NCCN guidelines: www.nccn.org). However, a large proportion of patients with metastatic UC are considered “unfit” for cisplatin [15]. In a recent consensus statement based on a survey of experts in the care of patients with genitourinary malignancies, the following criteria were selected to define “unfit”: ECOG PS 2, creatinine clearance less than 60 mL/min, Grade 2 hearing loss, Grade 2 neuropathy, and/or New York Heart Association Class III heart failure [11]. Patients meeting at least one of these criteria were considered “unfit” for cisplatin.

Whether the same prognostic variables identified in studies of patients receiving cisplatin-based chemotherapy applied to “unfit” patients receiving carboplatin-based therapy for advanced UC was previously unknown. This question was addressed in a dataset derived from a randomized phase II/III trial...
comparing two carboplatin-based chemotherapy regimens (gemcitabine + carboplatin (GCa) and methotrexate/carboplatin/vinblastine (M-CAVI)) in patients with UC who were deemed ineligible (“unfit”) for cisplatin-containing chemotherapy due to an ECOG PS of 2 and/or impaired renal function (glomerular filtration rate [GFR] ≤ 60 mL/min) [10]. Notably, the median survival was 8.1 months in the M-CAVI arm and 9.3 months in the GCa arm, considerably shorter than the expected 14–15 months for patients treated with cisplatin-based combination chemotherapy. Using the variables previously defined by Bajorin and colleagues [3] (KPS 80% and presence of visceral metastases), risk groups were constructed, with median overall survival times of 12.0, 9.3, and 5.5 months for patients with zero, one, and two poor prognostic variables, respectively. A subsequent analysis of this dataset further refined this prognostic model with the addition of low baseline hemoglobin [16]. In general, cisplatin-ineligible patients have a poorer prognosis, which may not only be due to treatment with purportedly inferior chemotherapy but also because of the generally poorer performance status of this subset. Whether renal function is an independent predictor of poor outcomes remains unclear. However, in the randomized trial of the EORTC comparing M-CAVI and GCa, patients eligible only due to impaired renal function, but with a good performance status, had a median overall survival of 12 months [10], compared with a median overall survival of 33 months for historical patients treated with MVAC with no poor prognostic factors [3].

Pathologic and molecular prognostic factors
Because all cases of muscle-invasive UC are high-grade, no further prognostic information can be derived from tumor grade in patients with metastatic disease [18]. Some morphological subtypes (e.g., micropapillary, plasmacytoid, etc.) of UC may theoretically be helpful in assessing prognosis; however, most studies evaluating the prognostic impact of histologic subtypes have focused on patients with localized rather than metastatic disease [19–21].

Invasive UC frequently shows alterations in the p53 tumor suppressor gene [22]. In addition, in 60% of UCs chromosome 17p, the location of p53, is lost [23]. The cyclin-dependent kinase (CDK) inhibitors p21 and p16 have also been linked to increased disease recurrence and progression to invasive disease [24]. Esrig et al. have demonstrated a strong correlation between mutant p53 expression and adverse clinical outcomes [25]. The prognostic relevance of p53 has not been consistently observed in additional studies [26, 27], though integration into a larger panel of biomarkers, including p21 and p16, may refine prognostic capabilities [28].

Ki67 is a commonly used marker of cell proliferation and positive immunostaining is considered a good correlate of biological “aggressiveness”. A large multi-center study has confirmed that Ki67 is independently associated with disease recurrence and overall survival in patients with UC [29]. In addition, the overexpression of survivin, which regulates mitotic progression and angiogenesis, has been shown to be associated with an aggressive nature of UC [30]. Again, the vast majority of these analyses have been focused on the impact of these biomarkers and outcomes in patients with clinically localized disease, and whether these biomarkers have a role in prognostication in patients with metastatic disease remains unknown.

Gene-expression profiling has been shown to convey prognostic information in patients with clinically localized bladder cancer, though difficulties with pre-analytic and analytic validity and questions regarding whether such information adds to that derived from standard clinical prognostic models have challenged incorporation into routine clinical care [31–34]. Gene-expression profiling has also been used to predict response to chemotherapy in patients with advanced bladder cancer [33] but the predictive (or potentially prognostic) value of such biomarkers requires additional validation and qualification before clinical use.
Next generation sequencing technologies have recently enabled surveys of the landscape of somatic mutations in urothelial cancer [35, 36]. For example, a study by Iyer et al. identified somatic mutations in 61% of tumors including mutations in the RTK-RAS-RAF and phosphoinositide 3-kinase/AKT/mammalian target of rapamycin pathways and regulators of G1-S cell cycle progression [35]. Such studies have been critical to finding novel drug targets for the treatment of advanced UC, though larger patient series with extended follow-up will be important to determining whether these genomic aberrations comprise distinct tumor subsets with differing prognoses.

### Treatment of poor risk patients

#### Choice of chemotherapy

“Poor risk”, as noted above, may be defined by patient-specific and tumor-specific factors. Thus far, only patient-specific factors routinely impact treatment decisions. Treatment for poor risk bladder cancer patients has not been addressed, *per se*, in specific trials. However, studies have been performed in cisplatin-ineligible patients and these studies, coupled with information derived from studies of cisplatin-eligible patients, have been extrapolated to inform treatment recommendations [2, 3, 10, 37] (see Table 28.1).

Performance status plays a critical role in determining prognosis and suitability for chemotherapy. Patients with PS ≥ 3 have historically been excluded from clinical trials and in such patients the risks of cytotoxic chemotherapy likely outweigh any potential benefits. Even patients with a slightly impaired PS (e.g., ECOG 2) have been excluded from many prior randomized phase III trials. In EORTC 30986 (randomized phase II/III trial of M-CAVI versus GCa for cisplatin-ineligible patients), patients with a PS 2 were eligible and PS 0–1 versus 2 was a stratification factor [10]. In patients with either a PS 2 or impaired renal function, the combination of gemcitabine plus carboplatin is reasonable; however, the optimal therapy for patients with both a PS 2 and impaired renal function remains unclear [10–12]. In the EORTC 30986 study, these patients experienced a very high rate of severe acute toxicity (approximately 25%), a very short median overall survival (5.5 months), and a 20% likelihood of receiving only one chemotherapy cycle. These study results were the basis for the treatment algorithm in the European Association of Urology guidelines, proposing that patients with both PS ≥ 2 and impaired renal function receive single-agent therapy, best supportive care, or are considered for specific clinical trials (EAU guidelines: www.uroweb.com).

In patients progressing after platinum-based chemotherapy, no international treatment standard has been established. In Europe, Australia, New Zealand, Singapore, North Africa, Russia, and some South American countries, vinflunine has been approved in this indication, providing a 23% risk reduction of death (absolute OS benefit of 2.6 months) [37]. In many countries, however, taxanes and

<table>
<thead>
<tr>
<th>Line and treatment</th>
<th>Cisplatin fit/unfit</th>
<th>Adverse prognostic factors</th>
<th>Grouping by number of adverse prognostic factors and OS (months)</th>
</tr>
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<tbody>
<tr>
<td>First-line MVAC</td>
<td>fit</td>
<td>KPS &gt;/= 80%</td>
<td>33.0 13.4 9.3 –</td>
</tr>
<tr>
<td>fit/unfit</td>
<td></td>
<td>PS 0/1 vs 2</td>
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<tr>
<td>First-line M-CAVI/ Carbo/Gem; [16]</td>
<td>unfit</td>
<td>Hb &gt;/= 12 or 13.6</td>
<td>17.4 11.2 8.3 5.5</td>
</tr>
<tr>
<td>unfit</td>
<td></td>
<td>Visceral mets/liver</td>
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<tr>
<td>First-line, M-CAVI/ Carbo/Gem [10]</td>
<td>unfit</td>
<td>KPS/PS 0/1 vs 2</td>
<td>12.0 9.3 5.5 –</td>
</tr>
<tr>
<td>untreated</td>
<td></td>
<td>Visceral mets</td>
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<tr>
<td>Second-line</td>
<td>–</td>
<td>PS 0 vs 1</td>
<td>14.2 7.3 3.8 1.7</td>
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<tr>
<td>Vinflunine [37]</td>
<td></td>
<td>Hb &gt;/= 10 mg/dL</td>
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<td></td>
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<td>Liver mets</td>
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Table 28.1 Outcome of urothelial cancer patients according to prognostic factors.
other single agents or combinations are used based mainly on small, single-arm phase II trials [38]. According to the NCCN (www.nccn.org) and European guidelines (EAU guidelines: www.uroweb.org; ESMO Clinical Practice Guidelines: www.esmo.org), the best choice for patients progressing or relapsing after platinum-based chemotherapy is enrollment on a clinical trial, if available. Of note, poor risk patients in the second-line setting with three adverse prognostic factors were shown to have a median OS of only 1.7 months. For such patients, best supportive care alone is likely the most appropriate choice.

**Practical considerations**

When using chemotherapy in patients with poor prognostic factors, excess myelotoxicity is common. This was demonstrated by the dose-finding study for EORTC 30986 [39]. Based on phase II data obtained in patients with non-small-cell lung cancer [40], the initial dose level of gemcitabine 1000 mg/m² on days 1 and 8 and carboplatin AUC 5 on day 1 every 21 days was selected. This regimen proved not to be feasible in a frail patient population with metastatic UC. Dose-limiting myelotoxicity was observed in six of eight patients, requiring dose reduction or delay in five patients. After reducing the carboplatin dose to AUC 4.5, while maintaining the gemcitabine dose at 1000 mg/m², hematological toxicity was less pronounced and this dose and schedule was utilized in the randomized study [12].

Whether or not poor performance status related to the underlying malignancy, as opposed to that related to comorbidities and age, confers similar prognostic and treatment implications is not entirely clear. A response to chemotherapy could theoretically result in an improvement in the former but not necessarily the latter. Nonetheless, this distinction is often difficult clinically and the literature on prognostic factors does suggest a decreased likelihood of response to chemotherapy in patients with visceral metastases, implying that chemotherapy may not improve symptomatology in such patients. In general, constitutional symptoms such as fatigue, weight loss, anorexia, and failure to thrive are typical signs of advanced or metastatic disease and denote a poor prognosis. In rare cases, however, patients may have constitutional symptoms due to potentially reversible complications of cancer or other comorbidities, such as renal failure due to bilateral ureteral obstruction. In such situations, addressing the cause of the deterioration may improve symptoms, functional status, and increase the likelihood of delivery of standard anticancer therapy. Therefore, recognizing the cause of a patient’s symptoms, rather than assuming that all symptoms in patients with advanced cancer are a direct systemic manifestation of the cancer itself, is important to optimizing care.

Derived from the Greek origin, prognosis means “foreseeing” and is a medical term for predicting an individual’s likely outcome [41]. When applied to large populations, prognostic estimates are often fairly accurate but translation of these estimates to individual patients is much more difficult. Several studies have demonstrated that many physicians are overly optimistic when giving prognostic information. In particular, they tend to overstate how long a patient might live independently from the treatment [42].

**Conclusions**

Poor risk UC might be defined by tumor- and patient-related factors. So far, only the latter (e.g., performance status, renal function, etc.) have been used routinely to guide treatment decisions. Given that UC is largely a disease of the elderly, often accompanied by renal dysfunction and other comorbidities, additional studies are needed to define the optimal treatment for poor risk patients and bridge the gap between treatment efficacy and effectiveness.

**References**


PART VI
Genomics and the current status of urothelial cancer
CHAPTER 29

Molecular events in muscle-invasive bladder cancer development

Jonathan Rosenberg¹, William Y. Kim², Jaegil Kim³, and David J. Kwiatkowski¹,⁴

¹ Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA
² Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
³ Broad Institute of Harvard and MIT, Cambridge, MA, USA
⁴ Brigham and Women’s Hospital, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

KEY POINTS

• Muscle-invasive bladder cancer is characterized by a high rate of both mutations and copy number changes in the genome.
• Mutations and copy number changes in ERBB family genes, \textit{EGFR}, \textit{ERBB2}, and \textit{ERBB3}, as well as \textit{FGFR3} are common, and potentially amenable to therapeutic targeting with kinase inhibitor or antibody approaches.
• Mutations in genes involved in PI3K-mTOR signaling are also common, including \textit{PIK3CA}, \textit{PTEN}, and \textit{TSC1}, and are potentially amenable to therapeutic targeting at multiple levels in this pathway, including PI3K, AKT, and mTOR inhibitors.
• Cell cycle gene mutations and deletion/amplification events are particularly common in bladder cancer, though seen in many cancers. Therapeutics attacking these abnormalities are needed, and CDK inhibitors are an active basic and clinical research area.
• Chromatin regulatory gene mutations are also particularly common in bladder cancer. These mutations have broad effects on gene transcription and are a current area of intense investigation for therapeutic development.
• Viral oncogenesis appears to play a role in a small number of urothelial cancers.
• Distinct RNA-expression subtypes of bladder cancer are recognized, and may correlate with response to chemotherapy.

Introduction

Genetic studies of bladder cancer have a deep and rich history, including the identification of the first oncogene, HRAS, in a bladder carcinoma cell line nearly 30 years ago [1]. Many other studies over the decades have identified a large number of genes that are consistently mutated in muscle-invasive bladder cancer, including \textit{TP53} [2], \textit{TSC1} [3], \textit{FGFR3} [4], \textit{PIK3CA} [5], and \textit{RB1} [6]. In addition, comparative genomic hybridization was used extensively to identify regions of chromosomal gain and loss in bladder cancer with identification of many consistent changes of potential importance in tumor development, including amplification of \textit{PPARG}, \textit{E2F3}, \textit{EGFR}, \textit{CCND1}, and \textit{MDM2}, and loss of \textit{CDKN2A} and \textit{RB1} [7–14]. Indeed, careful examination of the prevalence of specific genetic mutations as well as studies in mouse models have led to the notion that there are two molecular pathways to urothelial tumorigenesis. Activation of HRAS or receptor tyrosine kinase (RTK) pathways appears to result in hyperplasia or low-grade, non-invasive bladder tumors, while loss of tumor suppressor genes such as \textit{TP53} or \textit{RB1} results in high-grade, invasive bladder cancer.

More recently, dramatic advances in the capability and cost of next generation sequencing (NGS) has enabled...
much more detailed studies of bladder cancer somatic genetics than was practical even five years ago [15–17].

**Somatic mutations and copy number variations in muscle-invasive bladder cancer**

Bladder cancer displays a large number and wide variety of DNA alterations as assessed by exome capture next generation sequencing (NGS) and Affymetrix SNP chip hybridization [15]. For example, in The Cancer Genome Atlas (TCGA) data, somatic copy number alterations (SCNAs) were inferred by analysis of Affymetrix SNP chip data, and were very common in these cancers, with an average of 204 segmental SCNAs and 22 genomic rearrangements per cancer analyzed. GISTIC was used to identify statistically significant recurrent focal SCNAs, to identify statistically significant recurrent focal SCNAs, and found 27 amplified and 30 deleted regions (Figure 29.1c). CDKN2A was the most common deletion target, with deletions seen in 47% of samples. Other genes that were likely or definite targets of deletion included: RB1, PDE4D, FAM190A, CREBBP, LRPIB, FOXQ1, WWOX, and KDM6A. Other deletions were too broad to enable identification of a clear single gene target. Genes that were focally amplified included many genes previously identified in bladder cancer as well as some novel findings: E2F3, SOX4, CCND1, EGFR, PPARG, MDM2, ERBB2, YAP1, CCNE1, MYC, ZNF703, FGFR3, MYCL1, and BCL2L1. Other chromosomal regions that contained more than a single gene, but were consistently amplified were a region on chromosome 1q22-23.2 containing PVRL4 and other genes, and a region on chromosome 8q22.3 containing YWHAZ and other genes. These findings are consistent with, but extend, other recent reports [11, 17–20].

Exome sequencing for comprehensive analysis of mutations in bladder cancer was initiated by the Beijing group, and was first reported in 2011 [16]. This initial study was then followed up by a more extensive report [17]. These investigators identified significant levels of mutation in 37 genes, including many well-known bladder cancer genes, and numerous chromatin-remodeling genes: KDM6A, ARID1A, CREBBP, EP300, KMT2A, NCOA1, CHD6, KMT2C [16, 17]. In the TCGA project, we employed whole exome capture NGS on 131 muscle-invasive bladder cancers, followed by MuTect analysis [21], to identify an average of 7.68 mutations per Mb of coding region, which is equivalent to 302 exonic mutations per cancer [15]. This rate is higher than all other cancers sequenced by the TCGA to date, with the exception of lung adenocarcinoma, lung squamous cell carcinoma, and melanoma, which are each somewhat higher but < 10 mutations per Mb [22]. Thirty-two genes showed statistically significant levels of recurrent somatic mutation (Figure 29.1b) by analysis using MutSig 1.5 [23]. MutSig examines the frequency of mutations in each gene with comparison to the size of the gene and other genomic features to enable robust identification of genes with a true high mutation rate. Three genes identified by MutSig were dropped from consideration as their expression was very low or undetectable in these bladder cancers as a whole, suggesting that they were due to chance or artifact, and did not contribute to bladder cancer development [15]. When MutSig analysis was limited to mutations present in the COSMIC database [12], an additional three genes were identified with significant mutation rates: ERBB2, ATM, and CTNNB1. Genes amplified or deleted by copy number analysis, and genes with significant rates of mutation can be grouped into several functional categories with potential therapeutic implications. Other groups have published similar, though more limited findings [24–26].

**Receptor tyrosine kinases**

Receptor tyrosine kinases were commonly subject to both activating mutations and amplification in the TCGA dataset that activate both MAPK signaling and PI3K-mTOR signaling pathways, promoting cell growth and survival [15]. Three members of the ERBB family and FGFR3 were affected. FGFR3 mutation and focal amplification, which are well described events in low-stage and grade urothelial carcinomas [27] are seen in approximately 11% and 3% of high-grade tumors, respectively (Figures 29.1.2, 29.2, and 29.3). For members of the ERBB family, EGFR mutation was not seen but focal amplification was identified in approximately 11%. ERBB2 was found to be mutated in 5% and amplified in 7%, and ERBB3 in 11% and 2% of tumors, respectively. Functional studies of ERBB2 and ERBB3 mutations have confirmed that many of the mutations seen in these genes are activating either in bladder or other cancers, and are also potential therapeutic targets for kinase inhibitor therapy [28, 29]. The amplification events seen in these genes are also potential therapeutic
**Figure 29.1** Mutations, genomic copy number alterations, and relative expression in muscle-invasive bladder cancer [15].

**a)** Mutation rate and type, histologic subtype, smoking status, gender, tumor stage, and cluster type for 131 muscle-invasive bladder cancers.

- **Mutation type:** Syn., Non-syn.
- **Genes with statistically significant levels of mutation (MutSig, FDR < 0.1) and mutation types:**
  - CCND3 (4%)
  - RHOA (4%)
  - ZFP36L1 (5%)
  - HRAS (5%)
  - BTG2 (5%)
  - PAIP1 (5%)
  - FOXA1 (5%)
  - RHOB (5%)
  - CDKN2A (5%)
  - FOXQ1 (5%)
  - TXNIP (7%)
  - KLF5 (8%)
  - TSC1 (8%)
  - NFE2L2 (8%)
  - ELF3 (8%)
  - ERCC2 (12%)
  - FGFR5 (12%)
  - STAG2 (11%)
  - ERBB3 (11%)
  - FBXW7 (10%)
  - RXRA (9%)
  - CDKN1A (14%)
  - EP300 (15%)
  - PIK3CA (20%)
  - KDM6A (24%)
  - ARID1A (25%)
  - MLL2 (27%)
  - TP53 (49%)
  - RB1 (13%)

**b)** Genes with statistically significant levels of mutation (MutSig, FDR < 0.1) and mutation types.
**Figure 29.1 (Continued)**

**c)** Deletions and amplifications for genomic regions with statistically significant focal copy number changes (GISTIC2.0). CN refers to absolute copy number. Note that two amplification peaks (*) contain several genes, any of which could be the target, as opposed to the single gene listed here.

**d)** RNA expression level expressed as fold change from the median (of all samples). RPKM values are shown for selected genes subject to mutation and/or focal copy number change. Tumor samples were grouped into three clusters (red, blue, and green) using consensus NMF clustering. Three samples with no copy number data and two samples with no mutations in these genes were not used in the clustering and are shown in gray. Group A (red) is labeled “focally-amplified” because it is highly enriched in focal SCNAs in several genes, as well as mutations in MLL2. Group B (blue) is labeled “papillary CDKN2A-deficient FGFR3-mutant” because it is enriched in papillary histology, nearly all samples show loss of CDKN2A, and the majority of samples have one or more alterations in FGFR3. Group C (green) is labeled “TP53/cell-cycle-mutant” since there are TP53 mutations in nearly all samples, as well as enrichment with RB1 mutations and amplifications of E2F3 and CCNE1.
Molecular events in MIBC development

targets, although the evidence for effective targeting and patient response is not clear at this time. HRAS and NRAS mutations were seen in 5% and 1% of bladder cancer, respectively (Figure 29.2, bottom left). These are also potential therapeutic targets but more clinical development is required [30].

**PI3-kinase-mTOR pathway genes**

The PI3K-PTEN-AKT-mTOR pathway is an important growth regulatory and apoptosis-evasion pathway in cancer cells, and is known to be altered in bladder cancer [31, 32]. Activating mutations in PIK3CA while more prevalent in lower grade and stage tumors [5] do occur in high-grade tumors as well, seen in 15% in the TCGA dataset, and focal amplification is also seen in 5% [15] (Figure 29.1, 29.2, and 29.3). In addition, several tumor suppressor genes in this pathway are subject to either deletion or mutational inactivation. PTEN was mutated in 3% and deleted in 13% (Figure 29.2). TSCI mutation, usually combined with deletion, was seen in 8% (Figure 29.2). TSC2 mutation was noted in 2%. All of these events are potentially targetable with drugs that inhibit PI3K, AKT, and/or mTOR. Two recent reports highlight the potential clinical value of targeting this pathway in patients with mutations [33, 34]. A sustained clinical response to everolimus (mTORC1 inhibitor) was seen in a single case of a bladder cancer with inactivating mutations in both TSCI and NF2 [33]. Another patient with sustained response to everolimus and pazopanib (FGFR3 kinase inhibitor) had an activating MTOR mutation [34]. Perhaps unfortunately, MTOR mutations are rare in bladder cancer. Effective therapeutic
Figure 29.3 Potential therapeutic targets in bladder cancer. Alterations identified in the TCGA project are analyzed by pathway (a, b), gene (c), and in comparison to other cancer types (d) [15].

(a) Alterations in the PI3K/AKT/MTOR pathway are mutually exclusive. Tumor samples are shown in columns, genes in rows. Only samples with at least one alteration are shown. AKT3 shows elevated expression in 10% of samples, independent of copy number (right panel).

(b) Receptor tyrosine kinases are altered by any of several different mechanisms (amplification, mutation, and fusion) in 45% of TCGA samples.

(c) Recurrent mutations in ERBB2 and ERBB3. The mutations shown in black are either recurrent in the TCGA dataset or are reported in COSMIC. Green: receptor L domain; red: furin-like cysteine-rich region; blue: growth factor receptor domain IV; yellow: tyrosine kinase domain.

(d) ERBB2 amplifications and recurrent mutations in several cancer types analyzed by TCGA. Mutations were counted only when they occurred at positions with recurrent mutations thought to be functional. Note that bladder cancer has more mutations but fewer amplification events in ERBB2 in comparison to breast cancer.
targeting of PI3K in the setting of PIK3CA mutations has proven more difficult, though intense investigation, both clinical and basic, continues at this time. For example, a recent study suggests that combined inhibition of PI3K and mTOR may be effective for PIK3CA mutations in cancer [35].

**Cell cycle gene mutations**

Mutation and copy number events affecting genes involved in cell cycle regulation have been known for many years to be common in bladder cancer [2, 6, 14, 36] and the recent comprehensive genomic analyses of high-grade bladder cancer have confirmed and extended these findings [15–17]. Mutations or deletions in the tumor suppressor protein p53 (gene TP53) are seen in 70% of bladder cancers in the TCGA dataset, with mutations seen in nearly half (49%) (Figures 29.1 and 29.2). p53 responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, and DNA repair.

As noted above, deletions affecting CDKN2A are seen in nearly half of all bladder cancer, and mutations are seen in another 5% (Figures 29.1 and 29.2) [15]. CDKN2A encodes two proteins, p19ARF and p16INK4A, which negatively regulate the p53 and pRB pathways, respectively. The ARF protein functions to sequester Rb, to enable cell cycle progression.

Hence, CDKN2A loss ablates two cell cycle control mechanisms at once.

CCDN1, encoding cyclin D1, and CCNE1, encoding cyclin E1, both of which regulate different cyclin-dependent kinases for cell cycle progression, are locally amplified in 10% and 12% of bladder cancer, respectively (Figures 29.1 and 29.2) [15]. RB1, encoding the retinoblastoma gene product, is a negative regulator of the cell cycle, primarily by binding to transcription factor E2F1. RB1 is subject to both mutation (10%) and deletion (15%) in bladder cancer (Figures 29.1 and 29.2), promoting cell cycle progression.

**Chromatin regulatory gene mutations**

Chromatin regulatory genes, or epigenetic regulators, are a set of genes that regulate the state of chromatin. Some chromatin regulatory genes covalently modify the histone proteins that bind to DNA (known as “writers”), other chromatin regulatory genes remove such covalent modifications (known as “erasers”), and additional chromatin regulatory genes “read” such histone marks to influence the state of transcription of nearby genes. Many of these genes are very large, have many interacting partners, and have more than one activity. Mutations in all three of these categories of chromatin regulators are common in bladder cancer (Figure 29.2) and were first described in great detail by the Beijing group [16, 17].

Mutations in KDM6A, an “eraser” demethylase acting on histone H3 at lysine 27, first described by Gui et al. in 2011 [16], are seen in 20–25% of bladder cancers [15, 16]. Since KDM6A is on the X chromosome, mutation in one copy ablates function in males, and mutation in the active copy in females has similar effects. MLL2, encoding a histone 3 lysine 4 (H3K4) methyltransferase of the trithorax group, is a “writer,” and was mutated in 27% of bladder cancers in the TCGA dataset [15]. ARID1A, encoding a member of the SWI/SNF family, has helicase and ATPase activity, is a “reader,” and was mutated in 25% of bladder cancers [15]. EP300, encoding a histone acetylase, is a “writer” which is also a transcription factor, and was mutated in 15% of bladder cancers [15]. Truncating mutations are significantly enriched over other mutation types in each of these four genes, further arguing in favor of functional significance. Several other chromatin regulatory genes were found to have mutation rates ≥ 10% in bladder cancer, but were not
statistically significant by formal MutSig analysis, due to the large size of these genes: *MLL3, MLL, CREBBP, CHD7*, and *SRCAP* [15]. Many other chromatin regulatory genes were mutated at lower frequency but were also enriched with truncating mutations, suggesting functional importance. Non-silent mutations in chromatin regulatory genes overall were significantly enriched in bladder cancer in comparison with the entire exome, in contrast with all other epithelial cancers studied to date in the TCGA project [15]. Copy number analysis demonstrated that the chromatin regulatory genes *CREBBP* and *NCOR1* were also common targets of deletion in bladder cancer, seen in 13% and 25%, respectively (Figure 29.1).

**Other mutations in bladder cancer**

The TCGA project identified multiple other genes which sustained significant rates of mutation beyond those involved in the four pathways described above [15], and space does not permit a description of all of them. Fifteen of 16 mutations in *ERCC2*, a nucleotide excision repair gene [38], were deleterious missense mutations, suggesting dominant negative effects [39]. *ERCC2*-mutant cancers also had significantly fewer C > G mutations than did *ERCC2* wild-type cancers, and they showed a trend toward a higher overall mutation rate [15]. Seven of 12 mutations in *RXRA* (retinoid X nuclear receptor alpha [40]) occurred at the same amino acid (five S427F; two S427Y) in the ligand-binding domain. Those seven tumors showed increased expression of genes involved in adipogenesis and lipid metabolism, suggesting that the mutations cause constitutive activation of genes involved in these pathways [15].

Eleven tumors (8%) had deleterious missense mutations in the Neh2 domain of *NFE2L2*, a transcription factor that regulates the anti-oxidant program in response to oxidative stress [41]. Those cancers showed a major increase in expression of genes involved in genotoxic metabolism and the reactive oxygen species (ROS) response. In addition, nine tumors had mutations in the redox regulator *TXNIP* [42] (five of them inactivating) and were mutually exclusive of those samples with *NFE2L2* mutations, providing another mechanism for dysregulation of redox metabolism. Predominant inactivating mutations were seen in *STAG2*, an X-linked cohesin complex component required for separation of sister chromatids during cell division [25]. *STAG2* mutations in bladder cancer were recently identified by multiple other groups as well [17, 25, 26, 43]. These studies vary in their results on the association of *STAG2* mutation with prognosis in bladder cancer, and whether loss of *STAG2* is associated with aneuploidy.

**Chromosomal rearrangements and viral integration and expression**

Bladder cancer has been associated with chronic inflammation and *Schistosoma hematobium* infection. A viral etiology for at least a subset of bladder cancers has long been postulated. Viral DNA sequences have been identified on occasion in bladder tumor tissue, but the precise role in pathogenesis has been unclear. Viruses sporadically identified have included human herpesvirus 8, human papillomavirus (HPV), and BK polyomavirus, often in the setting of immunosuppression [44–48]. However, none have proven causative to date [49].

Through the use of next generation sequencing technology, large-scale assessment of viral sequences with tumor specimens is feasible. As part of the TCGA analysis, low-pass, paired-end whole-genome sequencing was performed in 122 urothelial tumors. Seven (6%) of 122 tumors contained viral DNA sequences. Furthermore, five tumors showed viral transcripts by comprehensive RNA sequencing analysis (RNA-Seq). The viral RNA transcripts identified included cytomegalovirus (CMV; *n* = 3), BK polyomavirus (*n* = 1), and HPV16 (*n* = 1). CMV sequences were not integrated into the tumor cell genome. Instead, they appeared to exist as a stable episome. Interestingly, in the HPV16-positive tumor the virus was integrated into *BCL2L1*, along with focal amplification of the locus. This gene is a member of the *BCL2* family, and is involved in regulating apoptosis. HPV16 and HHV6B DNA were identified in two other samples without concomitant RNA expression. Taken together, these data suggest that viral oncogenesis may play a role in the development of selected urothelial carcinomas, although, at least in muscle-invasive urothelial carcinomas, the frequency is low.

In addition to viral sequences, low-pass whole-genome sequencing is able to identify translocations, amplifications, and gene–gene fusions. Several structural aberrations were identified with potential clinical relevance, including recurrent (*n* = 3) *FGFR3–TACC3* fusions due to an intrachromosomal translocation event on chromosome 4. These fusions were recently described
in glioblastoma as well as in bladder cancer, and are predicted to be constitutively activating by leading to auto-dimerization of the protein [17, 50, 51]. In addition to FGFR3, ERBB2 was a translocation target, with four cases showing fusions of ERBB2 with novel partners, with uncertain functional significance [15].

**mRNA, microRNA, and protein expression**

Multiple studies examining the gene expression profiles of bladder cancer have now been published [15, 37, 52–58]. Although there are similarities among most of these studies, there has not been full consensus as to the number or characteristics of expression-based subtypes of bladder cancer. One likely contributor to this variability is the heterogeneity of samples used, in that some reports studied both non-invasive and invasive bladder cancers. Here we focus on the TCGA findings because samples were limited to high-grade, muscle-invasive tumors; RNA-Seq was used to determine expression (which provides greater accuracy and dynamic range); and multi-platform analysis was performed, enabling integration of expression data with copy number, miRNA, and mutation data. Four mRNA expression subtypes of bladder cancer were identified in the TCGA dataset (termed Clusters I–IV) (Figure 29.4); while parallel analysis of miRNA data suggested five independent miRNA subtypes. Cluster I was highly enriched for cancers with FGFR3 mutation, amplification, high expression, and/or FGFR3–TACC3 fusion. Cluster I was also enriched for cancers with papillary morphology (Figure 29.4 top). These observations support the concept that FGFR3 is a fairly consistent driver gene in Cluster 1, and suggest that this subset of muscle-invasive bladder cancers may have arisen out of non-invasive cancers that progressed. STAG2 mutations were also enriched in mRNA Cluster I. However, no other gene mutations were significantly correlated with mRNA subtype, suggesting that factors other than mutation are determinants of RNA subtype.

Both Clusters I and II had high levels of ERBB2 mRNA expression, which was confirmed by analysis of ERBB2 protein expression using RPPA (reverse phase protein lysate microarray) (Figure 29.4 bottom). Clusters I and II were also notable for elevated expression of estrogen receptor beta (ESR2) signaling. In contrast, Clusters III and IV showed low levels of Her2 and ESR2 expression but expressed high levels of epithelial lineage genes such as KRT14, KRT5, KRT6, and EGFR (Figure 29.4 middle), which are known to be expressed in the basal layer of urothelial cells. In addition, Clusters III and IV expressed relatively low levels of markers of urothelial differentiation, such as UPK3A and CDH1 (E-cadherin). CDH1 is lost in cells undergoing epithelial to mesenchymal transition (EMT). Interestingly, Clusters III and IV also expressed relatively low levels of the miR-200 family of miRNAs (Figure 29.4 middle bottom), which are well known to regulate EMT. The RNA subtypes did not appear to have significant differences in survival, although the power of this analysis is reduced due to the heterogeneity of the cases collected, the relatively short follow-up at the time of this writing, and the limited number of events among these 131 bladder cancer patients.

Recently, Choi et al. have reported that they identified three molecular subtypes of MIBC that resembled molecular subtypes of breast cancer: basal, luminal, and p53-like [37]. Further, they reported that p53-like cancers were resistant to neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin chemotherapy. If validated, these observations are very important in the selection of treatment approaches for bladder cancer.

**Pathway analysis/therapeutic targets**

Multiple cancer pathways have been implicated in the development of bladder cancer. Low-grade, non-invasive tumors tend to be characterized by FGFR3, PIK3CA, and RAS activating mutations, while muscle-invasive and metastatic tumors frequently possess mutation of the retinoblastoma and p53 proteins [5, 13, 31, 59, 60].

One consistent theme throughout all of the genomic characterization of bladder cancer is that the most commonly altered pathway is the p53/Rb cell cycle pathway. It seems to be mutated by one mechanism or another in the vast majority of tumors studied (93% in the TCGA) (Figure 29.2). These alterations most commonly affect TP53 and CDKN2A, resulting in inactivation of the p53 and/or Rb components of the cell cycle apparatus. Alterations were also commonly noted in several potentially druggable oncogenes, including PIK3CA, ERBB2, ERBB3, and FGFR3 (Figures 29.2 and 29.3). While targeting these alterations has not yet been shown to have clinical benefit in bladder cancer, studies focused
on subject cohorts selected for specific mutations have yet to be performed. Interestingly, we observed that there is significant mutual exclusivity among the alterations within each of the PI3K/AKT/MTOR and RTK/RAS pathways, meaning that alterations are typically seen in only a single pathway gene per tumor (Figure 29.3). Clinical evaluation of agents targeted at alterations in these pathways in genotype-selected subgroups of bladder cancers will hopefully yield significant improvements in outcomes.

**Figure 29.4** mRNA expression clusters in bladder cancer, and correlation with histology, mutations, and miRNA expression. Integrated analysis of mRNA, miRNA and protein datasets led to identification of distinct subsets of urothelial carcinoma [15]. Papillary histology, FGFR3 alterations, FGFR3 expression, and reduced FGFR3-related miRNA (miR-99a-5p, miR-100-5p) expression are enriched in Cluster I. Expression of epithelial lineage genes and stem/progenitor cytokeratins are high in Cluster III, many of which have some degree of squamous histology. Luminal breast markers, urothelial differentiation factors, and miR-200s are enriched in Clusters I and II. **ERBB2** mutation and estrogen receptor beta (**ESR2**) expression are also enriched in Clusters I and II.
Summary

Many groups have contributed to a well-developed picture of the genomic alterations associated with urothelial carcinoma. Several comprehensive genomic analyses have allowed for the integration of mutations with other features such as copy number alterations, miRNAs, and mRNA subtypes. Arguably the most important finding to come from these projects is the recognition that urothelial carcinomas have a high rate of potentially clinically actionable genomic alterations, for which targeted therapeutics are either already FDA-approved for other cancer types or are in late-stage clinical development. Given the relative paucity of therapeutic advances in the treatment of bladder cancer over the past two to three decades, the future appears bright for thoughtful, biomarker-driven exploration of targeted therapies in this underserved disease.

References


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CHAPTER 30

Cancer stem cells and intrinsic subtypes in bladder cancer

Keith Syson Chan and David J. McConkey

1 Department of Urology, Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA
2 Departments of Urology and Cancer Biology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

KEY POINTS

• Like the normal urothelium, bladder cancers contain stem cells that can regenerate the tumor after injury (surgery or therapy).
• These stem cells express biomarkers that are shared by basal cells within the normal urothelium, including KRT5, KRT14, and CD44.
• Muscle-invasive bladder cancers can be grouped into intrinsic basal and luminal subtypes similar to the ones found in breast cancer.
• Basal bladder cancers contain high expression of stem cell and EMT biomarkers, and they have a propensity to produce invasive disease.
• Basal bladder cancers are regulated by STAT3 and p63, transcription factors that also control the fate of normal urothelial stem cells.
• Luminal bladder cancers are enriched with biomarkers that are shared by the umbrella cells of the normal urothelium and are controlled by PPARγ, a transcription factor that has been implicated in urothelial terminal differentiation.
• The existence of bladder cancer stem cells and intrinsic subtypes has important implications for prognostication and clinical management with conventional and biological therapies.

Introduction

Bladder cancers are characterized by clinical and pathological heterogeneity. Non-muscle-invasive cancers are rarely life threatening but are prone to repetitive recurrences, and a subset of them progress to become muscle-invasive and potentially life threatening. It is currently difficult to accurately predict which tumors are at highest risk for progression beyond the information provided by T stage, grade, and whether there is associated carcinoma in situ. A significant fraction of muscle-invasive cancers (at least 50%) can probably be cured by radical cystectomy (RC) alone, while the remaining patients require systemic chemotherapy integrated with either RC or radiotherapy.

There are a number of clinical high-risk features that can be used to help identify this potentially lethal subset of tumors. Despite this, there is an inherent understaging of muscle-invasive cancers that occurs in up to 40–50% of patients, mandating that we develop the tools to accurately distinguish biologically aggressive from more indolent muscle-invasive cancers. Fortunately, several recently completed large-scale genomics projects, breakthroughs in the isolation of cancer stem cells, and our understanding of the origins of bladder cancer are shedding light on this important void and promise to change this situation. Biomarkers have already emerged from these projects that show promise to improve prognostication and selection of targeted therapies. In this chapter we will review this
progress and conclude with our thoughts about the immediate and long-term implications of these findings.

**Stem cells**

Stem cells are the most primitive cells within an organism with the unique capacity to: (1) self-renew for the maintenance of a stem cell pool, and (2) undergo multi-lineage differentiation to form more mature and specialized cells. There are several types of stem cells with increasingly limited differentiation potential: totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells [1]. Totipotent stem cells can give rise to and specialize in any cell type in an organism. The zygote is the earliest possible totipotent stem cell that can fully develop into all three germ cell layers: ectoderm, mesoderm, and endoderm, and into extraembryonic tissues [1, 2]. Embryonic stem (ES) cell lines that are typically derived from the inner cell mass or epiblast of the blastocyst [3] are pluripotent stem cells. Unlike totipotent stem cells, pluripotent ES cells lack the ability to form extraembryonic tissues but can fully develop into all three germ layers [3]. Multipotent stem cells are limited in their potential to give rise to cells in multi-lineages, examples of which are adult tissue stem cells such as hematopoietic stem cells, bulge stem cells in skin, and intestinal stem cells. Hematopoietic stem cells can give rise to multiple downstream lineages such as the myeloid (monocytes, macrophages, neutrophils, dendritic cells, etc.) and lymphoid lineage (T, B, and NK cells) that eventually form all mature blood cells in the system [4]. Bulge stem cells in skin are multipotent and can form multiple lineages, including the epidermis, hair follicle, and sebaceous gland [5]. Unipotent cells are able to give rise only to a single lineage. For instance, basal stem cells in the epidermis can give rise only to mature cells within the epidermal compartment [5]. These classical developmental stem cell studies support a unidirectional hierarchical model, where primitive stem cells gradually lose their potency while differentiating into mature lineages that carry out the specialized functions of a particular tissue type.

Nevertheless, Yamanaka and colleagues revolutionized stem cell biology by demonstrating that four transcription factors (Oct4, Sox2, Myc, and Klf4) can induce pluripotent stem cells from terminally differentiated or adult somatic cells – a process known as reprogramming – while the cellular products are known as induced pluripotent stem cells (iPS cells) [6]. This finding opened up an active and controversial research area, and studies are underway to determine whether terminally differentiated cells can de-differentiate into more primitive stem cells, in physiological or disease states (including cancer), when they are exposed to the appropriate environmental stimuli, genetic, and/or epigenetic alterations.

**Bladder cancer stem cells: implications for cancer heterogeneity**

**Normal bladder urothelial stem cells**

The bladder urothelium (mucosa) is histologically classified as transitional epithelium and is comprised of at least three to six layers of basal, intermediate, and superficial/umbrella cells [1, 7–8]. The adult human urothelium is a slow-cycling epithelial tissue that undergoes renewal every three to six months under normal homeostasis [1, 8]. However, upon pathological (e.g. bacterial-induced) or chemically induced (e.g. cyclophosphamide) injury [9], basal cells of the murine urothelium rapidly proliferate and the urothelium is completely regenerated within 72 hours [10]. In a study where rat urothelium was exposed to protamine sulphate, which induced restricted abrasion of umbrella cells while sparing the intermediate cell layer, the intermediate cells possessed the regenerative capacity to form a functionally intact urothelium within ten days [11]. The urothelium also displays properties of plasticity, where it can undergo metaplastic transdifferentiation. For example, squamous metaplasia of the trigonal region of the bladder is commonly seen [12], as is metaplastic transformation in cystitis glandularis [13]. These characteristics of a slow-cycling urothelium with the capacity for rapid regeneration upon insult, while possessing a unique capacity to transdifferentiate into other cell types in response to pathological conditions support the existence of normal adult stem cells within the bladder urothelium. Indeed, studies using the classical pulse-chase labeling approach to locate urothelial stem cells have been performed in the urinary bladder [14–16]. In this label-retaining assay, cells are exposed to labeled or synthetic nucleosides such as 3H-thymidine and 5-bromo-2’-deoxyuridine (BrdU), respectively. Cells that are replicating and synthesizing new DNA (during S phase) incorporate these nucleosides. Repeated nucleoside incorporation ensures the labeling of all cell populations, including stem cells. Upon subsequent
These basal LRCs also express β4 integrin and were found to be highly clonogenic in an in vitro stem cell assay [15]. On the other hand, another study repeated the localization of LRC in the rat bladder using a different synthetic nucleoside 5-ethynl-2-deoxyuridine (EdU) [16]. The authors demonstrated that LRC distribution is random, with no clear evidence of preferential labeling to basal cells [16], in contrast to the previous reports [15]. These contrasting results are likely attributable to differences in labeling efficiency due to the slow-cycling properties of the normal urothelium, as well as the length of the chase period, and further investigation is therefore warranted to clarify this discrepancy. Lineage-tracing experiments in mice have verified that basal cells can give rise to all layers of mouse urothelium [18], supporting a basal cell origin of stem cells. In specimens of human urothelium, another study measured naturally occurring mitochondrial DNA mutations as markers of clonal expansion. The results revealed that patches of clonally related urothelial cells from the basal layer were always connected to patches of intermediate and umbrella cells [19]. Collectively, the bulk of the data from rodents and human tissues strongly suggest that urothelial stem cells are basal in origin.

**Bladder urothelial cancer stem cells**

It is perhaps not surprising that the cancers that arise from hierarchical tissues such as the urothelium would retain parts of the cellular hierarchical organization present in normal organs. One model that can explain this cancer hierarchy and heterogeneity posits the existence of functional cancer stem cells that: (1) are enriched for tumor-initiating potential, (2) are equipped to undergo self-renewal, and (3) can differentiate to generate cellular heterogeneity of a tumor [20]. These cancer stem cells do not necessarily arise from normal stem cells, but perhaps, like the example of the iPS cells discussed above, they may also be derived from differentiated progenies by acquiring the functional properties of cancer stem cells via genetic or epigenetic alterations (this will be discussed in a later section).

**Cell surface markers that are used to isolate cancer stem cells**

The most common method for isolation of cancer stem cells utilizes cell surface staining and fluorescence-activated cell sorting (FACS) to fractionate cancer cell subpopulations, followed by interrogation using in vitro sphere-forming assays and in vivo xenotransplantation to verify their functional properties. Monoclonal antibodies that preferentially bind to the basal (MoAb 21.48) or superficial (MoAb 5.48) layer of the normal urothelium have been generated [21], and their preferential binding in urothelial carcinomas has been investigated. A high degree of MoAb 21.48 (basal) staining was observed in high-grade UC specimens, whereas MoAb 5.48, an antibody with higher specificity for superficial cells, showed more diffuse staining in well-differentiated tumors [21]. These early studies were likely the first to examine urothelial cancer development in parallel with normal urothelial developmental biology, and they support the notion that the cellular heterogeneity and hierarchical tissue organization seen in the normal urothelium are conserved in tumors. These findings were recently validated by several groups analyzing primary bladder cancer specimens [22–24], xenografts from passaged cancers [26], or established bladder cancer cell lines [27]; all presented strong evidence for a basal origin of cancer stem cells. In brief, using primary or early in vivo passage tumors cells from bladder cancer patients, antibodies specific for CD44, which is expressed in normal urothelial basal and intermediate cells, were used to isolate cancer cells that were at least 10–200 fold enriched for tumor-initiating cells and could be serially passaged in immunocompromised mice to recapitulate the heterogeneity of original tumors [22, 23]. In another study, 67L-kDa laminin receptor (67LR), a basal cell marker expressed at the tumor–stroma interface and upregulated in 80% of high-grade invasive urothelial carcinomas [26], and another marker CEACAM6 (CD66C) were used to isolate tumor-initiating cells in bladder cancer xenografts. 67LR bright cells and CEACAM6 negative cells were demonstrated to be the tumor-initiating cells [26]. Another study utilized an antibody specific for a CD44 splice variant (CD44v6) to show that a CD44v6⁺ EMA⁻ tumor cell subpopulation contained bladder cancer stem cells using an in vitro colony formation assay [28].
Cancer stem cell status sub-classifies bladder cancers into basal, intermediate, and differentiated subtypes

Additional findings added to the complexity of this bladder cancer stem cell model. Subsequent studies revealed that 58% of tumors do not express the basal cell marker CD44 [22], but these CD44-negative tumors still have cancer stem cells that were marked by a different combination of cell surface markers (CD90−/CD44−/CD49f+) [1, 24] or cytokeratin markers (CK14/CK5/CK20). CK14 was identified as the primitive cancer stem cell marker upstream to CK5 and CK20 [1, 24, 25], while basal cells preferentially express CK5 (which co-localizes with cell surface marker CD44), and CK20 expression is restricted to terminally differentiated cells [22]. CD90 was identified as a stem cell marker that is co-expressed with CK14, and loss of CD49f was identified as another terminal differentiation marker [1, 24]. With these marker combinations, urothelial carcinomas were risk-stratified into three biological subtypes on the basis of their differentiation status: basal, intermediate, and differentiated subtypes [1, 24]. The most primitive tumor cell subpopulation within each tumor subtype contained cancer stem cell characteristics [1, 24]. Importantly, the most primitive basal subtype correlated with worse clinical outcomes, and KRT14 expression alone correlated significantly with poor patient survival in three independent datasets [1, 24]. KRT14 gene expression was a strong predictor of worse survival, independent of tumor stage and grade [1, 24]. These findings provided the biological basis for the subsequent identification of the “intrinsic subtypes” of bladder cancer by The Cancer Genome Atlas Project and other groups, which will be introduced below [29–31].

Intrinsic subtypes of bladder cancer

The fact that cancers are heterogeneous has been appreciated for decades. However, visualizing this heterogeneity in primary human tumors at high resolution (at the molecular level) only became possible with the development of methods to visualize mRNA expression patterns at the whole genome level. Early work confirmed that mRNA expression profiling could be used to distinguish different hematological malignancies [32], and it was soon appreciated that molecular subtypes could be identified within B cell lymphomas that contained features characteristic of different stages of normal B cell differentiation [33]. However, the most influential studies were performed in cohorts of human breast cancers, where at least five different “intrinsic subtypes” were identified (basal/triple negative, claudin6, Her2+, luminal A, and luminal B) [34, 35] that have since been demonstrated to behave clinically as distinct disease entities [36] and the survival for certain subtypes (e.g. Her2+) has been drastically improved following the introduction of targeted therapies. As had been observed in lymphomas, it was recognized that the intrinsic subtypes of breast cancer possessed molecular features that were shared by normal breast epithelial stem cells and downstream differentiated cells at different lineages (e.g. basal and luminal) at different stages of differentiation [37].

Several earlier studies also used gene expression profiling to visualize bladder cancer heterogeneity. Gene expression profiling easily distinguished NMIBCs from MIBCs [38–42], and more recently the LUND group used gene expression profiling to identify molecular subtypes within NMIBCs and MIBCs that shared molecular markers (including KRT5, KRT14, and KRT20) with the basal and superficial layers of the normal urothelium [43, 44]. Additional strong experimental support for the existence of intrinsic subtypes of bladder cancer has come from whole genome RNA expression analyses performed by The Cancer Genome Atlas (TCGA) and two other groups [29–31]. All three groups concluded that the intrinsic subtypes of MIBC closely resemble the basal and luminal subtypes of breast cancer (Figure 30.1). Consistent with the previous conclusions [24, 43], basal tumors were characterized by advanced stage and metastatic disease at presentation and were associated with poor clinical outcomes [29, 30] and with enrichment in cancer stem cell signatures indicative of their biological involvement [30]. Luminal tumors were enriched with activating FGFR3 mutations and translocations [29, 31], suggesting that they may progress from NMIBCs [43] and therefore may be vulnerable to FGFR-directed therapies [45].

Clinical trials demonstrated that the intrinsic subtypes of breast cancer are differentially sensitive to neoadjuvant chemotherapy (NAC). Fractions of basal, Her2+, and luminal B tumors, characterized by high proliferation rates, are chemosensitive, whereas the luminal A tumors that are characterized by low proliferation rates are resistant to NAC [36, 46–48]. The same situation appears to exist in bladder cancer, where NAC response rates were
very low in the subtype that is most similar to luminal A breast cancers (MD Anderson “p53-like” tumors, which are similar to TCGA’s “cluster II”) [29, 31]. Nonetheless, depending on the classification method (Figure 30.1), as many as 50% of these “p53-like” tumors can be grouped as basal cancers. While immune infiltration has been implicated in NAC sensitivity in breast cancer [48], a subset of basal MIBCs also contains signatures characteristic of immune infiltration [29]. It remains to be determined whether the immune system plays a causal role in chemotherapy-induced tumor regression and will require studies in preclinical mouse models.

**Transcriptional control in the intrinsic subtypes of bladder cancer**

The similarities between the normal urothelium and basal and luminal MIBCs extend to the transcription factors that control them. Studies in the former have implicated the epidermal growth factor receptor (EGFR) and downstream signaling through STAT3 and p63 in the control of basal cell biology, whereas peroxisome proliferator activator receptor-gamma (PPARγ) drives terminal differentiation [1]. Interestingly, expression of the EGFR, STAT3, and TP63 are also enriched in basal MIBCs [49], whereas PPARγ amplification and overexpression are enriched in luminal MIBCs [29, 31, 50], suggesting that they may still be under the control of the same transcription factors. The evidence that supports this idea will be summarized next.

**Transcription factors in basal bladder cancers**

STAT3 signaling has been implicated in a variety of different cancers, but its potential role in bladder cancer has not been investigated until recently. Ho et al. used the KRT5 promoter to drive expression of a constitutively active form of STAT3 in the basal layer of the normal urothelium in mice [51]. Subsequent exposure to the bladder-selective chemical carcinogen N-butyl-N-(4-Hydroxybutyl) nitrosamine (BBN) led to direct progression to carcinoma in situ (CIS) and subsequent invasive bladder urothelial carcinoma (UC) development, bypassing the non-invasive tumor stage [51]. Interestingly, STAT3-driven CIS and invasive UCs were highly enriched with CK14+ cancer stem cells [51], one of the phenotypic features for basal bladder cancers [1, 24, 29–31].

![Figure 30.1 Biological and clinical features of the intrinsic subtypes of bladder cancer. Muscle-invasive bladder cancers can be grouped into “basal” and “luminal” subtypes on the basis of their differentiation status. The basal subtype can be further divided into “EMT-like” (TCGA Cluster IV) and “stem-like” (TCGA Cluster III/squamous) based on differential expression of basal cytokeratins (KRT5, KRT6, KRT14, which are expressed at low levels in the “EMT-like” tumors) and EMT transcription factors (ZEB1, ZEB2, which are expressed at high levels in the “EMT-like” tumors). Clinically, basal tumors are associated with advanced and metastatic disease at presentation and poor survival. The luminal subtype can also be subdivided into “luminal” (TCGA Cluster I) and “p53-like” (TCGA Cluster II) based on differential expression of proliferation and cell cycle biomarkers. Clinically, luminal tumors are enriched with papillary histopathological features and longer survival. However, depending on the classification methodology (MDA, UNC and tumor differentiation classifications), as many as 50% of “p53-like” cancers can be grouped into ‘basal’ MIBC subtype and are resistant to neoadjuvant MVAC chemotherapy.](image-url)
Analysis of the gene expression signature that is present in primary basal MIBCs supports the idea that STAT3 activation is a central feature of their biology. Using the “upstream regulators” function within Ingenuity Pathway Analysis (IPA) to identify the transcription factors that were activated or inhibited within each MIBC intrinsic subtype, the analysis identified STAT3 as the top activated transcription factor in basal tumors [29]. To explore this relationship further, STAT3 expression was knocked down in the basal (squamous) cell line ScaBER and whole genome mRNA expression profiling was used to visualize the changes in gene expression that occurred. Many canonical basal biomarkers (CDH3, KRT6, KRT14, TP63) were strongly downregulated (W. Choi, unpublished observations), confirming that their expression was controlled by active STAT3.

Another transcription factor that plays a major role in basal cancer biology is the p53 family member, p63. The protein localizes to the basal layer of the normal urothelium [15], and studies in knockout animals demonstrated that it is required for formation and/or maintenance of the urothelial basal layer [52]. Early studies using mixed cohorts of NMIBCs and MIBCs concluded that p63 was downregulated in MIBCs, but more recent studies indicate that TP63 expression (and in particular expression of the ΔNp63α isoform) is actually enriched in basal tumors [29, 52, 53]. To more directly examine p63’s role in promoting basal gene expression, p63 was knocked down in human UM-UC14 MIBC cells and gene expression profiling was used to create an active p63 gene expression “signature”. Using gene set enrichment analyses (GSEA), we confirmed that this active p63 signature was significantly enriched in primary basal MIBCs [29]. Furthermore, p63 knockdown led to downregulation of basal/stem cell biomarkers (KRT5, KRT14, CDH3, CD44) in most human bladder cancer cell lines in vitro, and chromatin immunoprecipitation (ChIP) confirmed that p63 interacts directly with the KRT5 promoter (W. Choi, M. Tran, unpublished observations). The fact that STAT3 knockdown reduced p63 expression suggests that STAT3 acts upstream of p63 to control basal cancer biology.

Transcription factors in luminal bladder cancers

Luminal breast cancers are distinguished from basal and Her2+ tumors because they are estrogen receptor (ER)-positive and respond to selective estrogen receptor modulators (SERMs) [36]. Similarly, the luminal subtypes of MIBC (equivalent to Cluster I and II in TCGA [31] and differentiated subtype [1, 24]) are also ER-positive [29–31], and IPA upstream regulator analyses indicate that their gene expression patterns are enriched with ER pathway activation [29]. The idea that some human bladder cancers might be dependent on ER signaling for proliferation and/or survival is supported by strong pre-clinical data [54–56], but the notion that estrogen has tumor-promoting effects is paradoxical and must be reconciled with the fact that the bladder cancer incidence is 2–3-fold higher in men than in women, and women may be more prone to basal tumors [30]. It is possible that, as is true with breast cancer, the ER has chemo-preventative effects in some contexts and tumor-promoting effects in others. Whether or not this proves to be true will require additional experimentation.

Another transcription factor that plays a central role in luminal MIBCs is PPARγ, parallel to its biological role in modulating urothelial cellular differentiation [1]. Luminal tumors express high levels of PPARγ, and a large fraction of them also contain PPARγ gene amplification [29–31]. A gene signature of PPARγ activation was generated by exposing two human bladder cancer cell lines to the PPARγ-selective agonist rosiglitazone, and subsequent GSEA confirmed that it was strongly enriched in luminal MIBCs [29]. Furthermore, canonical luminal MIBC biomarkers (KRT20 and the UPKs) were strongly induced by rosiglitazone in both cell lines [29], and chromatin immunoprecipitation (ChIP) confirmed that PPARγ binds directly to the KRT20 promoter in human bladder cancer cell lines and primary luminal MIBCs from patients (M. Tran, unpublished observations). These observations harken back to the hierarchy of differentiation within the normal urothelium, where PPARγ has been implicated [1, 57, 58].

Finally, luminal MIBCs and breast cancers are both characterized by GATA3 expression [29–31]. The transcription factor plays a well-established role in luminal differentiation in the normal breast epithelium, and in breast cancers, GATA3 expression correlates with differentiation, with downregulation observed in high-grade cancers [59]. Reintroduction of GATA3 into GATA3-negative, undifferentiated human breast cancer cells caused differentiation and blocked invasion and metastasis in mouse models [59]. Additional efforts in pre-clinical mouse models are required to define GATA3’s effects in bladder cancer.

Guided by previous findings from breast cancer subtypes, we are highly enthusiastic that further
elucidation of the functional roles for these important transcription factor networks in regulating basal and luminal (or differentiated) subtypes of bladder cancer will likely expedite the introduction of new targeted therapies into the clinic to improve patient survival.

**Role of EMT in “stemness” and metastasis**

As discussed above, there is evidence that basal and luminal cancers may arise from phenotypically distinct cancer stem cells. However, recent studies of “stemness” in pre-clinical models of human breast cancer have concluded that cancer stem cells may be generated from phenotypic differentiated cancer cells via induction of p63 and epithelial-to-mesenchymal transition (EMT) to induce “de-differentiation” [27, 60–63]. The latter is a process that plays central roles in embryogenesis and wound healing, where epithelial cells display reduced homotypic adhesion and cell polarity with increased invasive and migratory capacity [64, 65]. EMT is controlled by a group of transcription factors (including ZEB1/2, SNAI/Snail, SNAI2/Slug, and TWIST) that directly inhibit the expression of the homotypic adhesion molecule, E-cadherin, thereby blocking its expression [64, 65]. The miR-200 family and miR-205 micro RNAs inhibit EMT by directly suppressing the expression of ZEB1 and ZEB2 [66].

Pre-clinical studies established that EMT plays important roles in cancer “stemness” and metastasis. Studies performed over a decade ago revealed that metastatic breast cancer cells overexpressed TWIST and that TWIST-induced EMT was required for metastasis [63]. Overexpression of TWIST was also sufficient to induce phenotypic and functional “stemness” in normal breast epithelial cells and human breast cancer cells [27]. These pre-clinical findings seemed inconsistent with the observation that solid tumor metastases tend to look just as “epithelial” as matched primary tumors do. However, this paradox has been addressed by more recent pre-clinical work establishing that EMT reversibility is also critical for productive metastasis. For example, enforced expression of TWIST dramatically increased the number of circulating tumor cells (CTCs) in a mouse model of human squamous cell carcinoma, but subsequent downregulation of TWIST was also required for efficient growth of metastases [67].

Transient associations with platelets in the vasculature appear to reinforce EMT in CTCs, providing a mechanistic explanation for the EMT reversibility that is observed when metastatic tumor cells enter the circulation (“EMT”) and then become more “epithelial” when they become regional or distant metastases (“MET”) [64, 68]. We have observed a very similar phenomenon in pre-clinical models of human bladder cancer metastasis [69], where Snail-induced EMT was required for CTC production, but subsequent downregulation of Snail and upregulation of “epithelial” biomarkers occurred in established lymph node and lung metastases (B. Roth et al. manuscript submitted). Considering that basal MIBCs and breast cancers are both enriched with cancer stem cell and EMT biomarkers, it is perhaps not surprising that basal MIBCs are more commonly associated with metastatic disease than luminal cancers are [29–31].

Basal tumors appear to possess more EMT plasticity than luminal tumors do. A recent study concluded that basal breast cancer cell lines spontaneously produce subpopulations that display stem-like and mesenchymal properties in two-dimensional culture vitro, whereas luminal breast cancer cell lines do not [60]. This high degree of EMT plasticity may be associated with particular, stem cell-like patterns of histone methylation (“poised” chromatin) within the ZEB1 gene, which permits rapid EMT in response to external stimuli [60]. Luminal breast cancers never produced stem-like cells in vitro, but they were capable of doing so in vivo, because “stemness” in luminal tumors is heavily dependent on interactions with the tumor microenvironment [60].

Recent analyses of basal and luminal biomarker expression in primary MIBCs [44] and xenograft models [26] have produced insights that may explain these differences in basal versus luminal tumor biology. Basal biomarker expression in basal tumors is relatively uniform, whereas basal biomarker expression in luminal tumors is restricted to the tumor–stromal interface, just as it is in the normal urothelium [26, 44]. Recent studies in luminal breast cancer “organoids” (i.e., tumor organ cultures) demonstrated that the edges of these tumors also contained basal biomarker (KRT14, p63) expression [62]. Interactions involving β1 and β4 integrins and specific extracellular matrix molecules drove basal biomarker expression in the edges of luminal tumors [62, 70, 71], and interestingly, β1 and β4 integrins are also both controlled by p63 [61]. Therefore, a major function
of p63 is to control adhesion to the extracellular matrix, and this adhesion controls basal biomarker expression.

The role of p63 in controlling EMT plasticity appears to be complex. On the one hand, one study concluded that p63 expression promoted TGFβ-induced EMT [72], consistent with all of the above discussion of p63’s relationship to “stemness”. However, p63 also promoted expression of the EMT repressor miR-205, leading to suppression of ZEB1/2 and inhibition of invasion [73]. We therefore wonder whether p63 plays some role in “priming” cells for EMT while preventing full EMT via miR-205 upregulation; this model predicts that downregulation of p63 (perhaps via platelet-mediated TGFβ signaling [68]) would be required for the more complete EMT that is observed in CTCs. It is conceivable that p63-mediated priming for EMT facilitates the “poised” chromatin that is present within the ZEB1 in basal cancer cells [60].

Conclusions and implications for clinical management

There is good consensus that basal bladder cancers are intrinsically aggressive, a phenotype that is linked to their expression of stem cell and EMT biomarkers. However, approximately half of them are sensitive to NAC [29]. Even though level 1 evidence supports its use in the clinical management of MIBC, utilization rates are still well below 50%. Therefore, one immediate action should be to increase the utilization of NAC, particularly in patients with potentially lethal basal cancers.

In the past, prognostic and predictive signatures were developed using cohorts that consisted of mixed basal and luminal tumors. Given the differences in the molecular control of basal and luminal biology, it seems likely that a more focused development of recurrence and progression markers within each subtype will be more successful. Again, breast cancer serves as the precedent, as recent work has demonstrated that subtypes within basal cancers exist that are associated with different clinical outcomes and responses to conventional and potentially targeted therapies [74].

Finally, one obvious prediction that arises from recent studies is that stem cell and intrinsic subtype biomarkers will identify tumors that are sensitive to targeted agents. Attractive targets in basal tumors include EGFR and STAT3, whereas the most attractive targets in luminal tumors are FGFR3, the ER, and ERBB2 [1, 29–31, 51]. Clinical trials with single agents targeting some of these pathways were performed with disappointing results [75, 76], but these trials were not informed by the deep genomic annotation provided by the TCGA’s bladder cancer project, so it is unclear whether the most attractive molecular targets were present at high prevalence in the cohorts of patients enrolled in these trials. Furthermore, no combinations of targeted agents have been evaluated to date. It would seem prudent to identify good pre-clinical mouse models of basal and luminal cancers and then use them to carefully characterize the cytostatic and cytotoxic effects of targeted agents alone and in combination with other targeted agents and/or chemotherapy.

Useful web links

3 http://www.ncbi.nlm.nih.gov/pubmed/24525232 – paper that identified the basal and luminal bladder cancer subtypes and showed that they responded differently to neoadjuvant chemotherapy.

References


Romih R and Jezernik K: Reorganisation of the urothelial luminal plasma membrane in cyclophosphamide treated rats.


Takahashi K and Yamanaka S: Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors.


CHAPTER 31

Multi-targeted agents in the treatment of urothelial carcinoma

Noah M. Hahn¹, Colin P.N. Dinney², and Guru Sonpavde³
¹Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, USA
²Department of Urology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
³University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL, USA

KEY POINTS

- A large number of multi-targeted agents with differing mechanisms of anti-tumor activity are under current clinical investigation for the treatment of bladder cancer.
- The investigation of novel bladder cancer agents is occurring at all stages of the disease. It is not limited to heavily pre-treated metastatic patients.
- Broad classes of agents under investigation include agents which target angiogenesis, epidermal growth factor family receptors including EGFR and Her-2, fibroblast growth factor receptors, MET, epigenetically silenced tumor suppressor genes, and the immune system.
- Further understanding of the molecular features which distinguish specific subsets of bladder cancer patients is needed to optimize and prioritize the clinical development of this wide array of multi-targeted therapeutic options.

Introduction

As discussed in previous chapters, the incorporation of platinum-based chemotherapy regimens into the care of muscle-invasive and metastatic urothelial carcinoma patients has produced tangible improvements in both overall survival and cure rates. However, these improvements have been modest and it appears that a plateau has been reached in regards to further improvements in outcomes with the usage of cytotoxic chemotherapy in unselected populations. Fortunately, both technology and drug development efforts in urothelial carcinoma have accelerated in the past decade. Specifically, The Cancer Genome Atlas (TCGA) project is seeking to define the biology of multiple tumor types including invasive urothelial carcinoma by comparing invasive tumors to normal controls across a comprehensive simultaneously-analyzed battery of molecular platforms. Recently published TCGA data from 131 urothelial carcinoma samples have demonstrated statistically significant recurrent mutations in 32 genes, with potential therapeutic targets in 69% of tumors [1]. These emerging data are creating a new era in which an improved understanding of tumor biology coupled with a growing army of therapeutics which selectively target key drivers of tumor growth offers promise for further improvements in urothelial carcinoma patient outcomes. This chapter will highlight the development of multiple new treatment approaches in urothelial carcinoma which aim to slow tumor growth by affecting multiple targets, including angiogenesis, fibroblast growth factor receptors, Her family receptors, MET signaling, epigenetically silenced tumor suppressor genes, and immune modulators.
Angiogenesis

As with most solid malignancies, angiogenesis is an attractive target in BC [2]. Sunitinib, sorafenib, pazopanib, and vandetanib are oral multi-targeted VEGF TKIs. All agents have been studied in several phase II urothelial carcinoma trials including neoadjuvant, adjuvant maintenance, front-line metastatic and post-platinum metastatic settings. Results of these studies are summarized in Table 31.1. The clinical trial data thus far with these agents have demonstrated modest activity in a small portion of urothelial carcinoma patients with expected rates of off-target toxicity when administered as a single agent. A full-dose combination with cytotoxic chemotherapy has thus far proven difficult.

In contrast to the VEGF TKIs, bevacizumab is a recombinant monoclonal antibody for circulating VEGF-A [14]. Compared to historical overall survival outcomes, phase II trial results of bevacizumab in combination with standard cisplatin–gemcitabine and carboplatin–gemcitabine regimens have been promising [12, 13]. Based on these data, a confirmatory intergroup phase III trial is ongoing in the US led by the Alliance.

Fibroblast growth factor receptors

Low-grade, early-stage UC tumors are characterized by mutations in the fibroblast growth factor receptor-3 (FGFR3) and the Harvey rat sarcoma viral oncogene homologue (HRAS) genes [2, 15]. FGFR3 mutations or overexpression promote FGFR dimerization and constitutive activation of downstream signaling pathways in the absence of ligand in up to 80% of early-stage UC tumors (Table 31.2) [16].

Table 31.1 VEGFR inhibitor urothelial carcinoma clinical trial results.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Organization</th>
<th>Ref</th>
<th>Population</th>
<th>N</th>
<th>Hem toxicity (Gr 3–4)</th>
<th>Non-hem toxicity (Gr 3–4)</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cis + Gem + Sunitinib</td>
<td>HOG</td>
<td>[3]</td>
<td>Neoadjuvant</td>
<td>9</td>
<td>67%</td>
<td>22%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cis + Gem + Sunitinib</td>
<td>MSKCC</td>
<td>[4]</td>
<td>Neoadjuvant</td>
<td>18</td>
<td>61%</td>
<td>11%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>UHMB</td>
<td>[5]</td>
<td>First line</td>
<td>38</td>
<td>5%</td>
<td>11%</td>
<td>8%</td>
<td>4.3</td>
<td>8.1</td>
</tr>
<tr>
<td>Cis + Gem + Sunitinib</td>
<td>USO</td>
<td>[3]</td>
<td>First line</td>
<td>36</td>
<td>70%</td>
<td>NR</td>
<td>49%</td>
<td>8.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>MSKCC</td>
<td>[6]</td>
<td>Second line</td>
<td>77</td>
<td>20%</td>
<td>11%</td>
<td>5%</td>
<td>2.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>PMH P2C</td>
<td>[7]</td>
<td>First line</td>
<td>17</td>
<td>0%</td>
<td>24%</td>
<td>0%</td>
<td>1.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Cis + Gem + Sorafenib</td>
<td>AUO</td>
<td>[8]</td>
<td>First line</td>
<td>98</td>
<td>NR</td>
<td>NR</td>
<td>53%</td>
<td>6.2</td>
<td>11.2</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>ECOG</td>
<td>[9]</td>
<td>Second line</td>
<td>22</td>
<td>NR</td>
<td>19%</td>
<td>0%</td>
<td>2.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>FINTM</td>
<td>[10]</td>
<td>Second line</td>
<td>41</td>
<td>7%</td>
<td>0%</td>
<td>17%</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Docetaxel +/– Vandetanib</td>
<td>DFCI</td>
<td>[11]</td>
<td>Second line</td>
<td>142</td>
<td>19%</td>
<td>50%</td>
<td>7%</td>
<td>2.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Cis + Gem + Bevacizumab</td>
<td>HOG</td>
<td>[12]</td>
<td>First line</td>
<td>43</td>
<td>42%</td>
<td>42%</td>
<td>72%</td>
<td>7.5</td>
<td>19.1</td>
</tr>
<tr>
<td>Carbo + Gem + Bevacizumab</td>
<td>MSKCC</td>
<td>[13]</td>
<td>First line</td>
<td>51</td>
<td>31%</td>
<td>20%</td>
<td>49%</td>
<td>6.5</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Cis = Cisplatin; Gem = Gemcitabine; HOG = Hoosier Oncology Group; MSKCC = Memorial Sloan-Kettering Cancer Center; UHMB = University Hospital del Mar, Barcelona; USO = US Oncology; PMH P2C = Princess Margaret Hospital Phase II Consortium; AUO = Association of Urogential Oncology; ECOG = Eastern Cooperative Oncology Group; FINTM = Fondazione IRCCS Istituto Nazionale dei Tumori Milan, Italy; DFCI = Dana Farber Cancer Institute; Ref = Reference; N = number of patients; Hem = Hematologic; Gr = Grade; Non-hem = Non-hematologic; RR = Response rate; PFS = Progression-free survival (months); OS = Overall survival (months); NR = Not reported.
Multi-targeted agents in the treatment of urothelial carcinoma

While FGFR3 mutations are highly associated with early-stage, low-grade UC, either an FGFR3 mutation or overexpression of the FGFR3 protein has been observed in over half of muscle-invasive UC tumors [17]. Thus, while FGFR3 mutations likely are an early event in the tumorigenesis of low-grade non-invasive UC tumors, overexpression of FGFR3 may still play a role in the continued proliferation of high-grade muscle-invasive UC tumors. Furthermore, increasing evidence demonstrates that fibroblast growth factor receptor-1 (FGFR1) is a crucial mediator of tumor angiogenesis [18].

Recent pre-clinical studies using an inhibitor of FGFRs 1–3 identified that FGFR1 was expressed in UC cells that co-expressed the “mesenchymal” markers ZEB1 and vimentin, whereas FGFR3 expression was restricted to the E-cadherin- and p63-positive “epithelial” tumor cells. Sensitivity to the anti-proliferative effects of an FGFR inhibitor (BGJ-398) was restricted to the “epithelial” cells and correlated directly with high FGFR3 expression. In contrast, BGJ-398 inhibited invasion but not proliferation in the “mesenchymal” UC cells, and in vivo, BGJ-398 did not inhibit growth within the bladder but rather prevented the production of circulating tumor cells (CTCs) and subsequent lymph node and distant metastases in mice bearing orthotopic “mesenchymal” UM-UC3 tumors. These results suggest that FGFR1 and FGFR3 have complementary roles in regulating proliferation, invasion, and metastasis in distinct subsets of human UC cells, which can be predicted by the EMT phenotype [19]. In additional pre-clinical tumor models, blockade of the FGF pathway has proven to be an effective method of overcoming resistance to VEGFR inhibitors [20]. Given the previously described importance of VEGF in UC progression, a strong rationale exists for combined VEGFR and FGFR inhibition in UC patients. The lack of benefit observed in a recent phase II trial of dovitinib (an oral VEGFR/FGFR3 TKI) in a heavily pre-treated metastatic UC population suggests that such an FGFR-inhibition strategy may be better suited in earlier stage patients where greater dependence on the FGFR-mediated pathways is expected [21].

### Her family receptors

The Her family of receptors mediate signal transduction pathways with critical roles in cell survival, metastasis, and angiogenesis [22]. Her-1 (epidermal growth factor receptor, EGFR) and Her-2 have been most extensively examined for therapeutic development.

EGFR is overexpressed in up to 70% of bladder UC tumors and is associated with a poor prognosis [23]. Initial in vitro work suggested the EGFR TKI gefitinib interacted synergistically with chemotherapy [24]. However, in a single-arm phase II study in chemotherapy-naive UC patients treated with gefitinib, cisplatin, and gemcitabine, an observed response rate of 51%, progression-free survival of 8 months, and an overall survival of 14 months did not appear better than historical controls of the chemotherapy alone [25]. Cetuximab is an EGFR targeted monoclonal antibody which has also been investigated in combination with chemotherapy in two randomized phase II studies in metastatic UC patients. Similar to the gefitinib experience, the combination of cetuximab with the front-line cisplatin-gemcitabine and second-line paclitaxel regimens yielded similar results to historical chemotherapy alone outcomes [26, 27].

Her-2 receptors are also overexpressed by immunohistochemistry in approximately half of patients with metastatic UC [23]. Trastuzumab is an Her-2 targeted monoclonal antibody which has demonstrated marked improvement in overall survival in Her-2 expressing breast cancer patients in both the metastatic and adjuvant settings when combined with cytotoxic chemotherapy [28–30]. A recent trial examined the combination of paclitaxel, carboplatin, gemcitabine, and trastuzumab in untreated Her-2 positive metastatic UC patients [31]. The combination was tolerable, although 22% experienced Grade 1 to 3 cardiac toxicity and three treatment-related deaths occurred. Seventy percent of patients responded to therapy. However, median time to progression and overall survival were very similar to standard cisplatin and gemcitabine regimen benchmarks at 9.3 and 14.1 months, respectively.

| Table 31.2 FGFR3 mutation and overexpression status according to T-stage. |
|----------------|----------------|----------------|
|                | Ta (%) | T1 (%) | T2 (%) |
| Mutation       | 67     | 42     | 13     |
| Overexpression | 13     | 15     | 39     |
| Total          | 80     | 57     | 52     |
Lapatinib is a specific EGFR and Her-2 targeted TKI. Over two-thirds of patients with metastatic UC overexpress one or both of these receptors [32]. Lapatinib has been investigated as a single agent in unselected patients as second-line therapy in a single-arm study in metastatic UC [32]. The response rates were disappointing; however, subset analysis suggested a survival benefit for patients overexpressing EGFR or Her-2. Therefore, lapatinib continues to be investigated in UC, and two studies are ongoing in the metastatic setting [33]. Clinical trial experiences with Her-targeted agents and key ongoing clinical trials are summarized in Table 31.3.

**Table 31.3 EGFR and Her-2 inhibitor urothelial carcinoma clinical trial results and ongoing studies.**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Org</th>
<th>Ref</th>
<th>Population</th>
<th>N</th>
<th>Hem toxicity (Gr 3–4)</th>
<th>Non-hem toxicity (Gr 3–4)</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cis + Gem + Gefitinib</td>
<td>CALGB</td>
<td>[25]</td>
<td>First line</td>
<td>58</td>
<td>44%</td>
<td>80%</td>
<td>43%</td>
<td>7.4</td>
<td>15.1</td>
</tr>
<tr>
<td>Cis + Gem + Cetuximab</td>
<td>SWOG</td>
<td>[26]</td>
<td>First line</td>
<td>56</td>
<td>34%</td>
<td>29%</td>
<td>63%</td>
<td>7.6</td>
<td>14.0</td>
</tr>
<tr>
<td>Carbo + Gem + Paclitaxel + Trastuzumab</td>
<td>UM/CTEP</td>
<td>[31]</td>
<td>First line</td>
<td>44</td>
<td>89%</td>
<td>28%</td>
<td>70%</td>
<td>9.3</td>
<td>14.1</td>
</tr>
<tr>
<td>cis/Cis + Gem + Trastuzumab</td>
<td>APRTIC</td>
<td>[34]</td>
<td>First line Her-2+</td>
<td>61</td>
<td>72%</td>
<td>16%</td>
<td>53%</td>
<td>9.3</td>
<td>16.8</td>
</tr>
<tr>
<td>Cis + Gem + Lapatinib</td>
<td>EORTC</td>
<td>[33]</td>
<td>First line</td>
<td>25</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Any first line chemotherapy + Lapatinib</td>
<td>QMUL</td>
<td>[33]</td>
<td>First line maintenance</td>
<td>220</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>UMun</td>
<td>[32]</td>
<td>Second line</td>
<td>59</td>
<td>7%</td>
<td>&lt;5%</td>
<td>2%</td>
<td>2.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Paclitaxel + Cetuximab</td>
<td>FCCC</td>
<td>[27]</td>
<td>Second line</td>
<td>28</td>
<td>14%</td>
<td>21%</td>
<td>25%</td>
<td>3.8</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Cis = Cisplatin; Gem = Gemcitabine; Carbo = Carboplatin; CALGB = Cancer and Leukemia Group B; SWOG = Southwest Oncology Group; UM = University of Michigan; CTEP = Cancer Therapy Evaluation Program; APRTIC = Association Pur La Recherche des Therapeutiques Innovantes en Cancerologie; EORTC = European Organisation for Research and Treatment of Cancer; QMUL = Queen Mary University of London; UMun = University of Münster; FCCC = Fox Chase Cancer Center; Ref = Reference; N = number of patients; Hem = Hematologic; Gr = Grade; Non-hem = Non-hematologic; RR = Response rate; PFS = Progression-free survival (months); OS = Overall survival (months); NR = Not reported.

**MET signaling**

The hepatocyte growth factor (HGF)–Met (MET) signaling pathway has been implicated as a common mediator of carcinogenesis, invasion, and metastases in multiple malignancies including urothelial carcinoma [35, 36]. In analyses of multiple UC cell lines, Cheng et al. demonstrated increased expression of MET in four of five cell lines examined. In addition, increased expression of MET within human UC tissues was observed in association with higher grade, higher stage, and larger tumors [35]. In a retrospective study of 31 patients with metastatic and muscle-invasive UC, a significant association between increased urine-shed MET and visceral metastases has been seen. Cabozantinib is a potent oral multi-targeted TKI of MET and VEGFR2 signaling, with an IC50 of 1.3 nmol/L and 0.035 nmol/L respectively [37]. In addition, cabozantinib also inhibits RET, TIE2, KIT, AXL, and FLT3. In RT4, T24M2, T24M3, and TCC-SUP UC cell line experiments, HGF-mediated increases in MET, pAKT/AKT, pMAPK/MAPK in addition to cell invasion and proliferation were all reversed by cabozantinib administration [38]. Preliminary results from an NCI-conducted human phase II cabozantinib study in refractory UC patients showed a response rate of 11% and stable disease > 16 weeks in 37% [39]. Other multi-targeted MET inhibitors with relevance to UC, but currently in development in other malignancies, include tivantinib, foretinib, crizotinib, MGCD265, and MK-2461 [40, 41] (Figure 31.1).

**Epigenetics**

Epigenetics is the study of changes in gene function not caused by DNA sequence changes. Two common epigenetic mechanisms leading to tumor suppressor gene
inactivity include hypermethylation of gene promoter regions and histone deacetylation. Both mechanisms inhibit the regular uncoiling of DNA necessary to expose critical coding regions required for gene transcription and cell replication. Thus far, the development of histone deacetylase inhibitors in bladder cancer has been disappointing, with rare tumor responses and unfavorable toxicity profiles. The discussion here, therefore, will focus on the development of hypomethylating agents.

High-grade, early-stage UC tumors are characterized by mutations or functional silencing of several key genes important in cell cycle control, cellular adhesion, apoptosis, and tumor suppressor functions. These genes include: CDKN2A (p16 and p14), WAF1 (p21), RASSF1A, CDH1 (E-cadherin), and GSTP1 [2, 15, 42, 43]. Frequently, these and other tumor suppressor genes are transcriptionally silenced by hypermethylation of cytosine-guanine (CpG)-rich repeat sequence islands within their promoter regions. Examination of UC tumor specimens reveals global hypermethylation in 76% of all UC tumors [44]. In addition, hypermethylation has been associated with progression to muscle-invasive disease and cancer-specific mortality [44].

5-azacitidine (AzaC) is a non-methylatable cytidine analog that is incorporated into DNA during S-phase. At high doses, AzaC demonstrates cytotoxicity, while low AzaC doses elicit DNA hypomethylation and cellular differentiation [45].

In an in vivo pre-clinical study, Hahn et al. treated 19 dogs with naturally occurring de novo invasive UC as...
part of a single-agent subcutaneous AzaC pilot trial [46]. Demonstrable size reductions in bladder tumors were observed in 10 of 18 dogs (56%). The observed disease control rate across all doses and schedules (CR + PR + SD) was 72%. While no consistent biomarker pattern emerged from pre- and post-treatment tumor methylation analyses, in the one dog that achieved a confirmed partial remission with paired tumor tissue available, a 6.8% absolute reduction in \( CDKN2A \) (\( p14ARF \)) methylation was observed.

In addition to intravenous and subcutaneous delivery routes, an oral formulation of AzaC has now been tested in human trials [47]. The oral AzaC formulation is currently under investigation in combination with carboplatin as an expanded cohort in metastatic UC patients in a phase I trial.

**Immune modulation**

Investigators have attempted for decades to develop therapies which modulate the host immune response to cancer. While early trials did not yield practice-changing results, our recent improved understanding of how to enhance specific portions of the immune response and diminish tumor escape mechanisms has renewed enthusiasm for immune-modulating approaches. The development of immune-modulating therapies in UC has a strong clinical rationale, particularly in early-stage disease where intravesical instillation of an immune modulatory agent such as BCG is a cornerstone of therapy.

Lenalidomide is a second generation thalidomide analog immunomodulating agent (IMiD). Lenalidomide was originally developed for use in hematologic malignancies where it was first FDA approved for myelodysplastic syndrome with deletion of 5q [48]. The exact mechanism of the anti-tumor effect with lenalidomide and other IMiDs is not clear. Recently, Lee et al. have studied the effects of lenalidomide in combination with BCG-induced cytokines in vitro and in combination with BCG in vivo. When lenalidomide, TNF-\( \alpha \), and FasL were combined, increased DNA fragmentation was observed in the MBT2 cell lines compared to any single-agent results. In addition, when lenalidomide was combined with BCG in MBT2 in vivo experiments, significant decreases in tumor size and increases in TUNEL assay apoptosis measurements were observed compared to lenalidomide or BCG administered alone [49]. Based on these results, lenalidomide is currently under investigation in UC patients in combination with BCG in the BCG-relapsing population and in combination with platinum-containing chemotherapy in metastatic patients (Table 31.4).

In addition to the IMiDs, other modulators of the immune system have made their way into the clinical care of cancer patients including an exciting new class of agents which target the immune checkpoints. In many malignancies, increased activity of the cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) pathway has been observed leading to inhibition of an anti-tumor-directed immunologic attack. As such, immune checkpoint

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**Table 31.4** Current immunomodulatory agent urothelial carcinoma clinical trials [33].

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Population</th>
<th>Regimen</th>
<th>( N )</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG</td>
<td>BCG-naïve NMIBC</td>
<td>SQ BCG priming + Intravesical BCG</td>
<td>232</td>
<td>1-yr RFS</td>
</tr>
<tr>
<td>MCC</td>
<td>BCG-relapsing NMIBC</td>
<td>BCG + lenalidomide</td>
<td>70</td>
<td>1-yr RFS</td>
</tr>
<tr>
<td>TCI</td>
<td>Metastatic cisplatin-eligible</td>
<td>Cisplatin + Gemcitabine + Lenalidomide</td>
<td>60</td>
<td>RP2D/1-yr PFS</td>
</tr>
<tr>
<td>NCI</td>
<td>Metastatic (multiple lines of therapy allowed)</td>
<td>Carboplatin + Gemcitabine + Lenalidomide</td>
<td>42</td>
<td>DLT</td>
</tr>
<tr>
<td>HOG</td>
<td>Metastatic cisplatin-eligible</td>
<td>Cisplatin + Gemcitabine + Ipilimumab</td>
<td>36</td>
<td>1-yr OS</td>
</tr>
</tbody>
</table>

SWOG = Southwest Oncology Group; Moffitt = Moffitt Cancer Center; TCI = Tisch Cancer Institute at the Mount Sinai Medical Center; NCI = National Cancer Institute; HOG = Hoosier Oncology Group; NMIBC = Non-muscle-invasive bladder cancer; SQ = subcutaneous; \( N \) = number of patients; RFS = Relapse-free survival (months); RP2D = Recommended phase II dose; PFS = Progression-free survival; OS = Overall survival (months).
inhibitors of CTLA-4 represent rational therapeutic interventions across a broad spectrum of malignancies [50]. Ipilimumab is a fully humanized monoclonal IgG CTLA-4 antibody which effectively inhibits CTLA-4 binding to HLA-B7 and thereby negates its immune inhibitory effect [51]. In a study of MB49 UC murine xenografts, combined antibody blockade of CTLA-4 plus local toll-like receptor stimulation demonstrated a complete response rate of 86%, with a corresponding increase in circulating tumor-specific CD107a expressing CD8+ T cells and a decrease in local T regulatory cells [52]. In humans, ipilimumab has demonstrated safety in a pilot trial of 12 pre-cystectomy patients with clinically localized UC. In this trial, all patients demonstrated an increase in CD4+ ICOShi T cells in tumor tissue and systemic circulation, and 8/12 patients had downstaging of their disease on final pathology review. Based on these data, ipilimumab is currently under investigation in combination with cisplatin and gemcitabine in the treatment of metastatic UC patients (Table 31.4). In addition to ipilimumab, other novel immune checkpoint inhibitors are being developed, including those that target the programmed cell death 1 (PD-1) and/or the programmed cell death 1 protein ligand (PD-L1) mediated pathways. In UC, expression of PD-1 by tumor-infiltrating lymphocytes (TILs) has been observed in 96% of muscle-invasive UC patients undergoing cystectomy, with moderate or marked expression seen in 43% of patients [53]. Clinical trials in UC patients are currently planned with agents targeting both PD-1 and PD-1L.

Lastly, it is generally accepted that the anti-tumor effect of BCG is elicited through the intense inflammatory reaction created within the urothelium after intravesical administration. In recent years, a better understanding of this mechanism has led to further investigations aimed at improving the relapse rate after BCG administration. In immunocompetent in vivo murine models, Biot et al. have demonstrated that the intensity of T-cell response and tumor control are both enhanced by pre-existing exposure to BCG through subcutaneous “priming” prior to intravesical BCG administration [54]. In addition, when examined retrospectively, the same authors observed that human patients demonstrating a positive PPD skin test signifying prior exposure to mycobacterium tuberculosis or prior BCG vaccination had significantly lower relapse rate after intravesical BCG administration for their UC than PPD-negative subjects. With these observations as a foundation, a randomized trial examining whether relapse rates can be decreased by subcutaneous BCG priming prior to intravesical BCG administration is now planned (Table 31.4).

Summary

As this chapter has outlined, a vast array of multi-targeted agents are under active investigation for the treatment of urothelial carcinoma. The number and variety of agents is unprecedented. The increased development efforts provide hope to all patients with urothelial carcinoma that improvements in clinical outcomes will follow. Advances in our understanding of which patients are most likely to respond to which treatments will be necessary to optimize the development efforts and speed improvements in patient outcomes.

Useful web links

1 www.bcan.org – Bladder Cancer Advocacy Network: information for patients on multiple bladder cancer topics including support groups, disease information, clinical trial opportunities, bladder cancer research initiatives, etc.

References

4 Balar AV, Iyer G, Apolo AB, et al. (eds): Phase II trial of neoadjuvant gemcitabine (G) and cisplatin (C) with sunitinib in patients (pts) with muscle-invasive bladder cancer (MIBC). 2012 ASCO Annual Meeting; 2012: Chicago, IL.


Multi-targeted agents in the treatment of urothelial carcinoma


PART VII

Optimizing healthcare delivery
CHAPTER 32

Patient navigation and cancer navigator programs

Scott M. Gilbert¹ and Michael Porter²,³
¹Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
²Department of Urology, University of Washington, Seattle, WA, USA
³VA Puget Sound Health Care System, Seattle, WA, USA

KEY POINTS

• Health disparities are a common problem in the healthcare system, and affect cancer patients significantly.
• Disparities among bladder cancer patients most profoundly affect blacks, women, and underinsured patients.
• Patient navigation programs are designed to reduce disparities by improving access to needed cancer services.
• Patient navigators are typically drawn from the local communities that they serve to ensure concordance in the cultural, ethnic, racial, and language makeup of the community.
• The first patient navigation program, the Harlem Breast Cancer Navigation Program, was effective in reducing barriers to needed cancer services among underserved women in Harlem, and resulted in higher evaluation rates, more prompt evaluation, diagnosis and treatment, and in an increase in the proportion of early-stage breast cancers diagnosed in the community compared to pre-program statistics.
• The success of the Harlem Breast Cancer Navigation Program in large part led to the Patient Navigator, Outreach and Chronic Disease Prevention Act of 2005, as well as Commission on Cancer requirements to integrate patient navigation programs into accredited cancer centers by 2015.

Introduction

Health disparities plague the US healthcare system, particularly among patients with cancer. As recently as 2010, estimates indicate that overall five-year survival for all persons with cancer combined is 10% lower among the poor compared to more affluent Americans. Further, more than 50 million (16.7%) of Americans live without any or adequate health insurance, raising additional access and care delivery concerns for those who are diagnosed with cancer [1]. These statistics, although fairly recent, are not substantially different from the issues facing poor and uninsured cancer patients 20 years ago. In response, patient navigation programs have been implemented to address gaps in cancer care and reduce disparities in access and outcomes among disadvantaged groups. The primary goal of navigation programs is to reduce or eliminate barriers that prevent patients from accessing or receiving high-quality care. As such, navigators facilitate access, timely diagnosis and treatment, and follow-up with care plans.

Patient navigation has been most robustly implemented and studied in breast cancer. The first navigation program was implemented in Harlem, New York in 1990 by Dr Harold Freeman, and resulted in more direct access and higher quality breast cancer care for poor African American and Latino women living in that community [2]. The success of the program spurred additional efforts to develop, implement, and study the impact of navigation programs across a number of cancers. Navigation programs have been shown to increase completion rates of, and decrease time to, breast biopsies.
in women with suspicious findings for breast cancer, decrease the percentage of patients presenting with late-stage breast cancer, and improve colorectal cancer detection. Patient navigation has more recently been adopted in policy initiatives targeting healthcare disparities. For example, the Commission on Cancer (CoC) adopted accreditation requirements that include implementation of patient navigators at CoC accredited sites by 2015 [3]. As a result, the number of cancer navigation programs will likely grow substantially in the near future. Although several pilot programs are currently underway, there are few efforts that target bladder cancer patients. The purpose of this chapter is to review the development and objectives of cancer navigation, outline policy initiatives that will integrate cancer navigation into cancer centers, examine some of the key healthcare disparities that have been observed among bladder cancer patients, and consider how navigation may impact those disparities.

Development of cancer navigator programs

Beginning in 1989, the American Cancer Society conducted hearings in several US cities addressing the burden of cancer among socially and economically disadvantaged groups. The resulting report, Report to the Nation on Cancer in the Poor, identified a number of gaps in cancer care that disproportionately affect the poor, including barriers to accessing care, inability to pay for care, higher levels of pain and suffering, higher burdens of personal and family sacrifice to gain access to and pay for cancer care, and a lack of culturally sensitive outreach and educational programs [4]. At the same time that the American Cancer Society was chronicling the myriad of issues that the poor face when trying to access cancer care, the country’s first navigation program was launched in Harlem, New York to reduce disparities in breast cancer treatment among poor African American and Latino women. Recognizing that financial barriers, lack of health insurance, poor communication with healthcare advocates and providers, and fear and distrust of the medical system hindered access to needed health services, Dr Harold Freeman established the Harlem Breast Cancer Navigation Program in 1990 [2]. The key elements and scope of the program focused on removing barriers to early screening and detection breast examinations, and navigation to ensure timely diagnosis and treatment. The program was, in large part, started out of necessity, as mortality data revealed significant differences among women living in these parts of the city. Prior to 1990, only 6% of women diagnosed with breast cancer in Harlem were detected at stage I disease; nearly half presented with stage 3–4 disease, and five-year survival estimates were only 39% [5]. In the years after the program was initiated, the statistics turned dramatically: of 325 women diagnosed and followed through the Harlem Breast Cancer Navigation program, 41% were diagnosed with early-stage disease. The proportion of advanced stage disease (stage 3–4) dropped to 21%, and five-year survival increased to 70% [6]. Dr Freeman credited two key elements to the program’s success: (1) provision of low- or no-cost examinations and mammograms according to clinical guidelines and standards, and (2) patient navigation to circumvent barriers limiting subsequent diagnostic evaluations and treatment [2]. The success of this breast cancer navigation model, in addition to greater general awareness of the potential for navigation to reduce disparities helped lead, to the Patient Navigator Outreach and Chronic Disease Prevention Act (HR 1812) passed by Congress and signed into law in 2005 [7]. This legislation amended the Public Health Service Act to allow the Secretary of Health and Human Services to grant funds supporting the development and implementation of patient navigation demonstration programs. As a result, a number of pilot navigation programs have been launched since 2005, and $74 million of federal money has been committed to further studying the effectiveness and impact of navigator programs [2, 8].

In 2012, the Commission on Cancer (CoC) and its principal supporting organization, the American College of Surgeons, announced program efforts designed to improve the delivery of patient-centered care at accredited cancer centers. The Cancer Program Standards 2012: Ensuring Patient-Centered Care, issued a Patient Navigation Process initiative as part of the Continuum of Care Standard, to be phased in across CoC accredited sites in 2015. Consistent with the Patient Navigator Outreach and Chronic Disease Act, the primary focus of the initiative is to address health disparities and barriers to care for patients. As stated by the CoC, “patient navigation in cancer care refers to individualized assistance offered to patients, families and caregivers to help
overcome health care system barriers and facilitate timely access to quality medical and psychosocial care” [3]. Beginning in 2015, the requirements for accredited cancer programs will include evaluation of the navigation process, and documentation and reporting of barriers to care. Initial patient navigation program activities will be evaluated in several key areas, including but not limited to identification of health disparities, description of the navigation process, identification of the population served and barriers within the community limiting or preventing receipt of timely cancer care, documentation of activities and program evaluation metrics, and description of potential quality improvement activities and future program development [3]. To be in compliance during CoC surveys, programs will be required to (1) conduct a community needs assessment at least once during the three-year survey cycle to address healthcare disparities and barriers to care for patients; (2) establish a patient navigation process and identify resources addressing identified barriers that are provided either on site or by referral to community-based or national organizations; (3) examine barriers to care and evaluate the navigation process each year and report findings to the cancer committee, and (4) modify or enhance the patient navigation process yearly to address residual or additional barriers identified during the community needs assessment [3]. As highlighted above, this scope of work will largely hinge on performance of a community needs assessment to identify the needs of the population, gaps in resources and barriers that prevent healthcare services, and potential areas where gaps and barriers can be overcome to ultimately improve the care provided to disparate groups.

**Principles of patient navigation**

According to Wells and colleagues, cancer patient navigation is a barrier-focused intervention that has several common characteristics [9]. First, navigation is provided to individual patients for a defined episode of cancer-related care, such as following up and evaluating an abnormal screening test. Second, patient navigation has a defined endpoint when the services provided are completed (e.g. diagnostic resolution after an abnormal screening test). Third, navigation targets a defined set of health services that are required to complete an episode of cancer care. Fourth, patient navigation focuses on the identification of individual patient-level barriers to accessing cancer care. Fifth, patient navigation aims to reduce delays in the continuum of cancer services, with an emphasis on timeliness of diagnosis and treatment and a reduction in the number of patients lost to follow-up.

Freeman and Rodriguez define patient navigation as a healthcare delivery support system with the principal function of eliminating barriers to timely delivery of healthcare to individual patients [1]. In their model of patient navigation, patient navigators may be assigned to specific phases of the patient navigation model, including prevention, detection, diagnosis, treatment, and survivorship. Furthermore, they define the following nine principles of patient navigation:

1. **Patient navigation is a patient-centered healthcare service delivery model.** The focus of navigation is to promote timely movement of an individual through the complex healthcare system, starting with the individual patient's unique circumstances.
2. **Patient navigation serves to integrate a fragmented healthcare system for the individual patient.** Patient navigation should strive to create a seamless flow through the healthcare continuum.
3. **The core function of patient navigation is the elimination of barriers to timely care across all segments of the healthcare continuum.** This is most effectively accomplished by a one-on-one relationship between the patient and navigator.
4. **Patient navigation should be defined with a clear scope of practice that distinguishes the role and responsibility of the navigator from that of all other providers.** Navigators should be integrated into the healthcare system.
5. **Delivery of patient navigation services should be cost-effective and commensurate with the training and skills necessary to navigate an individual through a particular phase of the care continuum.**
6. **The determination of who should navigate should be determined by the level of skills required at the given phase of navigation.** This spectrum includes trained lay navigators through to trained health professionals such as nurses and social workers.
7. **In a given system of care there is the need to define the point at which navigation begins and the point at which navigation ends.**
8. **There is a need to navigate patients across disconnected systems of care, such as primary care sites and tertiary care sites.**
9. **Patient navigation systems require coordination.**
The patient navigator is the individual assigned to work directly with individual patients within the framework of a patient navigation system. The role of the navigator in relation to other healthcare professionals, such as nurses and social workers, remains a topic of debate [10]. As described in Freeman’s nine principles of navigation, the skill set and qualifications of the navigators are dictated by the phase of navigation in which the navigator is participating in patient care. Therefore, the credentials of the navigator should correlate with the navigation of program goals and phase of navigation. For example, a navigator working with patients with abnormal screening tests may require a different skill set than a navigator working with patients during the active treatment or survivorship phases of their disease. The former needs skills related to coordination of appointments, transportation, and assisting with financial issues, while in the latter, the navigator may need knowledge of the usual course of therapy and an understanding of the side effects of therapy. The navigator’s main goal is to overcome barriers to completing the course of cancer care. Barriers may include a lack of resources to pay for care, difficulties navigating complex systems, communication and language barriers, transportation and childcare issues, or fear and/or mistrust issues. System-based barriers identified include coordination of receipt and processing of outside medical records, such as pathology and radiology reports, diagnostic or consultation information prior to provider visits, as well as scheduling complexities, particularly in regards to multidisciplinary care. In most programs, navigators are identified from the communities that they serve, and thus are typically similar in terms of demographic, social, and racial/ethnic background as the target patient population. The intent is to ensure culturally sensitive interactions and engagement, and thus increase the likelihood that patients will follow-up within the healthcare system program of care. In the early breast cancer programs, navigators were generally identified as dedicated people from the community that the clinic and programs served who could identify and communicate with the population that was being served, but also had a solid knowledge of the system of care and clinical and administrative workings of the healthcare environment through which they guided patients.

Several descriptive and qualitative studies have examined the role of the navigator. Jean-Pierre et al. analyzed patient navigator interview data and categorized patient navigator tasks into two different types of interventions: instrumental and relationship [11]. Instrumental interventions were defined as task-oriented, such as assisting patients in arranging transportation or making appointments. Relationship interventions involved efforts by the navigator to strengthen interpersonal relationships between the patient and providers. Davis et al. identified four themes from patient interviews to describe the role of the navigator [12]. These themes included (1) addressing access to care needs, (2) addressing emotional and practical concerns, (3) addressing patient family concerns, and (4) being involved throughout the continuum of care from diagnosis to survivorship. In another study, Lin and colleagues identified the three most common barriers that patient navigators spent their time working on with patients [13]. These included (1) insurance and out-of-pocket expenses, (2) transportation issues, and (3) helping manage feelings of fear associated with cancer. Based on these studies, it is clear that the role of the navigator is not strictly defined, and although there are common themes, the role and qualifications of the navigator are defined by the navigation system and phase of care with which the navigator is involved. Figure 32.1 displays many of the central roles of the patient navigator in relationship to community health workers and case managers [2].

Disparities in bladder cancer

A large body of research has consistently demonstrated higher mortality rates among minorities and low-income groups [14–16]. This disparity has been attributed to differences in access, differential utilization of health services, more limited resources, lower levels of health literacy, limited outreach programs to promote healthy behaviors, and higher prevalence of risk-promoting behaviors, such as smoking, among disadvantaged groups [17, 18]. Among bladder cancer patients, previous research has documented disparities in care received and outcomes among minorities, low-income groups, and women. For example, although bladder cancer incidence rates are lower among African Americans, bladder cancer related mortality rates are as much as 70% higher than whites. In addition, studies have shown that African Americans consistently present with more advanced stages of bladder cancer.
Patient navigation and cancer navigator programs

Compared to whites [19–22], and that this difference may be exaggerated among black women. In one study, blacks presented with non-localized, potentially incurable disease approximately 10–12% more often than whites, and suffered 4–7% lower survival over a 25-year period [23]. Disparities in how blacks are treated compared to whites have been suggested as well. Barocas and colleagues found that black patients are more commonly treated by low-volume surgeons and at low-volume hospitals, and experienced higher rates of adverse outcomes compared to white counterpart patients treated with cystectomy [24]. In another study, black patients treated for bladder cancer were significantly more likely to die from bladder cancer than whites (HR 1.23, 95% CI: 1.07–1.42), despite relatively few differences in the type of care they received. Even after accounting for minimal differences in treatment intensity and provider effects, survival among blacks remained poorer (HR 1.22, 95% CI: 1.06–1.42) [25].

Gender disparities have also long been noted. Women are more likely to experience delays in care, present with later-stage disease, and have lower survival compared to men [23, 26–28]. The oft-noted difference in late-stage presentation is likely closely linked to delays in referral and evaluation. Untimely referral may signal under-evaluation or misdiagnosis of microscopic or gross hematuria, which are commonly presumed to result from urinary tract infection in women. Recent evidence form a large population study supports these sources of delay.

In a large study examining clinical encounters for gross hematuria and subsequent diagnosis of bladder cancer, Cohn et al. noted that women who were subsequently found to have bladder cancer were significantly more likely to be diagnosed with a urinary tract infection initially (OR 2.32, 95% CI: 2.07–2.59), and a larger proportion of women were diagnosed with bladder cancer greater than six months after the initial claims evaluation for hematuria (17.3% vs 14.1%) compared to men [29]. Such delays may explain the higher mortality rate suffered by woman diagnosed with bladder cancer, which has been estimated at a 5% absolute decrease in five-year survival after adjusting for age and expected mortality [30]. Another study showed that women are frequently less likely to be referred for urologic evaluation compared to men [31]. Although more likely to present with a delayed diagnosis, survival appears lower among women across stages, raising questions regarding unappreciated factors that may contribute to survival differences among men and women other than presentation with more advanced disease [28].

Disparities often result from barriers in access or timeliness of care. Several studies, for example, have shown that outcomes are similar regardless of race, if access is equivalent [32, 33]. Sociodemographic and economic factors have also been linked to access to healthcare, as well as the risk of presenting with late-stage cancers. Access may be limited by financial barriers, such as low income, problems securing transportation to clinics and

Figure 32.1 Patient navigator roles and relationships with community health workers and case managers. Source: Vargas et al. 2008 [2]. Adapted with permission from the American Cancer Association.
hospitals and lack of health insurance, or by limited awareness regarding unhealthy behaviors that increase risk or ignorance of signs and symptoms that result in later presentation. Lack of health insurance or under-insurance has been linked to differences in cancer outcomes, such as late-stage presentation. For example, Mouw and colleagues found that men with less education (less than a high school degree) were 20% more likely to develop bladder cancer compared to men with an education beyond a college degree, even after adjusting for behavior risks such as smoking [34]. Compared to privately insured individuals, those with no insurance or covered by Medicaid more frequently present with later-stage cancers [35–38]. As in other cancers, socioeconomic factors and access to healthcare are closely associated with bladder cancer outcomes [39]. For example, patients who lack insurance or are covered by Medicaid are twice as likely to present with regional disease (as opposed to local disease), and 60% more likely to be diagnosed with locally advanced bladder cancer compared to those who have private health insurance. Uninsured and underinsured patients are also less likely to receive aggressive local treatment, such as cystectomy [37, 40]. Differences in care such as this likely translate to poorer outcomes. One study, for example, reported a 50 to 70% increased risk of death among uninsured or Medicaid insured bladder cancer patients [41]. Another demonstrated that among bladder cancer patients, those with no insurance had significantly lower survival (increased risk of death HR 1.76, 95% CI: 1.14–2.71) compared to patients covered by private insurance or with Medicaid [42].

The role of the patient navigator in reducing disparities

Patient navigation programs and navigator activities address several Affordable Care Act objectives to target and reduce health disparities in the US. These include: (1) prevention and early detection, (2) healthcare access and coordination, (3) insurance coverage and continuity, and (4) diversity and cultural competency [43]. For example, patient navigators can further improve utilization of early detection and preventative services by facilitating and increasing access to the healthcare system for underserved or uninsured groups. This is one of many critical issues in battling disparities. Although the use of screening tests has increased for all races and ethnicities over the past two decades, prevention and early detection still fall short of Healthy People 2010 goals [44], and without proper guidance and access, many underserved (e.g. minority, low-income, and un/underinsured) patients would not be able to receive preventative care or undergo early cancer evaluation.

Patient navigation is the main way that racial/ethnic minorities are directed to Federally Qualified Health Centers where preventative and screening care are provided to underserved groups [45–47]. Navigators may also help patients negotiate the health system to improve access to providers, establish referral and follow-up appointments, and receive recommended healthcare. This includes counseling and guidance through system barriers that might otherwise prevent disadvantaged individuals from seeking or successfully obtaining care, such as raising awareness of early detection and screening programs, addressing insurance issues that may prevent appointments from being scheduled, helping to overcome other financial barriers that would make clinic visits less likely without navigation, bridging language barriers that may prevent non-English-speaking patients from receiving a comprehensive evaluation, and by providing education and support to patients so they can more fully engage with their providers and the healthcare system [43, 48].

In addition to mitigating or eliminating structural, system, and practical barriers, navigators may further reduce disparate access and care through more appropriate, culture-sensitive counseling, advice, and guidance. This is a paramount component of navigation, given that the same racial and ethnic minority groups who experience greater difficulty accessing healthcare also tend to harbor greater distrust of the healthcare system. For example, previous research in this area has demonstrated that patient distrust contributes to delays in treatment, lower quality care, and higher rates of non-adherence, as well as a lower likelihood of compliance and follow-up [49, 50]. Navigation, in turn, is one of the most direct ways to address cultural issues and to foster and rebuild trust in the healthcare system so that disadvantaged groups start on an equal footing and are more likely to follow-up for continued care [48,51]. Other research has shown that provision of emotional support and providing helpful information are the most important services offered by navigators and navigation programs [52].
Measuring the impact of navigation programs

Despite the many potential inroads that navigation programs may establish to reduce disparities in cancer care, consensus regarding how to evaluate the impact of navigators has not been fully sorted out. In response to the common concern that outcomes pertaining to published reports of navigation programs have been inconsistent, the American Cancer Society hosted the National Patient Navigation Leadership Summit in 2010 to tackle the question of how best to measure the impact of patient navigation. The summit resulted in a group of proposed core metrics that can be used to assess the success and results of patient navigation programs. These proposed measures were discussed in a series of papers published in a special supplement of Cancer in 2011. Proposed measures included adherence to screening guidelines, likelihood of presenting with early-stage disease, continued follow-up care, and patient endorsement regarding perceived barriers and qualitative aspects of patient-provider interactions during health encounters (Table 32.1). A full review of the proposed metrics is beyond the scope of this chapter; however, detailed descriptions and discussions of potential core measures can be found in several articles [48, 53, 54].

Table 32.1 Health disparities, navigator activities, and potential measures of the impact of patient navigation.

<table>
<thead>
<tr>
<th>Health disparity</th>
<th>Navigator activity</th>
<th>Measures of impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventative care/early detection</td>
<td>Educate patients regarding screening and early detection guidelines and recommendations</td>
<td>Probability of screening according to guidelines</td>
</tr>
<tr>
<td>Timely cancer screening</td>
<td>Identify providers/clinics for screening evaluations</td>
<td>Percentage of cancer cases diagnosed at early stage</td>
</tr>
<tr>
<td>Early-stage disease detection</td>
<td>Educate patients regarding early signs/symptoms of cancer</td>
<td>Reduction in cancer incidence rates</td>
</tr>
<tr>
<td>Population cancer rates</td>
<td></td>
<td>Change in cancer incidence rates</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare access and coordination</td>
<td>Assist patients with identifying a primary care medical home</td>
<td>Increased likelihood of usual source of care or medical home</td>
</tr>
<tr>
<td>Medical home or usual source of care</td>
<td>Assist with appointments as needed</td>
<td>Increased likelihood of at least one visit/evaluation yearly</td>
</tr>
<tr>
<td>Annual evaluation</td>
<td>Facilitate ancillary care, medications, and equipment as necessary</td>
<td>Decreased comorbidities</td>
</tr>
<tr>
<td>Patient–provider relationship</td>
<td>Provide and coordinate patient education</td>
<td>Decreased perception of problems obtaining care</td>
</tr>
<tr>
<td>Ability to obtain timely care</td>
<td>Assist with transportation needs</td>
<td>Increased cancer knowledge</td>
</tr>
<tr>
<td>Evidence-based care</td>
<td></td>
<td>Change in preventative health and wellness behaviors</td>
</tr>
<tr>
<td>Compliance with recommendations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insurance coverage</td>
<td>Determine eligibility for Medicare, Medicaid, or public health and safety net programs</td>
<td>Increased probability of obtaining and maintaining insurance coverage</td>
</tr>
<tr>
<td>Coverage</td>
<td>Assist with applications</td>
<td>Increased percentage of patients receiving evidence-based care</td>
</tr>
<tr>
<td>Continuity</td>
<td>Monitor eligibility renewal dates and assist with renewal to ensure continuity of coverage</td>
<td></td>
</tr>
<tr>
<td>Diversity/cultural competency</td>
<td>Serve as support during visits</td>
<td>Increased perception that the provider listened, showed respect, and spent adequate time with patient</td>
</tr>
<tr>
<td>Language barriers</td>
<td>Facilitate communication between providers and patients, particularly</td>
<td>Receipt of language assistance</td>
</tr>
<tr>
<td>Cultural conflicts</td>
<td>regarding expectations, needs, and perspectives</td>
<td>Health literacy scores</td>
</tr>
<tr>
<td>Trust in physician and healthcare system</td>
<td>Identify and access community resources</td>
<td></td>
</tr>
</tbody>
</table>

Few studies have examined the efficacy of cancer patient navigation programs. In 2011, Paskett et al. performed a systematic review of the published literature on cancer patient navigation. They focused their search on original studies that reported quantitative, qualitative, or mixed method results of cancer screening, diagnosis, clinical trials, or survivorship [55]. The authors identified 17 cancer patient efficacy studies and 16 descriptive or qualitative studies. The overwhelming majority of these studies reported on cancer patient navigator programs targeted toward patient populations at higher risk of not receiving adequate cancer care due to cultural, economic, geographic, or social disparities. This systematic review had several notable findings. Eight of the identified efficacy studies tested the impact of patient navigation on screening rates for breast, cervical, or colorectal cancer. The majority of these reported results favoring the navigation intervention compared to non-navigation control groups, suggesting that patient navigation in this setting improves cancer screening. One study evaluated the effect of a navigation intervention on breast cancer stage at diagnosis. They noted an increase in stage 0 disease from 12.4% to 25.8% after implementation of the intervention. They also noted a reduction in stage 4 disease from 16.8% to 9.4%. It should be noted that this study also included community outreach, so it is difficult to know how much of the reduction in stage can be attributed to the navigation portion of the intervention. Finally, seven of the identified efficacy studies focused on measuring treatment outcomes. The results from these studies were mixed, ranging from no statistically significant improvements to modest improvements in satisfaction and quality of life, as well as fewer missed days of radiation therapy.

Other authors have proposed evaluating cancer patient navigation programs in terms of cost effectiveness. Ramsey et al. describe the framework for measuring cost effectiveness in the navigation setting using similar techniques for other cost-effectiveness analyses [56]. They defined the incremental cost effectiveness of navigation (ICEN) as:

\[
\text{ICEN} = \frac{(C_{\text{nav}} - C_{\text{uc}})}{(E_{\text{nav}} - E_{\text{uc}})}
\]

where \(C_{\text{nav}}\) and \(C_{\text{uc}}\) are the total costs of navigation and usual care, and \(E_{\text{nav}}\) and \(E_{\text{uc}}\) are the effectiveness of navigation and usual care. Effectiveness may be measured using intermediate outcomes for navigation targeted at different phases of cancer care (e.g. screening rate, diagnostic resolution, completion of therapy), or it may assess the overall effectiveness of a program in quality-adjusted life years. This latter measure has many methodologic and practical challenges that are beyond the scope of this chapter. Only one recent study evaluated the cost effectiveness of a patient navigation intervention. Lairson and colleagues reported on a patient navigation intervention aimed at colonoscopy for colon cancer screening [57]. Comparing two different navigation interventions of different intensity to usual care, they found that the incremental cost effectiveness ratio (with effectiveness defined as receiving colonoscopy) varied between $906 and $1957 between navigation interventions of differing intensity.

**Conclusion**

Disparities in access, care, and outcomes are pervasive across healthcare and affect cancer patients significantly. Among bladder cancer patients, health disparities include differences in access, treatment, and survival across social, economic, racial, ethnic, and gender lines. Patient navigation programs have shown early promise in reducing barriers to access and treatment, but have not yet been developed, implemented, or studied broadly in bladder cancer. As additional evidence quantifying the efficacy and impact of patient navigation programs becomes available, the rationale to develop bladder cancer navigation programs will likely build. These efforts will most likely develop from grassroots efforts, particularly among invested stakeholders, such as clinicians and researchers affiliated with CoC accredited cancer centers. Such programs may move the needle and reduce disparate access, care, and outcomes.

**Useful web links**

References

CHAPTER 33

Impact of health services on compliance and outcomes

Heather Honoré Goltz¹,², Marc A. Kowalkowski³, G. John Chen⁴, and David M. Latini⁵

¹ College of Public Service, University of Houston-Downtown, Houston, TX, USA
² Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, Houston, TX, USA
³ Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA
⁴ Division of Health Services Research, University of Kansas School of Medicine, Kansas City, KS, USA
⁵ Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA

KEY POINTS

• Little work has been done on adherence to follow-up schedules in either early- or late-stage bladder cancer.
• The few studies that do exist focus on patient-level variables, many of which are not clinically modifiable intervention points, and all the studies are descriptive.
• Emerging work with early-stage patients has identified patient-level factors such as fear of cancer recurrence/progression and disease-specific literacy that can be targeted in intervention studies.
• New tools, such as survivorship care plans, are emerging that can target both patient factors and systemic factors that affect adherence.
• Research is needed on urologist-related and other systemic factors that affect adherence.
• Studies are needed that focus on multi-level interventions to improve adherence with cystoscopy and post-cystectomy follow-up.

Introduction

Two organizations – the American Urological Association (AUA) and the National Comprehensive Cancer Network (NCCN) – influence the intensity and types of bladder cancer surveillance in the United States. A third major organization, the European Association of Urology (EAU), influences bladder cancer surveillance both in Europe and worldwide. While the AUA, NCCN, and EAU bladder cancer surveillance guidelines are based on expert opinion or “retrospective experience,” they differ widely on one primary issue – intensity of follow-up. The EAU guidelines contain explicit risk stratification and lower-frequency follow-up regimens than the AUA or NCCN [1, 2].

In terms of non-muscle-invasive disease (NMIBC), the current AUA guidelines recommend a cystoscopy every three months for the initial two-year period post-treatment, every six months for an additional two to three-year period, and then annually thereafter [3]. Similarly, the NCCN recommends cystoscopy in three to six month intervals for the first two years, with longer intervals thereafter [4]. In contrast, the EAU guidelines vary surveillance intensity and duration based on NMIBC patients’ risk levels. EAU guidelines state that patients with “low risk” tumors should receive cystoscopy at three months after the initial treatment; patients with negative results then undergo another cystoscopy nine months later and then annually for five years [5]. Low-risk patients who are recurrence-free after five
years may discontinue cystoscopy or use less-invasive surveillance techniques for follow-up. The EAU recommends “life-long” cystoscopic surveillance for patients with “intermediate” or “high-risk” tumors [6]. Additionally, AUA, NCCN, and EAU guidelines recommend upper tract imaging for high-risk NMIBC patients. Urinary biomarkers may be used as part of surveillance, but are not currently recommended as a standard of care by any organization [3, 5].

Guidelines for surveillance of muscle-invasive disease (MIBC) and metastatic disease also differ between the AUA, NCCN, and EAU. Current AUA and NCCN guidelines recommend post-cystectomy follow-up in three to six month intervals for the first two years, with longer intervals thereafter [3, 4]. EAU (2013) guidelines for post-cystectomy follow-up with MIBC survivors suggest renal ultrasounds, cytology, and laboratory tests at three months post-surgery; depending on clinical characteristics of the primary tumor, CT scans or thoracic/abdominal MRIs with upper urinary tract are also recommended. These procedures, excluding renal ultrasounds, are repeated at six months post-cystectomy and at six-month intervals thereafter. After five years of surveillance, EAU guidelines recommend that “functional” and not “oncological surveillance” be used in imaging for urothelial carcinoma, regardless of cystectomy status.

Given that none of the current guidelines provide an “ideal surveillance regimen” for bladder cancer [2], a number of recent studies have investigated optimizing this process [7–9]. However, such efforts have to balance the need for clinical efficiency with potential implications for patient outcomes. For example, van der Aa and colleagues [10] highlight the relative importance of results of the first three-month cystoscopy post-diagnosis. According to their meta-analysis, positive cystoscopic results for tumor recurrence or progression at the three-month mark were the strongest prognostic factor for tumor recurrence among NMIBC survivors. Even so, a later study by Strope and colleagues [8] determined that the intensity (i.e., frequency) of surveillance for many, but not all, individuals in a sample of SEER NMIBC patients was concordant with the risk profiles for their bladder cancers. As many as one-fifth of the NMIBC patients in the sample with the highest and lowest risk received surveillance that was discordant with the risk profiles for their cancers. Specifically, almost 10% of low-risk NMIBC patients received high-intensity monitoring, while over 20% of high-risk patients received low-intensity follow-up.

Existing health services and behavioral medicine research indicate that a number of macro-level (i.e., health systems) and micro-level (i.e., patient) factors affect patients’ and survivors’ compliance with treatment and surveillance, and resulting health outcomes. The current chapter will provide a brief overview of clinically- and operationally-modifiable micro and macro factors, as well as evidence-based recommendations for increasing compliance with surveillance and health and psychosocial outcomes.

**Macro factors**

The delivery of optimal surveillance care of cystoscopy requires patients to be compliant with the monitoring plan initiated by their urologists AND urologists to practice guideline-concordant care. The only study that examined Medicare NMIBC patients’ adherence to the guidelines recommended care showed that nearly 60% of Medicare fee-for-service patients with NMIBC did not receive optimal surveillance with cystoscopy [11]. However, this study did not measure urologists’ adherence, so we do not know whether the low utilization of surveillance cystoscopies was due to patient factors related to compliance and/or the urologist’s adherence to guideline recommendations. Thus, the true effect of patient compliance on receipt of the guideline-recommended surveillance care is currently not known in routine practice settings. More recent research suggests that rising costs of outpatient care may be influencing providers to offer less intensive follow-up to high-risk patients [8]. In a 2011 study, Dalbagni and colleagues found that urologists varied widely in their post-cystectomy surveillance and, as a group, did not adhere to pre-determined schedules [11].

Economic factors impacting patient/survivor adherence to treatment or surveillance include, but are not limited to, employment status, short- and long-term disability insurance, health insurance, disability and retirement benefits, and healthcare costs [12]. Udell and colleagues recently conducted cost comparisons of direct expenditures using the AUA and EAU guidelines for a 2010 cohort of Medicare patients with low-grade NMIBC [2]. Based on their results, the cost of using AUA guideline-concordant surveillance was
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approximately $US14,500 per patient, or approximately $510.7 million for the five-year total cohort costs. Use of EAU guideline-concordant care was estimated to cost approximately $US6,700 per patient, resulting in healthcare cost savings of almost $US275 million over the same five-year period. While much of this medical expenditure may be absorbed by public or private insurance, bladder cancer patients, caregivers, and families still contend with potential non-covered costs such as co-insurance and deductibles [13]. Additional costs such as transportation, parking, prescription drugs, or lost time from work and the resulting reductions in wages are also not included in many studies on the economic impact of bladder cancer surveillance.

Micro factors

The 2006 Institute of Medicine (IOM) report, From Cancer Patient to Cancer Survivor: Lost in Transition, [12] highlights a number of psychosocial, economic, and familial/relationship issues impacting cancer patients’ and survivors’ ability to access quality health services and related health outcomes. A cancer patient’s or survivor’s psychological and emotional health, resilience, self-efficacy (i.e., belief in his/her ability to effectively perform a health behavior such as managing a treatment-related symptom), cancer knowledge, health literacy, treatment preferences, and fear of recurrence are a few of the psychosocial factors that influence motivation and likelihood of compliance with treatment and surveillance. Familial and relational factors include marital or relationship status, family dynamics, peer and social support, and support networks. Any one psychosocial, economic, or familial/relational factor, or several in combination, may influence whether patients successfully transition from active treatment to the long-term surveillance and health promotion efforts associated with the survivorship period [12].

Bladder cancer treatment and surveillance protocols, in particular, can be intensive and invasive. Research by van der Aa et al. [14] represents one of the few existing non-epidemiologic studies of bladder cancer patients’ self-reported experiences with routine cystoscopy. A substantial number of patients reported “quite” or “very” discomfoting or painful experiences during preparation for cystoscopy and introduction of the cystoscope, as well as during and immediately after the cystoscopy. In the one-week period following the procedure, over one-fourth of participants reported painful urination (28.7%) or increased frequency and urge to urinate (27.1%). Smaller numbers reported having fever (1.3%) and some degree of hematuria (7.5%). While short-duration physical symptoms are routinely discussed as part of cystoscopic surveillance, of greater concern are the numbers of respondents who reported on the psychosocial impact of cystoscopy. Approximately 20% reported that post-cystoscopy physical symptoms had an impact on their ability to participate in daily activities and 12% reported impacts on social activities.

In terms of bladder cancer survivorship, a number of patient- or micro-level factors influence whether NMIBC and MIBC survivors are compliant with cystoscopic surveillance. Using Surveillance, Epidemiology and End Results (SEER)-Medicare data, a number of micro-level factors were associated with non-compliance including patients’ age, geographic location, race/ethnicity, socioeconomic status, and tumor characteristics. NMIBC patients who were African American, over age 75 years, had multiple comorbid health conditions, lived in urban or low-income communities, and had poorly differentiated bladder tumors were less likely to be adherent to bladder cancer surveillance.

A Medicare-based study by Chamie and colleagues [15] also found patient-level variations in compliance with NMIBC surveillance. Female gender was found to independently predict higher likelihood of compliance with cystoscopy, whereas higher educational attainment was associated with higher likelihood of compliance with urine cytology testing. Advanced age (≥ 80 years) was associated with a higher likelihood of non-compliance with urine cytology testing. A recent study by Dalbagni and colleagues [11] also found widespread non-compliance with surveillance among post-cystectomy patients.

More recent studies on bladder cancer highlight the economic costs of surveillance and impact on patients’ and survivors’ quality of life and health outcomes. For example, another study published by Chamie et al. [16] demonstrated higher survival rates among NMIBC patients who received at least half the amount of recommended surveillance care. However, these studies rarely address micro-level factors impacting compliance with cystoscopy surveillance [17]. The few existing studies exploring micro-level factors’ impact on treatment intensity and
access to care highlight factors that are well known to impact access and health outcomes, but are not necessarily clinically modifiable (e.g., race/ethnicity, socioeconomic status). The following are research study results highlighting clinically modifiable micro-level factors that the current authors have identified as potentially impacting compliance with cystoscopic surveillance.

**Health literacy and disease-specific literacy**

According to the IOM, health literacy may be defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions” (p. 32) [18]. This concept includes, but is not limited to, the writing, reading, numerical, listening, and speaking skills necessary to procure and understand health information. A number of studies have demonstrated linkages between low health literacy, adherence to treatment or surveillance, and poor health outcomes [19–23].

Beginning in 2007, an interprofessional group of urologists, social workers, psychologists, and epidemiologists began the Bladder Cancer Outcomes Study (BCOS), a cross-sectional mixed-methods study focused on bladder cancer health-related quality of life, symptom management, and barriers and facilitators of access to treatment and surveillance in early-stage patients. Later, a small sample of later-stage patients was recruited for the quantitative phase of the study. Survivors were recruited from the internet, a private medical school, and available medical records, forming a five-item NMIBC literacy test. Survey items were dichotomously scored (1 = knowledge present; 0 = knowledge absent) and summed, producing disease-specific literacy scores.

In the disease-specific literacy analysis, participants completed one-hour telephone-based qualitative surveys (NMIBC n = 117; MIBC n = 18) or semi-structured qualitative interviews (NMIBC n = 26). Study-eligible survivors were less than four years post-bladder cancer diagnosis, had no history of radiotherapy, and were fluent in written and spoken English. Cystectomy, which might indicate a history of higher-grade tumors, was not an exclusion criterion for participating in either study.

BCOS investigators used both qualitative and quantitative data to examine overall patient literacy [24]. Qualitative participants (n = 26) were also assessed using the seven-item Rapid Assessment of Adult Literacy in Medicine-Short Form (REALM-SF). In terms of educational attainment, the majority of participants completed high school or some degree of college coursework (88.5%). Their REALM-SF scores varied based on race-ethnicity and gender. Overall, male participants (n = 22) averaged 6.1 points on the REALM-SF, which corresponds to moderate health literacy, or 7th or 8th-grade reading level, and indicates such participants will experience difficulty reading and understanding most patient education materials. Female participants (n = 4) averaged 6.5 points. All African American male participants (n = 3) received scores corresponding to low-to-moderate health literacy, whereas the majority of white male participants (n = 19) received scores corresponding to moderate-to-high health literacy. Most female participants (n = 3) received REALM-SF scores of 7 points, indicating high health literacy, or high school reading level and ability to read and understand most patient education materials. Yet, a number of male and female participants reported little disease-specific knowledge, and even confusion about their bladder cancer treatment and surveillance histories.

BCOS investigators conducted a follow-up secondary analysis of mixed (qualitative and quantitative) data that explored NMIBC survivors’ disease-specific literacy [25]. Disease-specific literacy was conceptualized as the ability to understand bladder cancer-specific knowledge; understand how this information applies to cancer diagnosis, treatment, and surveillance; and apply this knowledge in making cancer care-related decisions. Researchers hypothesized that disease-specific literacy would be associated with more advanced understanding of bladder-cancer-specific information such as clinical and disease characteristics (e.g., stage and grade, risk factors), common treatments, and surveillance protocols.

Four survey items were combined with a fifth item evaluating congruence between reported stage/grade and available medical records, forming a five-item NMIBC literacy test. Survey items were dichotomously scored (1 = knowledge present; 0 = knowledge absent) and summed, producing disease-specific literacy scores. Two coders independently analyzed verbatim qualitative transcripts for evidence supporting the presence or absence of each item; these items were then summed to produce disease-specific literacy test scores for interviewees. Any discrepancies in qualitative interview coding were settled via consensus-building.

In the disease-specific literacy analysis, participants were primarily male, of older age, and self-reported their race/ethnicity as white. Fifteen percent of study participants were current smokers and the majority of participants were former smokers. Survey respondents
were not queried concerning pre-diagnosis bladder cancer awareness; however, 12% reported having family histories that were positive for bladder cancer. Additionally, four qualitative interviewees (15.4%) reported that a relative or peer had been diagnosed with bladder cancer.

Most study participants knew their treatment histories (90.1%) and understood primary bladder cancer risk factors or practiced risk reduction (84.6%). Fewer knew their bladder cancer stage/grade (41.3%) or whether their family health history included bladder cancer (23.8%). Less than 40% of participants had accurate understanding of their bladder cancer stage/grade.

Bivariate analyses revealed significant differences in disease-specific literacy test scores based on sex, educational attainment, and relationship status. Females, participants with some college education, and those who were currently married scored significantly higher on the test (all \( p < 0.05 \)). Race/ethnicity and time since bladder cancer diagnosis were not significant in bivariate analyses. In multivariate linear regression analysis controlling for socio-demographic and clinical variables, older age (\( \beta = -0.03 \)), male sex (\( \beta = -0.54 \)), and unmarried status (\( \beta = -0.24 \)) predicted lower disease-specific literacy scores (all \( p < 0.01 \)). Higher educational attainment (\( \beta = 0.26 \)) predicted higher literacy scores (\( p < 0.01 \)).

Findings from this exploratory study suggest that many individuals at high risk for bladder cancer have little pre-diagnosis disease awareness and limited understanding of important prognostic factors (e.g., tumor stage). Bladder cancer awareness and knowledge, as well as the ability to apply this information to screening, treatment, and surveillance, are essential for disease-specific literacy. Patients and survivors who have adequate disease-specific literacy are better able to participate in surveillance activities, which increase early detection rates and heavily impact survival rates. Study findings support the need for disease-specific education and psychosocial and symptom management resources for bladder cancer patients, survivors, and caregivers. Proposals for interventions and recommendations for resources are given later in this chapter.

**Barriers and facilitators to cystoscopic adherence**

BCOS qualitative data were examined to determine factors associated with adherence to cystoscopic surveillance [24]. Interview data from a subsample consisting of the first ten transcribed interviews were evaluated using holistic content and constant comparative qualitative analyses to identify common themes reported across interviews. Emerging themes revealed detailed information on the impact of NMIBC across multiple domains, including psychosocial, economic, familial/relational, and healthcare.

Participants in this subsample ranged in age from 52–85 years, and were white (70%) or African American (30%), male, married or in long-term relationships (90%), and had completed high school (90%). The majority of participants reported ongoing concerns about the surveillance process (e.g., pain and/or anxiety associated with cystoscopy). Participants also reported several potential barriers to cystoscopic adherence including, but not limited to, transportation or commuting to cystoscopy appointments; concerns with medical and non-medical financial costs associated with cystoscopy (e.g., time off from work, fuel costs, clinic/hospital parking).

Potential facilitators associated with adherence to surveillance schedules included social and emotional support from significant others, relatives, and peers; spirituality or religion; trust in urologists’ expertise and judgment; and trust in and good communication with nursing staff. The most commonly endorsed facilitator of cystoscopic adherence was participants’ desire to receive “good” test results (i.e., results indicating they are tumor-free). If results were positive for the presence of recurrence or progression, participants indicated that they were at least reassured by having participated in early detection. Interestingly, all participants noted that they had never missed cystoscopy appointments. Even when appointments had to be rescheduled by themselves or their urologists, these survivors reported 100% compliance with appointments. Findings from the larger qualitative study, including interviews with four female NMIBC survivors, mirrored those of the subsample.

While the adherence rates reported in this small exploratory study are unheard of in clinical settings, their stated barriers and facilitators to cystoscopic adherence warrant closer inspection. Bladder cancer patients and survivors similar to study participants who reported experiencing anxiety or depression about the surveillance process or who had lower disease-specific knowledge might benefit from health education and promotion programs that are age-, culturally-, and linguistically-appropriate. In such cases, increasing disease-specific literacy may reduce context-specific mental health symptoms and increase adherence.
Additionally, cancer patient navigation programs and services are designed to reduce barriers to participating in screening, treatment, and surveillance [26, 27]. Implementing such programs in urology clinics or cancer centers may also facilitate greater adherence to cystoscopy among bladder cancer survivors, reducing progression, morbidity, and mortality rates.

**Fear of recurrence**

Fear of recurrence (FOR), particularly as it may contribute to non-adherence to surveillance, is understudied among NMIBC patients and survivors. BCOS investigators conducted secondary analyses of mixed data exploring NMIBC survivors’ FOR [25]. The researchers used dichotomized survey responses to a five-item FOR measure and then coded qualitative interview \( (n = 143) \) transcripts by locating passages that were exemplars indicating the presence or absence of a specific item on the FOR measure. The resulting FOR scores ranged from 0, meaning no FOR, to 5, meaning high FOR. The mixed data were analyzed using \( t \)-tests and stepwise regression procedures in SAS v9.2.

Survivors in the combined samples were diverse, ranging in age from 29–87 years, non-white (8.4%), and female (25%). While their scores indicated moderate FOR, recurrence anxiety varied based on cystectomy status. NMIBC survivors with histories of cystectomy scored significantly lower on the FOR measure \( (p < 0.001) \). Even after adjusting for time since diagnosis and other demographics, participants without histories of cystectomy scored significantly higher in terms of FOR \( (p < 0.001) \).

When researchers consulted qualitative interview transcripts to enhance their understanding of these findings, content analysis of the qualitative data revealed that participants associated their intact bladders with bladder cancer. Its presence was a reminder of the high rates of disease recurrence and potential for cystectomy. In contrast, participants who had undergone cystectomies tended to believe that the bladder cancer surgery had “cured” them and removed all chances for disease recurrence.

Given the moderate levels of fear of cancer recurrence found in these samples of NMIBC survivors, it is not difficult to imagine that this is not an isolated phenomenon. Comprehensive bladder cancer survivorship care should include psychoeducation and, when necessary, appropriate referrals to mental health and other specialists to address the unique and varied needs of this population. Tailoring such efforts to actual disease risk and recurrence profiles may help to alleviate chronic anxiety and FOR, as well as increase rates of compliance with surveillance.

As the previous studies demonstrate, much more translational and health services research is needed to accurately document clinically modifiable factors and develop the interventions necessary to improve patients’ and survivors’ access to quality bladder cancer care and participation in surveillance appropriate to their disease risk. Such interventions may provide direct and indirect effects on bladder cancer health outcomes such as early detection, delay of tumor recurrence or progression, and reduced morbidity and mortality rates.

**Potential interventions/recommendations**

The 2008 IOM report, *Cancer Care for the Whole Patient*, describes several psychosocial, economic, and familial/relational factors that affect the health and healthcare of cancer patients and survivors [28]. These issues include needs for health information, emotional support, disease self-management, lifestyle/behavioral change, material and logistical resources, financial resources, and management of work, school, and family life balance. Based on these issues, the report provides a model of psychosocial healthcare and suggests a number of formal services as part of a suggested standard of quality cancer care.

A number of complex and dynamic micro- and macro-level factors impact whether bladder cancer patients and providers are adherent to guideline-recommended cystoscopic surveillance. Identifying clinically modifiable factors and understanding interrelationships among these factors and how they impact delivery and receipt of optimal surveillance is important for the design and implementation of effective health service interventions. The following interventions have demonstrated effectiveness across a number of cancer sites and are concordant with formal services recommended in the aforementioned 2008 IOM report.

**Interventions for providers and medical settings**

The 2008 IOM report suggests that the patient and family develop a partnership with the provider team (pp. 7–8). As part of this partnership, the patient/family-provider team will identify existing psychosocial
needs and develop and implement a plan addressing these needs. As an important first step, urologists will need to consider the diverse needs of bladder cancer patients and survivors in developing a tailored approach to the provision of biomedical care. While urologists necessarily serve as the primary medical provider and head of the care team, individual patients and survivors may benefit from a multidisciplinary team approach that includes allied health and mental health specialists such as wound/ostomy care nurses, physical and occupational therapy, social workers, and dieticians [29]. This provider team approach would aid urologists in integrating biomedical and psychosocial information into a care plan; simplify communication internal to the team and external referrals; and facilitate more efficient and effective cancer care delivery, including active surveillance for bladder cancer recurrence and progression. This type of team approach currently exists in a number of healthcare systems and settings, including Veterans Affairs (VA) and the University of Texas M.D. Anderson Cancer Center, and can be adapted to many practice settings.

In addition to multidisciplinary teams, the IOM also recommends formalized bladder cancer survivorship care plans [12]. Cancer survivorship care plans (SCP) are “living,” portable documents consisting of two primary components. The first part is a treatment summary that contains a record of the patient’s cancer diagnosis, tumor characteristics, treatments received, and any supportive services received during the treatment phase of cancer care. The second part, which is the true “care plan,” includes referrals for providers overseeing follow-up care and surveillance, information on late- or long-term cancer and treatment effects, health promotion and disease prevention activities, and cancer-specific community resources. Previous research studies by the Bladder Cancer Advocacy Network (BCAN) Survivorship Working Group have resulted in the first bladder-cancer-specific SCP [30, 31]. This SCP incorporates the 2005 IOM recommendations, care plan materials from organizations from the American Cancer Society, LiveStrong, and Journey Forward, and findings from research studies with bladder cancer patients, urologists, nurses, and other health and medical professionals. Findings from the BCAN investigators indicate that the bladder cancer SCP has good acceptability among patients and providers and is considered a feasible tool for facilitating communication and referrals among medical specialists, the patient care team, and primary care physicians once survivors transition back to routine general medical care [31].

An earlier study by the BCAN investigators identified gaps in bladder cancer survivorship programs and services at a number of US comprehensive cancer centers [32]. Specifically, this study identified a lack of patient navigation programs and services for bladder cancer survivors receiving care at these centers and other hospitals or clinics. Patient navigators may be peers or trained health professionals (e.g., social workers, nurses) who specialize in multi-level assessment of patients/survivors and their biomedical and psychosocial care needs [24]. Their role focuses primarily on removing barriers to accessing quality care and navigating healthcare settings or systems; assisting patients/survivors and caregivers in procuring appropriate resources and referrals; and advocating for information, resources, and referrals on behalf of the patient/survivor. Urology clinics and high-volume bladder cancer care settings should consider implementing patient navigation programs to assist patients in obtaining necessary community resources and medical supplies; reminding patients/survivors about, and accompanying them to, appointments; and reducing obstacles to access to and compliance with cystoscopic diagnosis and surveillance.

A final set of recommendations relate to electronic health records and health information technology. The 2010 Patient Protection and Affordable Care Act contains provisions for improving health information technology and supporting the widespread use of electronic health records (EHR). EHR are currently used in a number of large healthcare systems including Veterans Affairs, where they facilitate communication among multiple medical and health specialties and also between patients and providers. Such electronic record management systems may also provide medical alerts to providers and patients, notifying them of laboratory and medical test results, upcoming appointments, and other information relevant to healthcare delivery.

Recent Pew Research Center data indicate that 91% of US adults have cellphones and 56% have smartphones [33]. Of adults using cellphones, approximately 81% send or receive texts, 60% access the Internet, and over 50% send or receive e-mail messages. When stratified by age, race/ethnicity, and socioeconomic status, the majority of adults aged 55–64 years (87%), 65 years and older (76%),
African American (93%), Hispanic (88%), and lower-income (86%) had cellphones or smartphones. Thus, with e-mail, texting, and Internet capability improving among older adults, minorities, and low-income individuals, urology providers and clinics should consider how best to integrate health information and wireless communication technologies into practice to facilitate better surveillance among patients and providers.

**Interventions for patients**

Many factors impacting adherence to bladder cancer surveillance (e.g., race/ethnicity, socioeconomic status) are not easily modifiable. However, there are a number of clinically modifiable factors for which general cancer and disease-specific patient education and health promotion interventions are particularly well suited. For example, research has demonstrated that health literacy has an impact on adherence to cancer care and health outcomes. Previous research on health literacy and disease-specific literacy has uncovered gaps in bladder cancer patients’ understanding of health information necessary for active involvement in the rigorous surveillance process. Designing and implementing health education/promotion interventions that are tailored to patients’ health literacy levels and enhance their disease-specific literacy may increase their adherence to surveillance schedules and other aspects of their bladder cancer care. Such programs should include information and resources on smoking cessation, maintaining healthy weight and nutrition, individual and family counseling/therapy, and other psychosocial factors that may decrease the risk of bladder cancer recurrence or progression while also improving health-related quality of life. Orientation to and participation in other services such as patient navigation and SCPs are essential components of quality cancer care and may facilitate additional gains in adherence to surveillance and quality of life.

**Useful web links**

5. www.cancercare.org – Cancer Care.

**References**

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CHAPTER 34
Quality of life and survivorship

Nihal E. Mohamed¹ and Cheryl T. Lee²

¹ Department of Urology and Oncological Science, Icahn School of Medicine at Mount Sinai, New York, NY, USA
² Department of Urology, University of Michigan, Ann Arbor, MI, USA

KEY POINTS

- Radical surgery and urinary diversion are associated with profound changes in health-related quality of life (HRQOL), particularly regarding sexual and urinary function.
- There is no consistent HRQOL advantage for specific types of continent and incontinent urinary diversions with respect to cancer control and survival rate.
- The selection of the types of urinary diversions is largely based on patient-specific characteristics, personal preferences, medical comorbidities, surgical issues, and the surgeon’s skill.
- Although multimodal bladder-preserving strategies offer some advantages over radical surgery, these treatment paradigms are costly, very complex, and require high patient compliance and close coordination of several clinical specialties.
- Despite the preponderance of studies that examined HRQOL in bladder cancer patients, the methodological limitations of these studies may limit the generalizability of their outcomes.
- The most commonly reported needs of bladder cancer survivors include informational needs (e.g., information about cancer prognosis, rehabilitation, surveillance, and changes in body image and sexuality) and supportive care needs (e.g., assistance with urinary incontinence, stoma care, and use of catheters and stoma appliances).
- Although the use of survivorship follow-up care plans is recommended by the Institute of Medicine (IOM) and the American Society for Clinical Oncology (ASCO), the need remains for further evaluation of the care plans and their efficacy to improve health care service outcomes in randomized controlled trials.

Introduction

In 2014 an estimated 74,690 men and women will be diagnosed with bladder cancer (BC) in the United States (US); 15,580 will die from their disease [1]. Elderly patients have higher incidence and death rates from BC compared to younger patients [2]. While men are three times more likely to develop BC than women, women present at more advanced stages and have worse survival rates than men [3]. The current standard of care for non-muscle-invasive bladder cancer (NMIBC) is transurethral resection of bladder tumor (TURBT) with or without adjuvant intravesical therapy, whereas radical cystectomy and urinary diversion are generally employed to treat muscle-invasive bladder cancer (MIBC) and high-risk NMIBC refractory to conservative therapy [4]. Efforts to improve health-related quality of life (HRQOL) through bladder preservation have led to trimodal chemoradiation and the use of orthotopic urinary diversion to mimic natural voiding patterns [2]. Nonetheless, BC treatment negatively affects HRQOL, impacting patients’ emotional well-being and physical and social functioning [5–7].
Some of the most profound changes in HRQOL have occurred with radical surgery and continent and incontinent urinary diversion. There have been no consistent advantages for the varying types of continent and incontinent urinary diversions with respect to cancer control and survival rate, and thus selection is largely based on patient-specific characteristics, including age, gender, medical comorbidities, surgical issues, treatment-related values, and personal preferences, as well as the surgeon’s skill [6, 8–12]. Though the merits and use of these urinary diversion options may be controversial, there can be no argument that the treatment burden for BC is significant regardless of the approach. Most of the research on adjustment to BC diagnosis, HRQOL, and emotional response following treatment has focused on MIBC, while few studies have examined these issues among patients with NMIBC. This chapter provides an overview of the most pressing HRQOL and survivorship issues facing patients with BC, including treatment burden and the differential impact of treatment, age, and gender on functional outcomes. A strategic approach to improving survivorship is discussed along with critical areas of future research [13, 14].

Bladder cancer and treatment burden

Treatment burden increases with treatment intensity. Although surveillance and endoscopic and intravesical therapies have all been associated with considerable physical and psychological effects [15, 16], treatment burden is more prominent among MIBC patients managed with cystectomy and urinary diversion [17]. In men, radical surgery traditionally includes the removal of the bladder, prostate, and seminal vesicles; in women, the urethra, reproductive organs, and anterior vagina have historically been removed along with the bladder [18–22]. These procedures have significant implications for urinary, sexual, bowel, and reproductive function as well as body image among both men and women [23]. In the recent past, however, strategies to preserve sexual and reproductive function in selected patients have led to prostate capsule and seminal vesicle sparing surgery in men and to vaginal-sparing surgeries in women, with preservation of the reproductive organs based on the patient’s fertility status. The median post-operative length of stay ranges from 7 to 14 days, while 90-day readmission and mortality rates are as high as 32% and 6%, respectively [24–27]. Post-operative complication rates range from 50% to 64% [8, 25–27].

Radiation therapy can be an effective treatment strategy in selected patients with MIBC [28]. The commonly reported side effects of radiation therapy include fatigue, nausea, vomiting, diarrhea, urinary discomfort (e.g., cystitis, pain during urination, bladder spasm, urinary urgency), and increased sexual problems (e.g., vaginal dryness among women, and erectile dysfunction among men). Trimodal therapy combines TURBT, chemotherapy, and radiation therapy in an attempt to attain long-term disease-free survival and bladder preservation, while maximizing HRQOL [29]. Although multimodal bladder-preserving strategies offer some advantages over radical surgery, these treatment paradigms are costly, very complex, and require high patient compliance and close coordination of several clinical specialties [30, 31]. Ultimately, like radical surgery, the treatment intensity and related burden (immediate and future) is substantial.

Health-related quality of life following bladder cancer treatment

Health-related quality of life (HRQOL) refers to an individual’s appraisal of and satisfaction with their current level of physical, emotional, and social functioning as compared to what they perceive to be possible or ideal [32]. Among BC patients, HRQOL is commonly assessed using generic measures, disease-specific measures, or both [33]. Generic HRQOL measures typically assess emotional and functional well-being; examples include the Profile of Mood State [34], the Medical Outcome Study’s 36-item Short Form Health Survey (SF-36) [35], Sickness Impact Profile (SIP) [36], and the Quality of Wellbeing Scale [37]. Measures assessing general cancer effects include the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire version 3.0 QLQ-C30 (EORTC QLQ-C30) [38] and the Functional Assessment of Cancer Therapy-General (FACT-G) [39]. These measures typically assess emotional, social, functional, and physical well-being following cancer treatment. Measures assessing BC-specific side effects (e.g., altered body image, erectile dysfunction, and difficulties in stoma care) include the EORTC’s Quality of Life Questionnaire QLQ-BLM30 (EORTC-QLQ-BLM30), the Functional Assessment of Cancer Therapy-Bladder
In general, the international medical literature on HRQOL in BC patients can be divided into two major research areas: (1) studies that examine HRQOL following intravesical therapy [e.g., bacillus Calmette-Guérin (BCG)] or transurethral resection of bladder tumor (TURBT) in patients with NMIBC [43]; and (2) studies that examine HRQOL differences across various types of urinary diversion after radical cystectomy. The NMIBC context is grossly understudied, but demonstrates advantages in general HRQOL for patients undergoing bladdersparing procedures compared to patients treated with cystectomy and urinary diversion [30]. Post-treatment outcomes, however, depend largely on patients’ needs and preferences [30, 31]. Although one study concluded that BCG-related side effects (e.g., pain, discomfort, voiding problems, infection) had no effect on HRQOL [15], another study found that patients feared recurrence and death, anticipated significant disease-related disruptions of their lives, and experienced an acute decline in HRQOL during the initial BCG treatment [16]. In contrast, patients treated with cystectomy are subject to significant decline in disease-specific HRQOL, particularly regarding sexual and urinary function [6]. Altered urinary function is largely associated with urinary diversion type (i.e., incontinent cutaneous, continent cutaneous, or orthotopic neobladder). Each diversion type has its own group of psychological burdens, ranging from negative body image to intrusive night time awakenings [11, 12, 23]. Additional distress may also arise from the well-described physical complications related to urinary diversion, including ureteral obstruction, renal insufficiency, urinary tract infection, urinary incontinence or leakage, urinary retention, and stoma-related complications, including skin irritation and stenosis [33]. The types of bowel utilized for certain diversions may also result in varied metabolic disorders owing to different absorptive characteristics of the section of bowel selected for reconstruction [33, 44]. Likewise, intestinal disorders such as secretory or osmotic diarrhea can further complicate urinary diversion recovery. Taken together, side effects from urinary diversion can greatly reduce the patient’s general and disease-specific HRQOL as well as the patient’s adjustment to physical, emotional, and practical post-surgical demands (i.e., use of stomal appliances, intermittent catheterization, medical therapies, etc.) [7, 23].

The differential impact of urinary diversions

It is well established that the choice of urinary diversion after cystectomy does not directly provide survival advantage for BC patients. Thus, the diversion choice is generally shaped by personal factors including perceived HRQOL associated with each type of urinary diversion [33]. However, perceptions about improved HRQOL for specific diversion types have not been confirmed. Studies examining the assumption that continent diversions (e.g., the Indiana pouch or orthotopic neobladder) have a buffering impact on general HRQOL as compared to incontinent diversion (e.g., the ileal conduit) have failed to show significant differences between diversion types in most relevant domains [43, 45, 46]. Although apparent HRQOL differences may not be evident, other important quality of life (QOL) concerns have emerged in the context of incontinent and continent diversion.

Incontinent diversion is associated with significant practical challenges and psychological side effects that can drastically reduce the patient’s emotional adjustment and well-being [33, 47]. These side effects include: (1) altered body image, sexual dysfunction and bother, and psychological barriers due to body image, urinary leakage, odor, and frequent stoma care; (2) difficulties in activities of daily living and social activities such as bathing and sleeping; and (3) practical barriers to participation in previously pleasurable hobbies and traveling [19, 21, 48]. In contrast, some patient groups deny significant restrictions in daily activities or social interaction despite substantial complaints about stomal leakage and challenges with appliances [43, 49]. Further evidence, though, supports common feelings of shock, hate, disgust, repulsion, embarrassment, devastation, and unacceptance in cancer patients requiring urinary and intestinal ostomies [50]. Ultimately, coping with an ileal conduit and its consequences may largely depend on the patient’s personal and social resources and the importance placed on body image, sexuality, and urinary control [33, 48, 51].

In patients treated with continent cutaneous diversion (e.g., Indiana pouch), body image is less disturbed and stoma care is infrequent as compared to incontinent diversion; but, failure to catheterize as frequently as needed can cause urinary leakage and serious medical conditions [48, 52, 53]. In addition, night time catheterization may result in a reduced amount and diminished quality of sleep [48, 52, 53]. In spite of the perceived
and real benefits of a continent cutaneous diversion on body image, the need for regular catheterization may limit patients’ activities of daily living and participation in work and social activities.

A major advantage of the orthotopic neobladder is that it maintains urethral voiding and thus preserves body image. Consequently, it may be more socially desirable than the incontinent diversion and continent cutaneous diversion [54]. In fact, patients with neobladder diversion may have better post-treatment social and physical outcomes related to bathing, sleeping, and traveling, and also fewer sexual problems and barriers than patients with ileal conduits [54]. Although daytime continence is achieved in almost all patients with neobladder diversion, night time continence is less likely to be achieved. Results from recent research in other patient populations demonstrated the negative impact of night time incontinence on increased depression and poor HRQOL [51, 55]. These factors may partially explain reports of better global urinary function in patients with ileal conduit diversion than those with orthotopic diversion in some patient groups [56].

**Treatment burden and health-related quality of life following treatment**

**Differential impact of age**

Bladder cancer disproportionately affects the elderly, a patient population that is vulnerable to impaired cancer survivorship. The mean age at diagnosis and at cystectomy is ~72 and 65 years, respectively [57–60]. It has been proven that physiological functioning declines with aging even in the absence of disease [3, 54]. This decline may also lead to negative changes in cognitive, emotional, physical, and social functioning [3]. Approximately 60% of adults aged 65 years and older experience these negative changes in functioning [3]. Among patients with BC, comorbidities, such as heart disease, stroke, arthritis, and urinary, hearing, and vision problems, increase with advancing chronological age [3, 58–60]. Since current health status and functioning are often key factors in determining eligibility for cystectomy, older patients are less likely to undergo radical cystectomy [3]. The reported utilization of cystectomy among BC patients is 55% for adults aged 55–59 years compared to 24% and 16% for those aged 75–79 years and 80–84 years, respectively [61]. Likewise, older patients are less likely to receive optimal doses of adjuvant or neoadjuvant systemic chemotherapy [3, 61].

Urinary diversion choice is greatly limited for elderly BC patients who undergo cystectomy; they are typically offered ileal conduits and not continent diversion [3, 61]. Studies that examined HRQOL and post-treatment outcomes among elderly patients treated for NMIBC showed that age could lead to a higher rate of complications, thus influencing the efficacy of intravesical therapy, especially immunotherapy. Perioperative morbidity rates are high among older patients treated with cystectomy for MIBC (30–60%) [3, 4, 55, 62]. One study found differences in overall complication rates for older adults receiving neobladders (vs. ileal conduits) [42], while another found no differences in daytime urinary continence [54]. Night time continence was almost 100% at five-year follow-up for adults aged 50 years or younger and 90% for those over the age of 60 [36]. The few studies that examined age-related differences in general HRQOL and satisfaction with treatment following cystectomy showed no significant differences among urinary diversion subgroups in any of the HRQOL domains examined (i.e., physical, functional, emotional, and social domains) [33, 59, 60]. However, elderly patients with neobladder diversion reported less satisfaction with treatment and outcomes compared to those with incontinent diversion or cutaneous diversion [33]. Beyond urinary continence and general HRQOL, few studies have focused on other HRQOL issues among post-cystectomy older adults, such as sexual functioning, psychological functioning, social relationships, body image, and gender roles. Research is greatly needed in this area.

**Differential impact of gender**

Gender differences in BC incidence, treatment, and cancer-specific mortality have been reported. Although BC incidence is 3–4 times higher in men, women are more likely to present with advanced-stage disease and have worse survival [1, 3]. Female gender is associated with increased risk for disease recurrence and cancer-specific mortality compared with male gender [62]. The gender differences in disease severity may be partially attributable to the fact that women, compared to men, experience significant delay in the diagnosis of BC when first presenting to a primary physician with symptoms [63, 64]. Women are more likely than men to require three or more referral consultations with a general practitioner, and to experience longer time intervals
between presentation and hospital referral [63]. Gender differences in the incidence and severity of disease may also stem from behavioral (e.g., smoking), environmental (e.g., exposure to carcinogens), and biologic factors (e.g., enzymatic processing of environmental substances, cellular and physiological responses) [3]. Further, societal factors (e.g., inequality in healthcare, provider bias, lack of knowledge and training in treating female BC patients, and type of health plan) may also play a role.

To date, there is no clear evidence that any of these factors fully explain gender differences in incidence and disease severity. A greater understanding of these issues is needed to reduce gender-based health disparities. Gender differences in HRQOL following cystectomy may also exist, particularly when considering the physical impact of neobladder diversion [65]. Urinary incontinence and deterioration of sexual function are more common among women compared to men following orthotopic diversion [65]. A recent comparison of HRQOL in women treated with various urinary diversions demonstrated worse FACT-BL scores in the physical and emotional domains, and a trend toward worse EORTC QLQ-C30 scores for appetite loss and fatigue in those with cutaneous continent diversion compared with women with incontinent diversion or orthotopic neobladder [65]. A more recent study found that female gender was associated with limitations in daily activities, anxiety, depression, and worse general HRQOL following cystectomy and incontinent diversion [7]. More studies are needed to examine gender-sensitive HRQOL measures in treatment outcomes and emotional adjustment following BC therapy.

**Health-related quality of life: outcome measures and methodological limitations**

Despite the preponderance of studies that examined HRQOL in patients with BC, the methodological limitations of these studies may limit the generalizability of their outcomes [33]. The majority of these studies were cross-sectional studies focusing mainly on examining HRQOL among MIBC patients, and were conducted in small patient cohorts from single institutions [33]. Of the few studies that examined the impact of NMIBC on patient HRQOL, most were conducted during a specific course of intravesical therapy. Thus, there is little information regarding the long-term impact of treatment for NMIBC [43]. Other methodological limitations of these studies include the paucity of both longitudinal and prospective research that have examined changes in post-treatment generic and disease-specific HRQOL and the scarcity of randomized controlled studies testing the validity and reliability of tools used in the assessment of disease-specific HRQOL [37, 43, 66]. Although the use of generic HRQOL measures allows for easy comparisons of emotional and functional status with other cancer populations, such measures are not sensitive to BC treatment-specific side effects [33]. This lack of sensitivity to treatment side effects may limit their ability to detect important aspects of BC treatment-related HRQOL and potential changes in post-treatment HRQOL [33].

Although both standardized and unstandardized measures have been used to examine disease-specific HRQOL, these measures generally lack sensitivity to gender- and age-specific treatment side effects (e.g., pain during sexual intercourse among women and difficulties in the use of stomal appliances and catheters due to age-related decline in manual dexterity). Given these methodological limitations, questions remain as to the nature of the information HRQOL research provides and whether this information is of clinical use during consultations with patients. Additionally, measures used to assess generic and disease-specific HRQOL fail to distinguish health-related problems, patients’ supportive care needs, and patients’ desire to receive professional attention or care for these needs/problems [23, 67]. With increasing emphasis on reducing healthcare costs and improving quality of care, sensitive and meaningful HRQOL measures are needed to better direct BC therapy, urinary diversion choice in surgical patients, and post-treatment recovery. Table 34.1 summarizes several studies and variations in HRQOL measures in patients undergoing NMIBC and MIBC treatment.

**Strategic approach to improving survivorship**

To improve survivorship, it is necessary to address the problem both at a system level and at a patient level. System-level approaches seek to improve follow-up care by addressing the patient’s needs, enhancing the
Table 34.1 Health-related quality of life in patients treated with continent and incontinent urinary diversion.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Location</th>
<th>Sample size</th>
<th>Scale(s) used</th>
<th>Principal findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective longitudinal studies of quality of life in patients treated with urinary diversion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardt [20] (2000)</td>
<td>Germany</td>
<td>24</td>
<td>SF-36, Self-design</td>
<td>Sexual func similar, all SF-36 domains returned to baseline by 1yr except physical func. Note: 75% would choose the same diversion</td>
</tr>
<tr>
<td>Somani [71] (2009)</td>
<td>UK</td>
<td>29</td>
<td>SEIQoL-DW, SWLS, EORTC QLQ-C30</td>
<td>“Family”, “health”, “relationships”, &amp; “finance” identified as biggest contributors to QoL</td>
</tr>
<tr>
<td><strong>Cross-sectional studies of quality of life in patients treated with urinary diversion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyd [45] (1987)</td>
<td>USA</td>
<td>87</td>
<td>BDI, POMS, Self-design</td>
<td>Pre-operative education important for adaptation. CCD: more likely to be sexually active</td>
</tr>
<tr>
<td>Mansson [72] (1988)</td>
<td>Sweden</td>
<td>40</td>
<td>Self-design</td>
<td>IC: more problems with stomal issues such as leakage + odor</td>
</tr>
<tr>
<td>Bjerre [73] (1995)</td>
<td>Denmark</td>
<td>29</td>
<td>Self-design</td>
<td>NB with greater incontinence, but IC with greater distress from leakage and lower body image</td>
</tr>
<tr>
<td>Gerharz [40] (1997)</td>
<td>Germany</td>
<td>131</td>
<td>Self-design</td>
<td>Similar coping strategies, social support. CCD: Better global QOL and fewer stomal issues</td>
</tr>
<tr>
<td>Okada [18] (1997)</td>
<td>Japan</td>
<td>63</td>
<td>Self-design</td>
<td>CCD: less local stoma problems; greater satisfaction Overall, high QOL in all groups</td>
</tr>
<tr>
<td>Hart [74] (1999)</td>
<td>USA</td>
<td>25</td>
<td>4 Self-report questionnaires</td>
<td>IC: worse social function</td>
</tr>
<tr>
<td>Kitamura [75] (1999)</td>
<td>Japan</td>
<td>36</td>
<td>EORTC QLQ-C30</td>
<td>Similar overall QOL between groups. IC: more trouble with public restrooms + travel</td>
</tr>
<tr>
<td>Fujisawa [76] (2000)</td>
<td>Japan</td>
<td>20</td>
<td>SF-36</td>
<td>Similar QOL between diversion types</td>
</tr>
<tr>
<td>McGuire [77] (2000)</td>
<td>USA</td>
<td>38</td>
<td>SF-36</td>
<td>IC: statistically lower mental well-being than population-based norm</td>
</tr>
<tr>
<td>Conde [78] (2001)</td>
<td>Spain</td>
<td>6</td>
<td>Self-design</td>
<td>IC: greater distress with urine leakage + lower body image</td>
</tr>
<tr>
<td>Hobisch [79] (2001)</td>
<td>Austria</td>
<td>33</td>
<td>EORTC QLQ-C30</td>
<td>NB better across all domains</td>
</tr>
<tr>
<td>Dutta [80] (2002)</td>
<td>USA</td>
<td>23</td>
<td>SF-36, FACT-G</td>
<td>NB marginally better on several domains</td>
</tr>
<tr>
<td>Protogerou [83] (2004)</td>
<td>Greece</td>
<td>58</td>
<td>EORTC QLQ-C30</td>
<td>Included matched 54 patient control group. IC with greater urine odor and day and night time leakage than NB or controls</td>
</tr>
<tr>
<td>Allareddy [84] (2006)</td>
<td>USA</td>
<td>56</td>
<td>FACT-BL</td>
<td>Compared to intact bladder (n = 177), sexual func lower in individuals undergoing cystectomy. Similar QOL between diversion groups</td>
</tr>
<tr>
<td>Gilbert [56] (2007)</td>
<td>USA</td>
<td>66</td>
<td>BCI</td>
<td>Urinary, bowel &amp; sexual differences exist by diversion type. NB may have worse urinary func</td>
</tr>
</tbody>
</table>

(Continued)
coordination of care and communication among healthcare providers through the use of a survivorship care plan. Patient-level approaches are strategies explicitly focusing on health education and health promotion through provision of print materials, Web-based tools, and/or health coaching. The needs of BC survivors include information about cancer prognosis, rehabilitation, surveillance, finances, medical systems, and changes in body image and sexuality [7, 13, 23, 33]. Supportive care needs also predominate as survivors require assistance with urinary incontinence, stoma care, use of catheters and stoma appliances, altered body image, sexual dysfunction, depression, and worries about recurrence [7, 13, 23, 33]. There is increasing evidence that addressing informational and supportive care needs of cancer patients improves not only survivor HRQOL, but also emotional adjustment and compliance with recommended care [68, 69]. Additionally, routine assessments of emotional distress and unmet needs have been emphasized by the American College of Surgeons’ (ACoS) Commission on Cancer (CoC) new accreditation standards for hospital cancer programs and the National Comprehensive Cancer Network (NCCN) Distress Management and Survivorship Guidelines [68]. To improve cancer survivorship, the Institute of Medicine (IOM) and the American Society for Clinical Oncology (ASCO) recommend the implementation of treatment summary and a personalized, follow-up care plan for patients as a mechanism to improve coordination and transition of care, patient–physician and physician–physician communication, and to address the physiological and psychosocial sequelae of treatment [70]. By 2015, provision of survivorship care plans to cancer survivors will be required from medical institutions seeking accreditation from the ACoS CoC. Lee and colleagues have developed and examined the acceptability, feasibility, and usability of a survivorship care plan for BC patients [13, 16]. However, the need remains for further evaluation of the BC care plan and its efficacy to improve healthcare service outcomes in randomized controlled trials.

Table 34.1 (Continued)

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Location</th>
<th>Sample size</th>
<th>Scale(s) used</th>
<th>Principal findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saika [59] (2007)</td>
<td>Japan</td>
<td>56 IC 31 CCD 22 NB</td>
<td>EORTC QLQ-C30, Satisfaction</td>
<td>Assessment of patients 75+ yrs old: Similar QOL between diversion types, including 31 with ureterocutaneostomy</td>
</tr>
<tr>
<td>Harano [85] (2007)</td>
<td>Japan</td>
<td>20</td>
<td>21 SF-36, Self-design</td>
<td>Similar QOL between diversion types</td>
</tr>
<tr>
<td>Sogni [60] (2008)</td>
<td>Italy</td>
<td>18</td>
<td>16 EORTC: QLQ-C30, QLQ-BLM30</td>
<td>Assessment of patients 75+ yrs old: Similar QOL between diversion types. NB: 56% and 25% daytime and night time complete continence rates</td>
</tr>
<tr>
<td>Hedgepeth [87] (2010)</td>
<td>USA</td>
<td>89</td>
<td>144 BCI, EORTC BIS</td>
<td>Included bladder-intact comparison group (n = 112); NB: Lower urinary function. Body image is similar between NB and IC Overall QOL similar between groups. NB: worse urinary control, better body image Overall QOL similar NB: Better physical function</td>
</tr>
<tr>
<td>Kikuchi [86] (2006)</td>
<td>Japan</td>
<td>20</td>
<td>14 15 FACT-BL</td>
<td>Overall QOL similar between groups.</td>
</tr>
<tr>
<td>Phillip [88] (2009)</td>
<td>United Kingdom</td>
<td>24</td>
<td>28 SF-36</td>
<td>NB: worse urinary control, better body image Overall QOL similar</td>
</tr>
</tbody>
</table>

Note: Urinary diversion type: IC = Ileal conduit; CCD = Continent cutaneous diversion; NB = Orthotopic neobladder; “Self-design” = questionnaires developed specifically for the study; SF-36: Medical Outcomes Study 36-Item Short Form; fxn = Function HADS: Hospital Anxiety and Depression Scale; EORTC BIS: European Organization for the Research and Treatment of Cancer Body Image Scale; SEIQoL-DW: Schedule for Evaluation of Individual Quality of Life-Direct Weighting; SWLS: Satisfaction With Life Scale; BDI: Beck Depressive Inventory; POMS: The Profile of Mood States; QOL: Quality of life.

Source: Mohamed et al. 2012 [33].
Conclusion

In summary, given the burden of BC treatment and side effects, there is a strong need for further examination of patients’ HRQOL, needs, and emotional adjustment following diagnosis and treatment. However, progress will be hampered by several issues. Despite the preponderance of studies that have examined HRQOL among BC patients, significant limitations exist regarding study design, methodology, and measures used, thus limiting generalizability. Studies that explore gender-, age-, and treatment-related differences in needs and post-treatment emotional well-being are still lacking. In 2015, new accreditation standards for hospital cancer programs involving patient screening for emotional distress will take effect. Surprisingly, the majority of medical institutions have yet to achieve compliance. Likewise, the vast majority of institutions have also struggled in attempts to integrate survivorship care plans into general practice. These areas of deficiency highlight the obstacles that investigators will be confronted with at multiple levels of experimentation and institutional implementation. It is clear that the BC community must be strategic in its research and education efforts to ultimately address the needs and challenges faced by our patients.

Useful web links

1 http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site
2 http://www.nap.edu/openbook.php?record_id=11613&page=R1
4 http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#supportive

References

80 Dutta SC, Chang SS, Coffey CS, et al.: Health related quality of life assessment after radical cystectomy: Comparison of


When examining bladder cancer, and the relationships between payers and healthcare delivery, the heterogeneity of the disease is apparent. Although bladder cancer is the fourth most common cancer diagnosis in men and the eleventh most common cancer in women in the United States [1], it is considered the most costly cancer to diagnose and treat [2]. Much of this expense comes from the work-up and treatment for the highly prevalent non-muscle-invasive bladder cancers. Concurrent with prevalent, low-risk cancer, a smaller percentage of patients have high-risk bladder cancer, driving mortality from the disease. These patients account for over 15,000 deaths from bladder cancer each year [3].

Delivery of care for bladder cancer patients must deal with these two disparate problems. Care is potentially overused in the large majority of patients with low-risk disease, but there can be substantial underuse of needed care in patients at risk of dying from bladder cancer. In this chapter we examine how payers and policy-makers have attempted to modify delivery of care to restrain the growth of healthcare costs. We will explore how such programs impact the delivery of care for bladder cancer patients.

**Appropriate use of care**

*Problems of underuse of needed care*

Low-quality care can result from the underuse of care proven to be effective. Unfortunately, such deficiencies have been found in bladder cancer care (Table 35.1). Radical cystectomy is provided to only a small portion of Medicare patients with muscle-invasive bladder cancer [4]. Amongst Medicare patients at high risk of recurrence, no patients received all of the recommended care to prevent recurrence and progression of their disease [5]. Furthermore, few physicians appear to provide intravesical chemotherapy after bladder tumor resection, a proven effective modality for decreasing recurrence [6]. Overall in non-muscle-invasive bladder cancer, 21% of patients received care that was of a lower...
Table 35.1 Levels of evidence and patterns of care from population-based data for NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer [36].

<table>
<thead>
<tr>
<th>NCCN Guideline recommendation</th>
<th>Level of evidence*</th>
<th>Compliance with recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate bladder tumor resection with muscle in the specimen</td>
<td>2a'</td>
<td>No studies identified</td>
</tr>
<tr>
<td>Intravesical chemotherapy within 24 hours of TURBT, unless large resection or suspected perforation</td>
<td>2a</td>
<td>3.2% of Medicare beneficiaries received post-TURBT intravesical chemotherapy from 1998–2002 [6]; 0.3% of patients in MEDSTAT database received post-TURBT intravesical chemotherapy between 1997–2004 [37]</td>
</tr>
<tr>
<td>For CIS: Random bladder biopsies, biopsies adjacent to papillary tumor, consider prostatic urethral biopsies</td>
<td>2a'</td>
<td>No studies identified</td>
</tr>
<tr>
<td>TURBT pathology report should include whether muscularis propria is present in the specimen, presence/absence of lymphovascular invasion, and presence/absence of CIS</td>
<td>2a'</td>
<td>No studies identified</td>
</tr>
<tr>
<td>Re-resection TURBT for any stage classification T1 urothelial carcinoma, incomplete resection, or insufficient/absent muscularis</td>
<td>2a'</td>
<td>Repeat TURBT was performed in 4.9% of Medicare beneficiaries from 1992–2005 [38]</td>
</tr>
<tr>
<td>Re-resection TURBT prior to bladder-sparing chemotherapy and/or radiation</td>
<td>2a'</td>
<td>No studies identified</td>
</tr>
<tr>
<td>Induction intravesical therapy for high-risk NMIBC</td>
<td>2a'</td>
<td>19.7% of Medicare beneficiaries received induction BCG for high-grade NMIBC after TURBT [5]</td>
</tr>
<tr>
<td>Partial cystectomy for solitary tumors in an amenable location with no associated CIS</td>
<td>2a'</td>
<td>Among patients undergoing extirpative surgery for bladder cancer in 1988–2000, 18% in SEER and 20% in the Nationwide Inpatient Sample underwent partial cystectomy [39]. Partial cystectomy performed in 30.4% of invasive bladder patients in Quebec in 1983–2005 [40]</td>
</tr>
<tr>
<td>Pelvic lymphadenectomy should be performed in conjunction with partial cystectomy</td>
<td>2a'</td>
<td>Pelvic lymphadenectomy was performed in 23% of patients undergoing partial cystectomy for invasive bladder cancer in Quebec in 1983–2005 [40]</td>
</tr>
<tr>
<td>Radical cystectomy should include pelvic lymphadenectomy with an extended lymph node template</td>
<td>2a'</td>
<td>Median lymph node yield among SEER patients with N+ disease treated with radical cystectomy between 1998–2002 was 9, with 49.0% of patients having lymph node yield ≥ 10 [41]. 70% of Medicare beneficiaries undergoing radical cystectomy underwent lymphadenectomy, of whom 22.0% had lymph node yield ≥ 10 [42]</td>
</tr>
<tr>
<td>Follow-up after radical cystectomy should include urinary cytology, serum chemistries, serial cross-sectional imaging, urethral washing</td>
<td>2a'</td>
<td>No studies identified</td>
</tr>
<tr>
<td>First-line chemotherapy with gemcitabine and cisplatin for neoadjuvant, adjuvant, and metastatic bladder cancer treatment</td>
<td>1 for metastatic 2a otherwise</td>
<td>Neoadjuvant chemotherapy was given to 1.4% of Medicare beneficiaries with stage 2 bladder cancer from 1992–2003 [43]. In 2003, gemcitabine accounted for 33% of the chemotherapy claims for bladder cancer patients [43]. 1.2% of stage III bladder cancer patients in the National Cancer Database received neoadjuvant chemotherapy in 1998–2003.</td>
</tr>
</tbody>
</table>

TURBT: transurethral resection of bladder tumor; CIS: carcinoma in situ; NMIBC: non-muscle-invasive bladder cancer; SEER: Surveillance, Epidemiology, and End Results national cancer registry.

Levels of evidence: 1 – high-level evidence with uniform NCCN consensus; 2a – low-level evidence with uniform NCCN consensus; 2b – lower-level evidence with NCCN consensus; 3 – any level of evidence, no NCCN consensus [44].
intensity than their cancer stage and clinical condition warranted [7]. Ideally, healthcare delivery would remove barriers to provision of needed care and reward the use of appropriate interventions.

Problems of overuse of care
Unfortunately, low-quality care can also result from using too many services. This is most commonly encountered among low-risk, non-muscle-invasive bladder cancer patients. No survival advantage has been found for higher expenditure on treatment for patients with non-muscle-invasive bladder cancer [8]. Despite this, many patients with low risk of clinical recurrence or progression receive high-intensity interventions [7]. Overuse of treatments and interventions leads to increased costs for patients and the medical system, and also introduces the potential for complications due to the interventions.

Summary
With the diverse nature of bladder cancer and the conflicting problems of overuse and underuse of care, development of effective interventions is complex. Unintended consequences develop when interventions do not account for the diversity in patients and disease. For instance, programs to restrain costs may inadvertently decrease needed interventions in higher-risk patients. Similarly, efforts to increase the use of cystectomy in more qualified centers may decrease access to care.

Modifications of the fee-for-service model

Centers of excellence and the Leapfrog Group
Efforts to define centers of excellence attempt to regionalize complex care to centers with the greatest expertise. Blue Cross Blue Shield of America (BCBSA) has taken the lead in these efforts, first in complex conditions such as bariatric surgery and coronary artery disease. Centers with these distinctions have proven to have lower complication rates than other hospitals. This program expanded to rare and complex cancers, including bladder cancer requiring cystectomy. The high-volume facilities participating in this program have resources that may maximize healthcare value, such as multidisciplinary care teams [9]. Regionalization of care does carry risk. Some patients may not be willing or able to travel to a center of excellence. Furthermore, some centers may not be able to handle an influx of patients, leading to delays in care that might compromise bladder cancer-specific and overall survival [10, 11].

An alternative model of encouraging concentration of complex care in specialized centers has emerged from the Leapfrog Group. This group uses metrics they expect providers to meet, and then provides incentives for providers to meet these metrics. Examples of these metrics include computerized order entry and evidence-based hospital referral. As a consortium of private and public healthcare purchasers with coverage of over 35 million insured lives [12], the Leapfrog Group raised national awareness about healthcare quality. However, the direct impact of the Leapfrog Group criteria on patient outcomes appears to be limited. Using the group’s Hospital Quality and Safety Survey, no discrimination in inpatient mortality could be determined [13]. Although their current metric does not stratify hospitals well, large groups of purchasers of healthcare do have the potential to move the bar for quality of care.

Pay-for-performance initiatives
Pay-for-performance programs are intended to financially reward physicians and healthcare systems for meeting certain performance goals [14]. No pay-for-performance initiatives are currently active that directly target bladder cancer patients. However, the Centers for Medicare & Medicaid Services (CMS) Physician Quality Reporting System (PQRS) is currently the most widely implemented program [15]. The program was originally a voluntary reporting system, but it became a permanent initiative with the Medicare Improvements for Patients and Providers Act of 2008 (MIPPA). Initially, compliance with the program provided up to a 1% incentive for providers; however, starting in 2013, non-compliance with the program incurs up to a 1.5% penalty in 2015, with continued increases in penalties up to 2% by 2016.

Central to pay-for-performance initiatives is defining a set of goals physicians need to meet. These goals can be quality targets, measures of patient safety, improved efficiency, or other initiatives. Currently, CMS has endorsed a total of 22 measure groups and 210 measures within its PQRS framework [16]. Measure group reporting involves reporting on a consecutive cohort of patients with a common condition. Such reporting does not apply to bladder cancer patients since bladder cancer is not a
condition represented in the measure groups. Thus, bladder cancer patients are most likely affected by the individual measures. The criteria for satisfactory reporting of individual measures are dependent on the mechanism practitioners utilize to submit their data to CMS, with acceptable compliance rates ranging from 50% to 80% on at least three measures. Group practices of 25 or more individuals may report on 29 quality measures for a pre-determined number of consecutive patients, depending on the size of the group practice. The AUA has attempted to simplify the process for urologists by highlighting the 16 measures that it believes to be most applicable to urologic practice [17]. No disease-specific metrics exist for bladder cancer patients.

As a quality improvement system, the PQRS is limited. Physicians choose which three measures to report. Thus, most physicians would simply opt to report only on measures for which they know they achieve high levels of compliance. As a self-reported metric, there is no mechanism to deter against failure to report on measures with poor performance.

**Development of new measures**

With no bladder cancer-specific measures currently being tracked, opportunities exist to develop new and appropriate quality measures for bladder cancer care. Quality measures in the United States are developed through the National Quality Forum (NQF) Measure Evaluation Criteria [18]. The NQF is a private not-for-profit organization formed in 1999. While the NQF does not develop quality or performance measures directly, NQF endorsement is required for all performance measures implemented in PQRS [19]. The NQF facilitates measure development in conjunction with sponsor organizations. Evaluation criteria examine the importance, evidence, scientific acceptability, usability, and feasibility of candidate performance measures. Importance signifies the magnitude of impact the measure will have on public health. As a common cancer with high expenditure on care, bladder cancer is an important condition. Evidence levels are ranked, with randomized trials being highest and expert opinion lowest. In bladder cancer care, instillation of mitomycin-C following resection of a bladder tumor would be high-evidence care. Conversely, many current measures with low evidence may be guideline-derived, but based only on expert opinion. Usability and feasibility refer to measure implementation. A usable measure is meaningful to report, with high-quality care associated with adherence to the measure and low-quality care associated with non-adherence. Work through quality collaboratives and specialty organizations helps to establish the usability of measures. A feasible measure is easily abstracted. More recently, feasibility has considered the facility of measurement in the context of emerging electronic health record platforms. Again, quality collaboratives can help document the feasibility of a measure.

As the prominent representative of urologists in the United States, the American Urological Association plays a large role in the development of quality indicators into performance metrics. The AUA does this through the Physician Consortium for Performance Improvement (PCPI). The PCPI is a physician-led program convened by the American Medical Association (AMA) with a mission to align patient-centered care, performance measurement and quality improvement” [20]. Membership may be granted to individuals or to groups, as is the case with the AUA. The PCPI is tasked with developing meaningful performance measures and currently over 70% of the measures in the CMS PQRS are PCPI measures. This is the mechanism through which new bladder cancer-specific metrics, if developed, would most likely be approved.

**New payment models**

**Bundled payment initiatives**

Bundled payments provide a single reimbursement for an episode of care. Such payments are not new. Surgeons have received bundled payments for the care surrounding surgery since 1984, when the Texas Heart Institute began charging flat fees for coronary artery bypass surgery [21]. However, such surgeon-level payments do not account for the variation in hospital expenditure, or the different surgical interventions patients with similar conditions may receive. In order to account for this variation, CMS launched an effort to evaluate bundled payments for inpatient surgery. Bundled payment systems provide clinicians and hospitals with a consolidated reimbursement for an index surgical episode [22]. Through the Acute Care Episode Demonstration Project, CMS is piloting bundled payments for certain cardiovascular and orthopedic procedures [23]. The idea of bundled payments is further promoted in the Affordable Care Act [24] and will likely be resilient against any changes in the electorate of the Federal Government that could lead to repeal of
the ACA. This is because private insurers are embracing the concept of bundled payments [25]. By incentivizing marginal profit, bundled payments reward efficient care and penalize episodes with high-cost services such as readmissions. Miller et al. reviewed Medicare payments for major inpatient surgeries to determine whether bundled payment programs could achieve cost savings [26]. Examining procedures such as colectomy and back surgery, they identified substantial variation in the cost of index surgical episodes, indicating an opportunity for cost savings. Post-discharge care, including readmissions, accounted for a large proportion of the variation between hospitals for each surgical procedure.

In bladder cancer care, the concept of a bundled payment shared between the hospital and physicians would be most applicable to cystectomy care. With a single payment, the hospital and surgeon would share an aligned interest in patient recovery and prevention of complications. Given the high cost of the index radical cystectomy admission and the high rates of readmissions following radical cystectomy for bladder cancer [27–31], bundling payments for cystectomy care could induce practice changes that improve healthcare quality and health outcomes for bladder cancer patients. How bundled payments would extend to the non-muscle-invasive setting is not yet clear.

**Accountable Care Organizations (ACOs)**

Accountable Care Organizations (ACOs) were a central feature of the Affordable Care Act. Mostly focused on primary care, these networks of healthcare providers with a catchment of at least 5000 Medicare beneficiaries will – similar to the goal of bundled payments – reward efficient high-value care. ACOs rely on a shared risk model where high-value care results in increased revenue to ACO members. Similarly, low-value care results in revenue withholding. ACOs prioritize chronic health conditions, so applicability to urologic care remains unclear. However, many bladder cancer patients may eventually be cared for within an ACO. Thus, urologists will likely interact with local ACOs.

**Quality improvement projects**

Clinician-led urological collaboratives have emerged that could achieve cost savings for patients receiving bladder cancer care. While many of these projects have focused on prostate cancer care, the principles developed could translate to the care of bladder cancer patients. The Urological Surgery Quality Collaborative (USQC) [32] has demonstrated that feedback reports of use of advanced imaging for staging localized prostate cancer helped reduce overuse of bone scans and computed tomography for low-risk prostate cancer patients [33]. The USQC has expanded into examination of bladder cancer care. Contrary to the findings from administrative claims, the authors found high levels of what they termed “judicious use” of mitomycin-C after TURBT [34]. Over 80% of cases were found to have appropriate use of mitomycin after surgery. Addressing bladder cancer quality will require this mode of transparent reporting of provider-specific outcomes with a greater level of data detail than can be abstracted from sources such as Medicare claims.

Quality collaboratives continue to grow. The Michigan Urological Surgery Improvement Collaborative (MUSIC) is working to reduce imaging overuse in low-risk prostate cancer [35]. Other stated goals include reducing variation in the discretionary use of androgen-deprivation therapy, especially in localized prostate cancer, and aiding the decision-making of prostate cancer patients diagnosed by MUSIC-participating urologists. Currently, MUSIC does not have a focus on bladder cancer care. In Washington State, capitalizing on the infrastructure of Surgical Care and Outcomes Assessment Program (SCOAP), a urological module, UroSCOAP, has been developed. While currently focused on prostatectomy care, planned future modules will examine non-operative management of prostate cancer, incontinence care, and the treatment of nephrolithiasis. Initiatives such as these can be leveraged into further improvements in care for bladder cancer patients. Key to further improvements in these collaboratives is engagement with stakeholders, including physicians, hospitals, and third party payers, to show the value of the programs for improving patient care, costs, and outcomes.

**Conclusion**

Bladder cancer care is susceptible to overuse of interventions and evaluations for low-risk non-muscle-invasive bladder cancer and underuse of life-saving therapies for high-risk muscle-invasive bladder cancer. The high cost of this care is likely to draw attention from payers and
policy-makers. Currently, efforts to address quality and cost of healthcare delivery derive from national policy and pay-for-performance initiatives, payer-directed efforts to identify hospitals that provide high-value surgical care, and emerging efforts such as urological quality collaboratives. Collectively, these efforts have potential to impact the care of men and women with bladder cancer.

Useful web links


References

Cancer patient advocacy

Cancer care involves a complex ecosystem of stakeholders, each of whom contributes to defining and delivering available treatments and the standard of care. These stakeholders include medical professionals, medical institutions, government agencies, pharmaceutical and biotechnology companies, insurance providers, and, of course, the patients themselves. While the degree of influence held by each stakeholder class may vary by country, reflecting different systems of healthcare delivery, cultural factors, and prevalence of disease, the mission of each of these stakeholders is universal: prevent, detect, treat, and cure cancer. Patients are not only at the center of this ecosystem – they have the potential power to influence, educate, and motivate and thereby bring significant changes to the cancer care landscape.

Patient advocacy organizations have long played an important role in increasing public awareness of health issues and in demanding improvement in approaches to treatment. The American Cancer Society, the first cancer patient advocacy organization, was founded in 1913 as the American Society for the Control of Cancer (ASCC) by a group of physicians and business leaders in New York City. At that time, a cancer diagnosis amounted to near certain death. Rarely mentioned in public, this taboo disease was steeped in fear and denial. The Society’s founders knew they had to raise public awareness about cancer if progress was to be possible. The members of the Society began their efforts by writing articles for magazines and professional journals, and recruiting physicians across the country to help educate the public. In 1945, the ASCC was reorganized as the American Cancer Society (ACS) [1]. ACS was instrumental in helping secure passage of the National Cancer Act in 1971, which revolutionized the “war on cancer” in the United States.

Soon thereafter, in 1974, First Lady Betty Ford announced that she had breast cancer and that she had undergone a mastectomy. Mrs Ford’s willingness to be forthcoming about her health condition – at a time
Bladder cancer patient advocacy: creating partnerships

when most people still whispered when talking about “cancer” – has been credited with launching the modern cancer patient advocacy movement. Indeed, as the details of her breast cancer were disseminated in the wake of her disclosure, there were widespread reports of tens of thousands of American women seeking to also have mammograms. Her direct usage of the very words “breast and cancer” was something that had rarely been done in the past. By further using her own condition to discuss screening, diagnosis, treatment options, and the emotional process of surviving a mastectomy, she not only raised public awareness but forever changed the perception of the disease [2].

Today, cancer is a common topic in the news, with many entertainers, politicians, sports figures, and business personalities raising public awareness by sharing their cancer diagnoses and treatments. Recognizing that the collective voice is more powerful than a single voice, hundreds of cancer patient advocacy organizations have been formed around the world. Many are devoted to a specific cancer type (indeed, for cancers such as breast, prostate, colon, and lung, there are dozens of organizations for each), while others are focused on issues common to all cancers (e.g., American Cancer Society, Canadian Cancer Society, and the European Cancer Patient Coalition). While each of these patient advocacy organizations may differ in specific mission and purpose, they all share the common belief that patient engagement in cancer care is essential to improving patient care and outcomes.

Although the term patient advocate can be used to describe people performing different tasks and addressing a variety of different problems, the “defining feature of a patient advocate is someone whose primary goal is to act in the best interests of patients, often those who are not able to advocate for themselves” [3]. Patient advocacy includes “interventions targeting individual empowerment, interpersonal interactions, organizational and cultural change, and policy development related to healthcare delivery and design” [4].

Not surprisingly, cancer patient advocacy and the associated interventions have different levels of maturity by country. US advocacy groups are typically the most mature, given longer histories and more experience. Canadian groups have made similar progress. While European advocacy groups are becoming more prevalent, “the maturity and effectiveness of these groups varies among countries and among cancer types” [5].

Though many of the European barriers to advocacy are similar to those experienced in other countries (survival rates for some cancers; securing and sustaining funding; establishing credibility; attitudes toward activism), variability in healthcare systems, European legislative complexity, and language are unique challenges that Europe must ultimately overcome [5]. The paucity of literature on other countries suggests generally low levels of maturity.

**Bladder cancer patient advocacy**

Bladder cancer was the last of the most common cancers to gain a voice in the patient advocacy community. Despite its prevalence (ninth most common cancer globally and sixth most common cancer in the US, where there are more than 70,000 new cases each year, and nearly 15,000 deaths), no bladder cancer patient advocacy organization existed in the United States until 2005, with the launch of the Bladder Cancer Advocacy Network (BCAN). BCAN was founded by Diane Zipursky Quale and her late husband, John Quale, a bladder cancer patient who died from the disease in 2008. BCAN’s mission is to increase public awareness about bladder cancer, advance bladder cancer research, and to provide educational and support services to the bladder cancer community. From its inception, the Bladder Cancer Advocacy Network has been a cooperative effort between bladder cancer survivors, their families and caregivers, and the medical community. More than 50 bladder cancer specialists, including urologists, medical and radiation oncologists, basic scientists, and pathologists serve on BCAN’s Scientific Advisory Board, ensuring the accuracy of information provided by BCAN and alignment with critical scientific goals [6].

Besides BCAN, there are few bladder cancer patient advocacy organizations around the world. Bladder Cancer Canada was founded in 2009 by bladder cancer survivors David Guttman and Jack Moon, and is supported by a Medical Advisory Board. Its priorities include improving patient support and raising funds for research [7]. Action on Bladder Cancer (ABC) is the only charity in the United Kingdom exclusively focused on improving the lives of people with bladder cancer, with its mission “to work with healthcare professionals, patients, their carers and the general public, to help
improve the care of people with bladder cancer through awareness raising, education and research projects” [8]. ABC has recently extended outreach to Scotland. The American Bladder Cancer Society was founded in 2007 with the “function to raise awareness of bladder cancer among the general public and the medical community, to advocate for the advance of research into a cure, treatment, early diagnosis and quality of life issues of survivors, to support bladder cancer survivors by providing community as well as by encouraging the concept of informed medical consumerism” [9].

Partnerships between bladder cancer patient advocacy organizations and medical professionals can lead to improved patient care and outcomes, additional bladder cancer research funds, and improved design and enrollment of clinical trials, which will lead to much-needed treatment advancements.

**Partnering to improve patient care**

Patient advocacy organizations can be instrumental in providing critical educational information to patients, recognizing that informed, proactive patients who understand their disease and treatment options have the best opportunity for an improved prognosis. Access to up-to-date educational tools, written from the patient perspective, can assist physicians in ensuring that patients will get answers to the many questions that arise – especially after the patient leaves the doctor’s office.

Advocacy groups frequently provide those patient-centric educational tools to patients. For example, the Bladder Cancer Advocacy Network, in conjunction with members of its Scientific Advisory Board, has published *Bladder Cancer Basics for the Newly Diagnosed*, a comprehensive guide offering information on bladder cancer diagnosis and treatment options to help patients make the most informed choices about their care. This resource, available online and in print, in both English and in Spanish, has been widely distributed to urology practices and medical centers. BCAN also offers patient “tip sheets” which include information on bladder cancer treatments and procedures from the perspective of survivors who have undergone the procedures themselves.

The growth of the Internet and social media has made access to medical information more readily available all around the world. Unfortunately, not all information on the Internet is accurate or helpful. The websites of bladder cancer patient advocacy organizations, especially those developed with the input of their respective scientific and medical advisors, offer a trusted resource for information [10].

As indicated in Chapter 33, bladder cancer patients, particularly those who are pre- and post-radical cystectomy, encounter a host of psychosocial issues, including body image, reorganization of daily activities, physical and emotional adjustments to treatment side effects, and overall uncertainty about the future. Patient advocacy groups can facilitate connections to other patients and psychosocial services through support groups.

The scientific community in general believes that support groups can enhance quality of life for many people with cancer. Cancer support groups present information, provide comfort, teach coping skills, help reduce anxiety, and provide a place for people to share common concerns and emotional support. Research has shown that people with cancer are better able to deal with their disease when supported by others in similar situations [11].

Patient advocacy organizations have facilitated the creation of bladder cancer support groups. Both BCAN and Bladder Cancer Canada have encouraged bladder cancer survivors and medical professionals to start support groups in their communities and in many instances have helped form partnerships between survivors and medical professionals. In addition, both organizations include information on their respective websites on existing bladder cancer support groups, directing patients to support groups in their own communities. The explosive growth of the Internet has enabled rapid growth in support group membership and global connections. BCAN, Bladder Cancer Canada, and the American Bladder Cancer Society also offer online support communities, connecting bladder cancer survivors with peers around the world.

Partnerships between patient advocacy groups and physicians can also be used to educate patients about clinical trials and the important role these studies play in developing effective new treatments for bladder cancer. Such efforts could greatly improve patient accrual to clinical trials, which are almost universally low. “Adult trial participation in the U.S. remains under 3%, with even lower participation rates among ethnic and racial minorities and people over 65” [12]. Bladder cancer’s
prevalence among people in their sixth and seventh decades exacerbates accrual challenges for clinical trials that target bladder cancer survivors.

In many cases, patients do not have a good understanding of what a clinical trial involves, and believe they may be compromising their care if they enroll in such a study. Even in cases where patients may be interested in participating in a clinical trial, finding information about bladder cancer clinical trials is challenging. Patient advocacy organizations have worked with members of the medical community to develop educational materials that fully explain the clinical trials process, disclose the possible risks and benefits, and encourage qualified patients to participate in trials. Each of the current bladder cancer patient advocacy organizations offers this information on their respective websites, as well as specific information on bladder cancer clinical trials. BCAN, in partnership with EmergingMed, also offers a free, confidential, and personalized matching service to help patients locate bladder cancer clinical trials that may be appropriate for them based on their unique diagnosis, staging, and treatment history and overall health [13].

Partnering to advance bladder cancer research

Funding is critical to advance the science and treatments of any cancer, and industry and government fund the majority of that research in the US. Patient advocacy groups can play a significant role in lobbying industry and government to prioritize and re-direct funds and focus to a specific disease. In the United States, the National Institutes of Health is the organization responsible for determining government funding levels across diseases. According to the NIH document Setting Research Priorities, “the nation’s health needs are evaluated in light of the following considerations:
- The number of people who have a particular disease.
- The number of deaths produced by a disease.
- The degree of disability produced by a disease.
- The degree to which a disease cuts short a normal, productive, comfortable lifetime.
- The economic and social costs of a disease.
- The need to act rapidly to control the spread of a disease.” [14].

Despite its prevalence, the tremendous impact on those diagnosed with the disease and their families, and the economic burden of the treatments on individuals and society, research funding for bladder cancer has languished for many years. Not surprisingly, meager results have been achieved. Since bacillus Calmette-Guérin (BCG) was initially approved by the FDA in 1990, only one new treatment (Valstar) has been approved for bladder cancer, with a very small and limited indication [15]. Patients with muscle-invasive bladder cancer who qualify for first line chemotherapy have been “stranded on a shallow plateau for nearly a generation” [16] – they have seen no improvement since the introduction of combination chemotherapy, specifically methotrexate, vinblastine, adriamycin, and cisplatin (MVAC), in the 1980s. For patients with advanced disease who do not respond to “first line” chemotherapy, there are no other approved treatment options. Bladder cancer is clearly an underserved disease.

This lack of advancement in treatment options stands in stark contrast to almost all other cancer types. Since 1998 when Valstar was approved, there have been more than ten new treatments approved for prostate cancer and for breast cancer; eight new treatments for colorectal cancer; and seven new treatments for lung cancer. In the past eight years alone, there has been an unprecedented level of drug development for kidney cancer, with seven new drugs approved [17].

Why is bladder cancer so far behind in research advancement? In the United States, the answer is, in part, a lack of funding by the federal government. Historically, the National Cancer Institute’s (NCI’s) funding for bladder cancer has been significantly less (on a per incidence basis) than all other cancers. Although bladder cancer is ranked in the top six cancers in the US in terms of incidence, it is only 22nd on the list of cancers for which the government funds research [18].

The experience of other cancer advocacy organizations demonstrates that, in many cases, governmental research funding follows the loudest voices. US government funding of breast cancer research has increased from $30 million to $850 million annually since the inception of Susan G. Komen for the Cure and other breast cancer advocacy organizations [19]. Similarly, federal research dollars for prostate cancer have increased more than twenty-fold since the Prostate Cancer Foundation began advocating for greater
awareness of prostate cancer and more governmental resources. Only recently has bladder cancer had a patient advocacy voice to demand more research attention. The missions of BCAN, Bladder Cancer Canada, and Action for Bladder Cancer include advocating for greater government attention to, and research funding for, bladder cancer.

Collaboration among researchers is a critical outcome that every disease state must achieve if the science of the disease is to move forward significantly. The ability of individual institutions and individual researchers to advance the science of any disease is limited today, and the complexity of cancer makes collaboration even more critical. Bladder cancer is no exception. Patient advocacy organizations can provide the impetus – as well as the mechanism – to promote this much-needed cooperation.

One of BCAN’s earliest accomplishments was the establishment of an annual Bladder Cancer Think Tank meeting, which focuses on identifying obstacles and creating solutions in bladder cancer research. The meeting is also a strong catalyst for collaboration, and has fostered discussions that have helped define priorities for bladder cancer research. As a result of these efforts, the public profile of bladder cancer is increasing, evidenced by the creation of a Bladder Cancer Task Force as part of the Genitourinary Steering Committee (GUSC) at the National Cancer Institute whose mission is “to harmonize an efficient, cost-effective, science-driven, and transparent process that will identify and promote the ‘Best Science’ in genitourinary cancer clinical research by addressing the design and prioritization of phase III trials and large phase II studies” [20]; bladder cancer’s inclusion in The Cancer Genome Atlas Project [21]; and FDA support to improve the design of bladder cancer clinical trials to help speed approval of new treatments [22].

Cancer patient advocacy organizations can also play a key role in advancing research by directly funding research proposals. With this in mind, BCAN launched its Young Investigator Awards in 2013. Each of these awards will be for $100,000 over a two-year period, and will fund researchers who are working in a research environment capable of supporting transformational bladder cancer research. Bladder Cancer Canada, in partnership with the Canadian Institutes for Health Research, is also funding a bladder cancer research fellowship [23].

**Partnering in clinical trials**

Patient advocacy organizations also play an important role in defining and calibrating the research priorities for bladder cancer. Furthering our understanding of diseases is fundamental to better treatments and outcomes. A critical element of the research process is the transition from theory and animal models to practical application, or what is often referred to as “bench to bedside.” This transition requires compelling data, typically gathered during clinical trials. The standard of care usually does not change without such data.

Recognizing that “communities affected by a disease must have a voice, and must be consulted” [24], the National Cancer Institute (NCI) has had direct input on clinical trials from patients since the early 1990s via a specific type of patient advocate that we will refer to as a “research patient advocate” to minimize confusion. Each of the four adult cooperative groups in the National Clinical Trials Network – SWOG, ECOG-ACRIN Cancer Research Group, the Alliance for Clinical Trials in Oncology, and NRG Oncology – as well as the Children’s Oncology Group, have research patient advocates supporting their clinical trials.

The Institute of Medicine, in its report entitled *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*, defines the partnership between research patient advocates and investigators this way:

> “Advocates also provide valuable input to study design and procedures, safety and confidentiality issues, feasibility, informed consent processes, and other factors important to potential research participants to help facilitate the development, implementation, and recruitment processes.”

Research patient advocates are often directly affiliated with patient advocacy groups for the disease they represent, and “seek not only to change how research is conducted but also to influence decisions about what research should be funded” [25]. They are assigned to work with investigators to represent the voice of the patient in the safe, efficient, and effective design, development, and delivery of clinical trials.

Mechanisms to improve the integration with investigators have been developed by research patient advocates. At SWOG, an adult cooperative group within the National Clinical Trials Network, the research patient advocates jointly developed *Ten Key
Questions Investigators Can Ask Their Patient Advocate [26] to provide a catalyst for productively engaging research patient advocates.

The Ten Questions reflect the major areas in which research patient advocates can add value to the clinical trial process. While the questions and their answers do not completely define the activities or areas of influence and input, they trigger the right discussion between the primary investigator, the full study team, and the research advocate.

For the Design stage, where concepts are first being reviewed and the greatest latitude in trial design exists, five questions were deemed most critical:

1. How important are the goals of this trial to the patient community … and why?
2. What patient-reported outcomes should be added as objectives?
3. What suggestions do you have to address issues that might make patients hesitant to enroll?
4. What other therapies or competing trials might keep patients from participating in this trial?
5. What benefits will this trial bring to patients in the immediate and long term?

At the subsequent Develop stage, the trial is subject to a great deal more rigor, with details being resolved operationally, strategically, and tactically. The questions then are more focused:

6. What concerns, if any, do you have with the eligibility criteria?
7. How can the informed consent package and other patient literature be improved so that the information is conveyed in simple, patient-friendly language?
8. What unanswered questions or areas of concern or confusion do we need to address with additional patient communication?
9. What barriers or issues do you see with regard to collection and banking of blood and/or tissue specimens for future research?

In the Deliver stage, plans are being executed and adjusted based on results. This would include the protocol and, of course, the accrual or recruitment plan. Research patient advocates should be asked this question during the Deliver stage:

10. How can your advocacy group and other organizations increase awareness about this trial?

Strong ties to patient advocacy organizations and a cross-section of the survivor community make research patient advocates more effective as they answer these questions and pose their own questions of the investigators. Without that support, the ability of a clinical trial to transform the standard of care and enable new treatments to become the pattern of practice is hindered.

Conclusion

While the work of BCAN and other bladder cancer patient advocacy groups globally represents significant and historically unprecedented progress, bladder cancer patient advocacy is relatively young by comparison to other cancers. However, it is gaining momentum. Strong partnerships have been formed and are delivering substantive and meaningful results to the bladder cancer survivor community.

We anticipate existing partnerships across the bladder cancer ecosystem will strengthen further. We also anticipate engagement of stakeholders that have heretofore played a minor role. By advancing partnerships throughout the ecosystem, we foresee increased awareness of bladder cancer, earlier diagnosis, brisker accrual to clinical trials, better treatment options, and reductions in the survivorship issues that are so prevalent among bladder cancer survivors today. As a result, bladder cancer survivors will live longer, and healthier, lives.

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