Bladder Cancer

A Practical Guide

Ashish M. Kamat
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Editors

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Preface

Yet another book on urothelial cancers?

The field of study for urothelial cancers, stagnant for a long time, has grown exponentially in the last decade. Keeping up with the advances in the field is challenging and exciting at the same time, and requires constantly being in tune with conference proceedings, and online webinars, since even journal publications are not able to keep pace with the speed of advances.

This book does not aim to replace those. What it aims to do is to provide a comprehensive, insightful, state-of-the-art review of the field, taking a practical, multidisciplinary approach. By inviting contributions from leading experts around the world, we have collected, in one place, a wealth of institutional and personal experience to bridge the gap between conventional textbooks and practical, hands-on experience to provide a concise yet comprehensive summary of the current status of the field that will help guide patient management and stimulate investigative efforts.

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Part I

Bladder Cancer

1 Bladder Cancer Screening, Signs and Symptoms, and Workup

Joshua J. Meeks

Introduction

Bladder cancer is the fourth most common cancer in men and sixth most common overall in the USA and ninth most common internationally [1]. Most will develop hematuria as the inciting event that leads to an evaluation and diagnosis of bladder cancer [2]. Unfortunately, despite an increased association with smoking, population-based methods to screen for bladder cancer have not been accepted by screening task forces, largely due to the low incidence of invasive cancer in a non-risk stratified population. Therefore, an evaluation for bladder cancer occurs only after symptoms are present (hematuria), and unfortunately 20% of patients will have locally advanced or metastatic bladder cancer. In this chapter, we discuss screening procedures, evaluation, and workup to result in a diagnosis of bladder cancer.

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Screening

To date, widespread screening for bladder cancer, even in "high-risk" patients, is not recommended by guideline committees [3]. The potential benefit of early detection has not balanced out disadvantages such as high cost, over-detection, and lack of specificity. Most screening trials have been structured to identify higher-risk individuals, but our knowledge of the causes of bladder cancer remains largely unknown as only half of patients are smokers, and the biology of tumors from non-smokers (gene-expression profiling and mutation analysis) has not been identified as a cause of most tumors [4].

Rationale for Screening

Screening for bladder cancer may have widespread benefits, largely dependent on identifying invasive tumors prior to muscle-invasive stages (stage II or greater). Patients diagnosed with stage I or less cancers can usually avoid the morbidity of radical therapy (cystectomy or trimodal therapy) and systemic toxicity from chemotherapy. Diagnosis at an earlier stage of disease could also decrease the cost of treating advanced bladder cancer [5]. A modest reduction in the risk of muscle-invasive or metastatic cancer will impact thousands of patients each year in the USA, and prior screening studies suggest that the reduction

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in risk may be as high as 80%. As an example of the potential benefits of screening, an evaluation of 48 patients with a history of aristolochic-acid-induced nephropathy identified 22 patients with non-muscle-invasive bladder tumors with only three deaths from bladder cancer in patients who refused screening by cystoscopy [6].

Prior Screening Trials

Screening using dipstick analysis was used in several large screening studies to identify patients at risk for bladder cancer. A total of 1575 men (aged ≥50 years) were screened at home with dipstick urinalysis (UA) for 14 consecutive days and the screening was repeated 9 months later in those with a negative screen [7]. Men with a positive dipstick UA underwent cystoscopy ($n = 283$) and 21 men were diagnosed with bladder cancer (1.3% incidence; including one with muscle invasion) [7, 8]. Stage at diagnosis and survival were compared to a contemporary 509 unscreened patients newly diagnosed with bladder cancer from the Wisconsin cancer registry. Screened men were less likely to be diagnosed with muscle invasive cancer than non-screened men (4.8% vs 23.5%) and had a significantly lower disease-specific mortality than unscreened men. No men with screen-detected bladder cancer died of bladder cancer, compared to 20.4% of non-screened men [8]. Britton et al. examined 2356 men aged 60–85 years for dipstick microhematuria weekly for 10 weeks [9]. Urine testing was positive in 20% of men and bladder cancer diagnosed in 17 men. No patient was diagnosed with muscle-invasive cancer, but more than half (9/17) had high-risk NMIBC (non-muscle invasive bladder cancer). A prospective bladder cancer screening study of 1500 high-risk subjects performed using a urine-based tumor marker test found an increased risk in subjects whose age was greater than 50 and in those who had more than 10 years of tobacco exposure or 15 years of occupational exposure, but the study did not detect an increase in the number of cancers [10]. In a trial of aluminum workers in Quebec in the 1980s, screening by cytology was implemented in patients with at least 10 years of exposure. In the Quebec cohort, screening increased the rate of early-stage tumors to 77% from 67% compared to the prior decade ($p < 0.1$) [11], but no improvement in cancer-specific survival was noted. These mixed data suggest that screening patients can result in early detection of bladder cancer, but unfortunately, a well-conducted screening study with an optimal control cohort has not been performed.

Identification of At-Risk Populations

The greatest known risk of bladder cancer is smoking [12]. Patients self-identified as former smokers (119.8 per 100,000 person-years; HR, 2.22; 2.03–2.44) and current smokers (177.3 per 100,000 person-years; HR, 4.06; 3.66–4.50) had higher risks of bladder cancer than never-smokers (39.8 per 100,000 person-years) [13]. Patients with Lynch syndrome have an increased risk of bladder cancer ranging between 2.3% for MutL homolog 1 (MLH1) mutations and 6.21% for MutS homolog 2 (MSH2) [14]. In a cohort study, patients with diabetes mellitus were at increased risk for bladder cancer (2.2, 95% CI, 1.3–3.8), with greater risk for those with the longest duration of exposure (OR for 16 or more years; 3.6, 95% CI, 1.1 to 11.2) and in those taking oral hypoglycemic medications (OR 3.3, 1.5–7.1) [15]. Evaluation of occupational exposures found a relatively slight increase in risk in metal workers exposed to salt-mining, textiles, carpets, and plastics (OR 1.23, 95% CI. 1.07–1.4) [16]. In an analysis of the PLCO cohort, risk stratification for male gender, smoking history, and age >65 increased the potential specificity of screening [17].

Burdens of screening for bladder cancer are minimal and screening characteristics of dipsticks Unlike screening for lung, breast, and prostate cancers, there is almost no harm in screening for bladder cancer. Home urine dipstick evaluation kits for microhematuria have been used in prior screening studies for bladder cancer. Although dipstick has a low positive predictive value, when repeated testing is performed, very few times diagnoses of bladder cancer are

missed (<1% with long-term follow-up and none within 1 year of screening) [8] with an AUC of 0.80 (95% CI 0.79–0.81) [18]. An evaluation of more than 46,000 patients in the Chicago-land area found that the dipstick UA had a sensitivity of 0.58 and a specificity of 0.81, with a positive likelihood ratio of 3.13 and negative likelihood ratio of 0.52 in the diagnosis of bladder cancer [18]. Most importantly, with regard to screening, dipstick urinalysis is rarely negative in patients with bladder cancer and our study found the rate of missed bladder cancer diagnosis to be 0.03% (12/33,750).

Degree of hematuria is directly related to the stage of cancer at the time of diagnosis Dr. Lotan conducted a multi-institutional cohort review of 1384 patients who were diagnosed with bladder cancer between August 1999 and May 2012 and reviewed the degree of hematuria, demographic information, clinical and social history, imaging, and pathology [19]. The association of hematuria severity with tumor stage and grade was evaluated. Patients were grouped by degree of hematuria and presentation including gross hematuria (n = 1083, 78.3%), microscopic hematuria (n = 189, 13.7%), and no hematuria (n = 112, 8.1%). The stage of diagnosis for microscopic hematuria was Ta/CIS (68.8%), T1 (19.6%), and ≥T2 (11.6%), while the stage for gross hematuria was Ta/CIS (55.9%), T1 (19.6%), and ≥T2 (17.9%). Multivariate analyses showed that gross hematuria was independently associated with higher pathologic stage disease (OR: 1.69, 95%CI: 1.05–2.71, p = 0.03). These results suggest that less hematuria is associated with lower stage and potentially long-term improvements in survival. Cytology has not been a reliable screening tool due to its low sensitivity of only 44%, but it has a specificity of 96% [20].

Cost Assuming a 50% reduction in downstaging in the patients diagnosed with screened positive compared to unscreened bladder cancer, a gain of 3.0 life years per 1000 subjects was anticipated at a cost savings of $101,000 per patient for the population [21]. The potential costs of screening include the costs of imaging and cystoscopic procedures for patients without bladder cancer.

Harms Cystoscopy is performed without anesthesia, nearly pain-free, and it takes approximately 90 seconds of the provider time to completely evaluate the bladder with a <1% risk of infection and no long-term morbidity. Unlike prostate or colon cancer in which early cancers may be indolent and asymptomatic, all bladder cancers will eventually bleed requiring surgical intervention and lead to patient discomfort.

USPSTF Bladder cancer screening is currently categorized as an "I" recommendation by the US Preventive Services Task Force because the data available to assess the balance of benefits and harms of screening asymptomatic adults are scarce and of poor quality [3, 22]. Although small cohort studies have been described, they lack a control cohort, with the same risk factors, but not screened for bladder cancer.

In practice We discuss screening with all patients with a family history, heavy smoking, or industrial exposure. After we discuss the lack of evidence to suggest screening for all patients, I believe that cancers detected earlier have a better outcome. If they would like to begin a screening program, we talk about the frequency and method of screening. For most patients, this includes a urinalysis, often yearly. For patients who want more frequent evaluation, I recommend evaluation with home-dipsticks that can be purchased from a pharmacy over the counter. A positive screen would then initiate a hospital-based confirmation, followed by cystoscopy and/or imaging evaluation.

Signs and Symptoms

Without another cause identified, urothelial carcinoma should be considered in all patients with gross hematuria. The rate of bladder cancer for men or women is 20% with gross hematuria, which is significantly greater than microscopic hematuria, in which bladder cancer is found in

only 5% [23–25]. Despite an AUA guideline, a full hematuria evaluation is rarely performed for microscopic hematuria, with our best estimate of 8% [26]. Yet, more patients with a full evaluation are likely to have a diagnosis of bladder cancer with 4.8% diagnosed with bladder cancer when both cystoscopy and imaging are performed, while only 0.3% were found to have bladder cancer with imaging alone [26].

Other symptoms of bladder cancer include pelvic pain, dysuria/urgency, UTI (urinary tract infection), and weight loss [25, 27, 28]. A stage delay, in which women are diagnosed with bladder cancer at a higher stage, has been described [29, 30]. This likely is impacted by delays in care due to the overlap in symptoms with UTI symptoms [31]. Urgency is a symptom found with patients who have CIS/carcinoma in situ [27]. Patients who have a smoking history and/or microscopic hematuria and urgency should have an evaluation for bladder cancer. Locally advanced bladder cancer can affect urinary and rectal control. These symptoms include urinary incontinence, urinary obstruction, rectal urgency, and azotemia from trigonal obstruction. Unfortunately, weight loss and decreased performance status are due to cachexia associated with metastatic bladder cancer [32].

Evaluation

The evaluation of the patient with hematuria should involve a history, physical exam, imaging, and cystoscopy. A history should identify the timing of gross hematuria, number of episodes, and any antibiotics/cultures obtained. Frequent hematuria treated with antibiotics and a negative culture are concerning for cancer. A smoking history should include number of pack years and duration since smoking if a reformed smoker. A family history of bladder cancer, colorectal cancer, or cancer syndrome should be noted with referral to genetic counseling. In those who have had prior hematuria, the time since the evaluation and what that evaluation included should be noted. If cystoscopy will be performed in the office, a prostate or pelvic exam can be performed during or after this evaluation or deferred until the OR if a TURBT is necessary. In our office, we arrange for a cystoscopy on the same date as the initial visit for hematuria to ensure the evaluation is completed. A CT-triphasic imaging of the ureters and renal pelvis is performed prior to visit and scheduled at the timing of the patient registration for patients with gross hematuria [33]. This streamlined approach (Fig. 1.1) decreased the time from referral to completed evaluation (41 vs 74 days, $p < 0.05$) with decreased cost of the evaluation secondary to fewer visits. In patients with microscopic hematuria, renal ultrasound may be just as accurate with significantly less cost [34]. Alternatively, if the imaging identifies a bladder mass, this is discussed with the patient at the initial visit and a TURBT is scheduled without a flexible cystoscopy in the office. At the time of cystoscopy, I don't send a cytology since this has no bearing on the surgery, and pathology will be obtained at that time. In addition to bladder tumor resection, an exam under anesthesia is performed to evaluate for a cT3+ bladder mass and/or a pT4a invasive tumor.

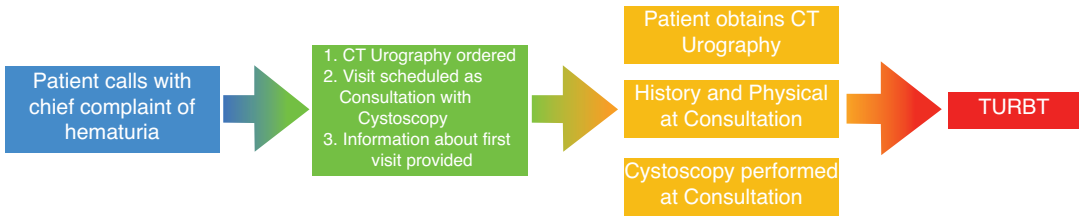

Fig. 1.1 Flow diagram of coordinated care for hematuria. Patients that schedule a "hematuria" evaluation are automatically given information about hematuria, scheduled to have a new consultation with cystoscopy and a CT urography is ordered for gross hematuria. This streamlined flow has reduced the time from referral to completion of evaluation and decreased the cost of evaluation by reducing the number of visits required

Conclusions

There is no well-controlled data to consider broad, non-risk stratified screening of patients for bladder cancer. Yet, those at high risk of bladder cancer may achieve a potentially earlier diagnosis with less morbidity and mortality. Future studies considering risk-stratified screening may improve survival. Currently, those with microscopic, but especially gross hematuria, should have a history, physical exam with cystoscopy, and imaging of the upper tracts (CT for gross hematuria and ultrasound for microscopic hematuria). Future algorithms may improve detection of cancer in patients with microscopic hematuria.

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2 Cystoscopy and Enhanced Diagnostics

Kamal S. Pohar

Introduction

It is estimated that more than 81,000 individuals in the United States will be diagnosed with bladder cancer in the coming year and 75% of the cases will be staged as nonmuscle invasive bladder cancer (NMIBC) [1]. At least half of these individuals will develop a recurrent bladder tumor and even more concerning 5–25% of recurrences eventually progress to muscle-invasive bladder cancer (MIBC) [2–5]. Reliable visualization of bladder tumors is crucial to the success of cancer surveillance strategies and curative intent transurethral resection of bladder tumor (TURBT). Almost all surveillance cystoscopies and the large majority of TURBT performed worldwide utilize white-light illumination. However, developments in technology have irrefutably determined that *carcinoma* in situ (CIS) and other low- and high-grade flat or subtle papillary lesions are often not visualized by standard white light cystoscopy (WLC) [6–9]. These initial studies suggested that TURBT solely dependent upon WLC has the potential to impact patient outcomes in a negative manner and there is considerable opportunity to improve upon our current standard of diagnostics.

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The cystoscopic equipment used in modern day urology practice is the result of two centuries of innovation and development. Each new development has improved the sensitivity of detection of bladder cancer and some advances improved the safety of the procedure, including reducing fire risk. After many decades of human ingenuity and advances in illuminating and visualizing the bladder, the German urologist Maximilian Carl-Friedrich Nitze in collaboration with Joseph Leiter introduced the first working cystoscope in 1878 [10]. The invention of the light bulb, refined hemispheric lenses, the Amici prism allowing for visualization of a true image and the Albarran lever all contributed to the widely used Brown-Berger combination cystoscope for much of the twentieth century [11]. Harold Hopkins discovered fiber optic technology in the mid-twentieth century and integrated the technology into the cystoscope in 1959. A few years later the system was purchased by Karl Storzas, it produced higher quality images with excellent illumination and later adopted by most physicians performing cystoscopy worldwide [12]. The integration of camera equipment, distal-chip sensor technology allowing for digital imaging and transmission of images to outside monitors led to our current day equipment for cystoscopy [11].

We are very fortunate, as practicing urologists, that systematic advances in innovation and technology have led to high-quality images of the bladder that allow us to provide a high level of

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patient care. Nevertheless, there is considerable evidence that white light optical equipment in current use, in both the office and operating room, do not allow for visualization of all bladder tumors. This chapter focuses on a number of enhanced diagnostics that are in various stages of clinical use and development and supported by varying levels of evidence so as to how much they improve upon WLC.

Photodynamic Diagnosis

Photodynamic diagnosis (PDD) of bladder cancer is dependent upon intravesical instillation of a fluorophore, preferentially sequestered by neoplastic cells, and the ensuing fluorescent signal detected by a blue light-emitting cystoscope. The initial investigation of the fluorophore, 5-aminolevulinic acid (5-ALA) and later the lipophilic hexyl ester of 5-ALA, as a diagnostic tool for bladder cancer, followed promising results of this agent in the detection of nonmelanoma skin lesions and head and neck cancer. A number of studies have consistently confirmed that the addition of fluorescence-assisted blue light cystoscopy (BLC) to WLC leads to better visualization of bladder tumors at the time of TURBT [6–9]. Rink et al. performed a review of 26 studies and found that PDD improved the detection of papillary tumors by 7–29% and CIS by 2–30% when compared to WLC, independent of the fluorophore used for the procedure. The fluorophore in current use for PDD is a substrate incorporated in the heme biosynthesis pathway. The hexyl ester derivative of 5-ALA, hexaminolevulinate (HAL; which is known as Cysview® in the USA and Hexvix® in Europe) has been approved by governmental regulatory bodies for use in the diagnosis of bladder cancer. The administration of HAL results in preferential accumulation of protoporphyrin IX and other photoactive porphyrins in the mitochondria of neoplastic tissue that fluoresce red when exposed to blue light between 375 and 440 nm [13, 14] (Figs. 2.1 and 2.2). Importantly, several studies confirm better visualization of bladder tumors leads to the desired clinical benefit of reducing

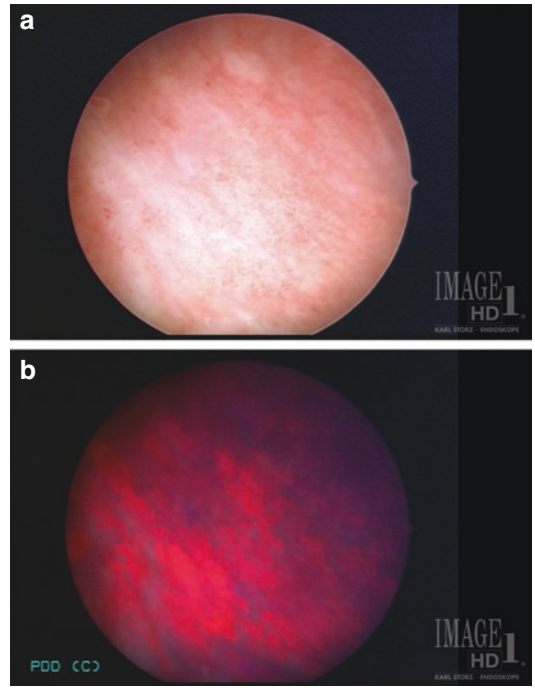

Fig. 2.1 (**a**) White light cystoscopy image of an abnormal area on the lateral bladder wall concerning for cancer. (**b**) Hexaminolevulinate-assisted blue light cystoscopy characterizes the abnormal area as well-demarcated multifocal papillary tumors appearing high-grade

tumor recurrences suggesting a better quality TURBT with HAL-assisted BLC [15–18]. Many of these studies were included in a meta-analysis that used raw patient data and the results presented as within-patient comparison for tumor detection and between-patient comparison for tumor recurrence. The meta-analysis determined that WLC missed 24.9% of Ta and T1 tumors and 26.7% of CIS tumors [19]. HAL-assisted BLC was associated with a 24% lower risk of recurrence at 12 months compared with WLC alone (35% vs 45%; risk ratio 0.76; 95% confidence interval [CI], 0.63–0.92; $p = 0.006$). The observed benefit was independent of tumor risk category (i.e., intermediate or high- risk NMIBC) or whether the tumor was primary or recurrent NMIBC.

It is important to emphasize that BLC used in combination with WLC maximizes the sensitivity of tumor detection. In a multicenter study of 311 patients with known or suspected NMIBC,

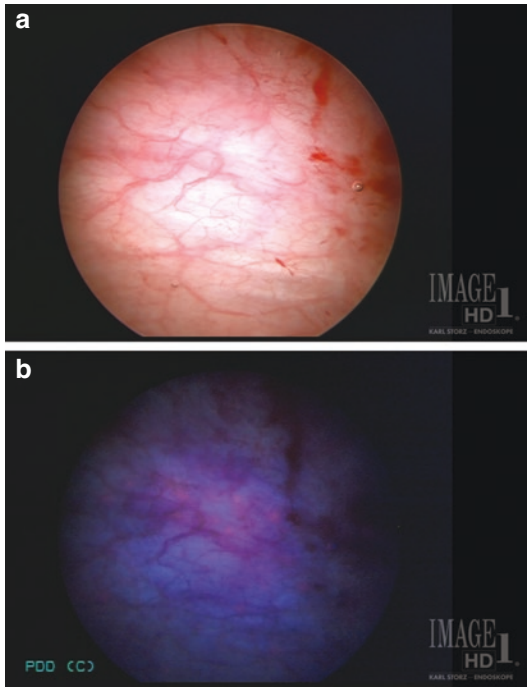

Fig. 2.2 (**a**) White light cystoscopy image of a normal appearing region of the bladder near the dome. (**b**) Hexaminolevulinate-assisted blue light cystoscopy demonstrates numerous small papillary tumors not identified by white light cystoscopy

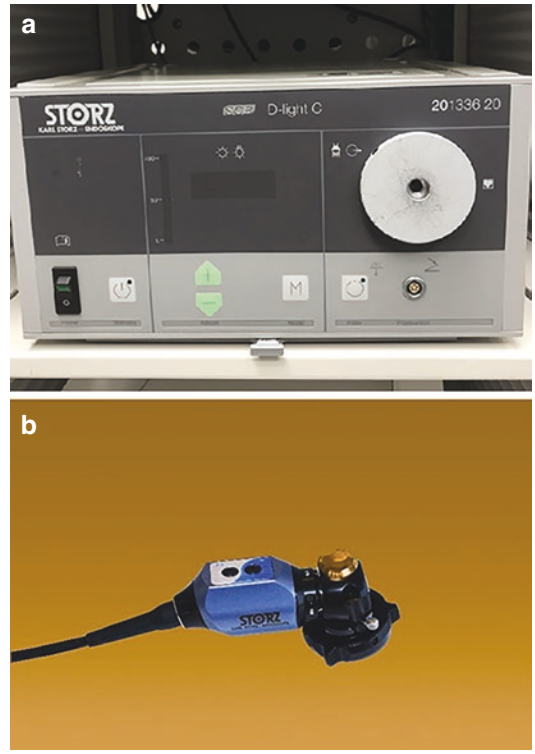

Fig. 2.3 (**a**) The D-light C-light (Karl Storz) light source contains a 300-watt xenon arc lamp with a band-pass filter capable of producing white and blue light for hexaminolevulinate-assisted fluorescence cystoscopy. (**b**) The photodynamic diagnostic camera (Karl Storz) has blue and silver buttons that allow the operator to switch between blue and white light in addition to controlling gain, shutter speed, and white light balancing. The gold dial is used to focus the camera

HAL-BLC missed 9% of tumors seen by WLC including a T1 bladder cancer. In the same study, HAL-assisted BLC detected at least one additional tumor compared to white light in 29% of patients and detected at least one additional T1 cancer in 15% of patients [8]. The study emphasizes the importance of the complementary benefit of using both blue and white light cystoscopy in the same patient to maximize benefit. Based on our own personal experience with HAL-assisted BLC, although uncommon, it is possible a patient with a positive cytology has both a normal blue and white light cystoscopy but random bladder biopsies detect the presence of CIS. Therefore, neither modality alone nor combined has perfect sensitivity for bladder cancer detection.

Currently in the United States, the Food and Drug Administration (FDA) has only approved the Karl Storz D-light C-light Photodynamic Diagnostic System® for PDD use in bladder cancer. Components of the system include a D-light C-light source in conjunction with the Tricam SL II and PDD camera head. The light source contains a 300-watt xenon arc lamp with a band-pass filter capable of producing white and blue light (Fig. 2.3). Specific PDD telescopes are required that contain a filter that is necessary to detect fluorescence. The PDD camera has blue and silver buttons that allow the operator to switch between blue and white light in addition to controlling gain, shutter speed, and white light balancing (Fig. 2.3). Understanding these controls can be useful to the urologist to optimize image quality. Default shutter speed is 1/15 second and can be changed by holding the silver button for greater than 3 seconds. While using blue light, a shutter speed of 1/15 or 1/30 second is recom-

mended. A one-second press of the silver button allows the operator to cycle through the gain settings to adjust lamp brightness during use [20].

Hexaminolevulinate (Cysview®) when packaged by the manufacturer arrives in a kit containing two vials that includes 100 mg of HAL powder in a glass vial and a 50 ml vial containing a sterile, nonpyrogenic solution labeled "diluent". Reconstitution of HAL is required for use and is possible at bedside or more remotely in the hospital pharmacy. Reconstituted HAL is immediately ready for intravesical use; however, if the patient is not ready for treatment it may be stored for 2 hours at 2–8 °C. The patient is straight-catheterized in the preprocedural area and HAL is slowly instilled in the bladder and allowed to dwell for 1–3 hours. If bladder dwell times exceed 3 hours normal bladder mucosa begins to respond to HAL and true bladder lesions and tumors become more difficult to identify leading to more false positive findings. Therefore, timing of drug delivery requires planning. There are very few contraindications to the use of HAL but include porphyria, active hematuria, and the very unlikely possibility of a prior adverse reaction to the drug.

There are several technical considerations to keep in mind while performing HAL-assisted BLC. Before examining the bladder, it is often best to position the cystoscope at the bladder neck where a reddish-pink fluorescence occurs from a tangential viewing effect confirming that HAL had sufficient contact time. Urine fluoresces green under blue light and routinely draining the bladder improves visualization throughout the course of the procedure. It is important to remember, blood in the bladder reduces the sensitivity of BLC and in cases of frank hematuria, HAL is contraindicated. It is recommended that TURBT is performed with white light as the dark blue light impedes depth perception and a strobe effect is often generated with quick movements. Therefore, there is a higher risk of bladder injury or perforation if the blue light mode is used during the actual performance of the TURBT but fulguration alone is likely safe with the blue light mode. It is also helpful to perform retrograde pyeloureterograms after the completion of BLC as contrast can reduce the ability to visualize bladder tumors.

A concern raised about PDD is the rate of false positives. However, several studies demonstrate the false positive rate is similar to WLC and with growing knowledge of scenarios that are more likely to increase false positives and experience with the technology these numbers should decrease with time [21, 22]. The study of Bazargani et al. illustrates in video format common false positive scenarios of fluorescence during HAL-assisted BLC that can help educate the urologist and reduce the number of unnecessary biopsies [22]. Possible false positive scenarios include: (i) tangential views of the bladder neck or side walls, (ii) inherent and expected fluorescence of the trigone, trabeculations, or cellules, (iii) inflammatory processes secondary to iatrogenic interventions (i.e., BCG, TURBT), (iv) idiopathic bright tiny spots, (v) site of prior ureterectomy/bladder cuff resection that leads to early fading lesions following irrigation. Unnecessary biopsy of these lesions can be avoided through simple techniques such as changing the angle of the cystoscopic view, several rounds of irrigation and avoiding HAL-assisted BLC too early after BCG instillation or prior resection.

The high-level evidence supporting the use of HAL-BLC was incorporated in the American Urological Association (AUA)–Society of Urologic Oncology (SUO) guidelines for managing NMIBC that states, "in a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence (Moderate Recommendation; Evidence Strength: Grade B)" [23]. Similarly, the European Association of Urology (EAU) guidelines also state, "fluorescence-guided biopsy and resection are more sensitive than the more conventional procedure for the detection of malignant tumors, particularly CIS." (Evidence Level: 1a) [24].

Blue Light Flexible Cystoscopy in the Clinic (Surveillance)

A large part of the care of NMIBC occurs in the office setting including diagnostic surveillance cystoscopy. Most of the time it is the findings of the office cystoscopy that determine whether biopsy or TURBT under anesthesia is necessary. The limitation of this approach is the procedure that is dependent upon white light illumination. Office based, white light cystoscopy has a high sensitivity for detecting papillary tumors but a known limitation is in detecting the presence of CIS as it may be missed in as many as 20% of patients [25]. As the body of evidence accumulated that earlier detection of tumors by fluorescence-assisted BLC at the time of TURBT led to less cancer recurrences, there was growing interest in studying whether incorporating blue light cystoscopy in the office surveillance setting could further improve patient care.

A clinical trial was recently conducted that evaluated whether the addition of HAL-assisted blue light flexible cystoscopy (BLFC) to white light flexible cystoscopy (WLFC) for patients with intermediate or high-risk NMIBC during office surveillance led to improved cancer detection [26]. The trial was an open-label, comparative, within-patient, controlled phase III study that included 304 patients enrolled by 17 centers in the United States. All patients received intravesical instillation of HAL at least 1 hour prior to cystoscopy. Each patient enrolled in the study underwent an initial evaluation with WLFC and then randomized on the procedure table whether or not to proceed with BLFC. The rationale for the randomization was to help ensure that the study physician performed the initial WLFC diligently as it was unknown whether BLFC would also be included in the care of the patient. At the conclusion of the cystoscopy, the trial mandated that a patient with any suspicious findings, by either white or blue light, needed further evaluated in the operating room, including HAL-BLC assisted TURBT. The primary efficacy end-point of the trial was the proportion of patients with histologically confirmed malignancy detected only by BLFC and not by WLFC.

Sixty-three of 103 (61%) patients taken to the operating room based on office cystoscopy findings had histologically confirmed bladder cancer on central pathology review. All but one of the suspicious lesions confirmed histologically to be cancer was visible by BLFC and importantly in 13 patients (21%) the cancer was only visible by BLFC and not WLFC. This included five patients diagnosed with CIS who had a normal white light cystoscopy and in none of these patients was the urine cytology positive or suspicious for cancer. This finding emphasizes the improved sensitivity of office-based enhanced cystoscopy in diagnosing CIS when compared to both WLFC and/or urine cytology. When generalizing the diagnostic value of the trial findings consideration that only 13 (4.2%) patients of the total enrolledwere cancer only seen by BLFC, albeit many high-grade. The false-positive rate of suspicious lesions was 9.1% for both BLFC and WLFC [26]. The findings of the study led to FDA approval to the use of HAL-assisted BLFC in the surveillance of NMIBC in 2019. Importantly, the study also confirmed the findings of prior retrospective institutional reports that repeat use of HAL in the same patient was not associated with a greater risk of side effects [27, 28].

Despite regulatory approval, the adoption of BLFC for surveillance of NMIBC remains limited in clinical practice. Equipment cost and added procedural time are practical considerations of implementing the technology. Equally important, evidence to confirm earlier detection of cancerous lesions at the time of surveillance cystoscopy leads to a clinically meaningful impact in patient care is required. Nevertheless, there is evolving limited real-world data using BLFC from European centers and a very recent report from the United States [29, 30]. The study of Lotan et al. reported on the prospective use of BLFC in a consecutive series of 322 procedures in 190 unique patients from two US medical centers [30]. BLFC was offered to patients based on the 2018 expert consensus statement for use of blue light cystoscopy in the office setting and included surveillance intervals in addition to the first follow-up three-month cystoscopy [31]. Most of the patients included in the real-world

study had high-risk NMIBC, received prior intravesical BCG (54%) and had recurrent NMIBC (70%). There were 26 (8%) office-based cystoscopies with negative white light findings but positive findings on BLFC and the majority of these patients had high-grade cancer (61.6%), including 8 patients with CIS. Of the patients that had both positive white and blue light findings, 27/83 (33%) had additional lesions only identified by BLFC. Importantly among patients with both positive white and blue light lesions on cystoscopy, biopsy revealed the findings were benign (false positive) in 25% of those who underwent office-based biopsy and 12% of those biopsied in the operating room. The study did not confirm the earlier detection of cancerous lesions by BLFC leads to a clinically meaningful improvement in patient care. As mentioned, unique considerations for BLFC include the patient needing to arrive at least 1 hour early allowing for HAL instillation and increased constraints on clinic staffing and space [30].

Narrow-Band Imaging

Narrow-Band Imaging (NBI) (Olympus®) relies on filtering out red light from white light resulting in green (415 nm) and blue (540 nm) bands that have differential depths of penetration that allow for enhancement of mucosal and submucosal vasculature [32]. Hemoglobin preferentially absorbs these wavelengths and results in dark appearing blood vessels that strongly contrast with the lighter background of normal mucosa thus enhancing the neovascularity of tumors. NBI is available on both flexible and rigid cystoscopes. Unlike fluorescence-based cystoscopy, NBI does not require additional preparation, time, and cost of instilling a fluorophore into the bladder.

Similar to PDD, there are a number of publications evaluating whether NBI improves cancer detection over WLC. Many of these studies were included in a meta-analysis that determined NBI increased detection of cancerous lesions by 9.9% on a per-patient basis and a 19.2% increased rate of detection on a per-lesion basis. The greatest utility of NBI was the increased detection of CIS as there was a 25.1% improvement on a per-patient basis and 31.1% increased detection on a per-lesion basis. The sensitivity and specificity of NBI was 95.8% and 73.6%, respectively compared to 81.6% and 79.2% for white light when analyzed on a per-patient basis (Fig. 2.4). Similar to the findings of studies of PDD, NBI should be

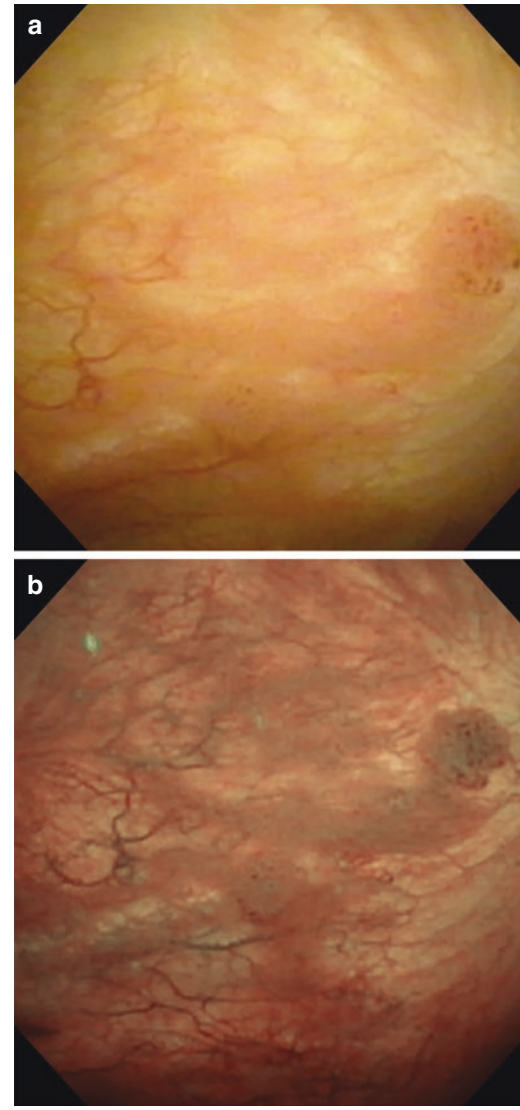

Fig. 2.4 (**a**) White light cystoscopy image identifying multiple papillary bladder tumors. (**b**) Narrow-band imaging improves bladder tumor visualization by enhancing the dark appearing blood vessels of the mucosa and submucosa in contrast to the lighter background of normal mucosa

used in a complementary manner to WLC to maximize the sensitivity of bladder cancer detection.

A network meta-analysis compared different enhanced technologies for bladder cancer detection. The study included randomized controlled trials using NBI, HAL-assisted BLC, and 5-ALA for PDD at the time of TURBT [33]. The analysis determined that NBI reduced tumor recurrence rates when compared to WLC (OR 0.47, 95% CI 0.31–0.72). The authors also concluded that each of the evaluated technologies, NBI and PDD regardless of fluorophore, reduced recurrence rates of bladder cancer when compared to WLC. There were no statistically significant differences when comparing NBI-directed TURBT to either of the PDD-guided approaches (HAL or 5-ALA). Another meta-analysis also reported that NBI-directed TURBT decreased bladder cancer recurrence risk at 3-months, 1-year, and 2-year when compared to white light (RR 0.39, 0.52, and 0.60, respectively, all $p < 0.01$) [34].

Despite the promising studies on the benefit of NBI for increased detection of bladder cancer, the findings of recent randomized clinical trials have reduced the enthusiasm for this technology. The largest of these trials was an international randomized controlled trial of over 1000 patients conducted by the Clinical Research Office of the Endourological Society (CROES) that compared white light and NBI on tumor recurrences in NMIBC. The study concluded that NBI-assisted TURBT did not reduce the cancer recurrence rate at 1 year ($p > 0.05$) when compared to white light TURBT, except in the low-risk group [35]. A similar conclusion from a randomized study that included a smaller number of patients determined no difference in bladder cancer recurrence rates at 1 year although NBI-assisted TURBT identified more cancerous lesions than conventional white light [36]. A third study with a novel study design also concluded there was no difference in recurrence-free survival or per-patient tumor detection when comparing NBI and white light [37]. This study prospectively analyzed the impact of a second-look NBI-cystoscopy or second-look white light cystoscopy after first-look white light cystoscopy in patients with NMIBC in the office setting. Six hundred patients were included in the study, following the first-look WLFC, the monitor was turned off for 10 seconds and all patients were randomized to one of the two diagnostic arms of the trial and second-look cystoscopy was performed with either white light or NBI by the same urologist. The study reported that second-look NBI cystoscopy detected more additional cancerous lesions when compared to second-look cystoscopy with white light ($p = 0.035$). However, it was very uncommon that second-look with NBI identified any tumor after a normal first-look white light cystoscopy (3 patients) as was the case with second-look white light cystoscopy (1 patient) ($p = 0.137$). After a follow-up of 48 months median recurrence-free survival after TURBT was no different in the two groups ($p = 0.373$).

After many years of investigation, the evidence suggests that NBI-cystoscopy detects more cancerous lesions when compared to white light in patients being followed for NMIBC; however, this does not convincingly translate into reduced cancer recurrence rates following NBI-assisted TURBT. The AUA-SUO guideline for NMIBC included a statement about NBI, "in a patient with NMIBC, a clinician may consider use of NBI to increase detection and decrease recurrence (Conditional Recommendation; Evidence Strength: Grade C)" [23].

Storz Professional Image Enhancement System (IMAGE 1 S)

Both PDD and NBI require special equipment that may not be readily available to all urologists and additionally PDD is dependent upon the intravesical administration of a fluorophore. As a response to these limitations, Karl Storz developed an endoscopic imaging platform, the Storz Professional Image Enhancement System, later named the IMAGE 1 S® camera system that utilizes conventional white light endoscopy and creates digitally contrasted images with four-unique software-based visualization modes. The spectra A and spectra B modalities shift the specific color rendering of the recorded visible spectrum on the

imaging system to improve color contrast. The Clara modality enhances local brightness and Chroma modality enhances the sharpness of the image particularly for red colors that often associate with the neovascularity of tumors. In essence, the IMAGE 1 S system incorporates data from a wide region surrounding each image pixel and requires much greater computational load than conventional edge enhancement to create the images. The final product is an endoscopic platform that presents multiple images to the urologist using digital image processing and contrast enhancement to highlight different aspects of the image (vasculature, depth, and illumination) obtained from WLC. A qualitative study that included 73 patients reported that Image 1 S complemented cystoscopy produced higher quality images of bladder tumors when compared to white light cystoscopy alone [38]. The investigators determined that combining the Clara and Chroma modalities were most beneficial as this improved identification of the boundaries of the tumors and identified additional areas of mucosal abnormalities in the images. The findings of the study led to an actively recruiting randomized controlled trial comparing Image 1 S (Clara + Chroma modality) versus conventional white light TURBT on patient outcomes in NMIBC [39].

Optical Coherence Tomography

Optical coherence tomography (OCT) is a high-resolution imaging platform that uses near-infrared light to measure the characteristics of tissue that include properties of texture and elasticity [40]. The current technology uses a 2.7 mm diameter probe that is passed through the cystoscope and allows for real-time examination of various depths of tissue penetration limited to 1–2 mm and yields high-resolution cross-sectional images. The greatest value of the technology may be differentiating invasive from noninvasive tumors at the time of cystoscopy; however, early reports also suggest increased cancer detection and better discrimination of epithelial lesions as cancerous or benign [41–43]. More recent studies have reported that three-dimensional OCT has a high sensitivity and specificity for the detection of CIS when compared to white light and other enhanced technologies including PDD and NBI [44, 45]. Certainly, the studies of OCT are preliminary and require considerable validation but it may have added utility when integrated with currently available platforms of fluorescence cystoscopy as it was reported to improve upon the false positive or unnecessary biopsy rate when compared to fluorescence cystoscopy alone [46]. Prospective clinical trials evaluating clinical efficacy and demonstration of real-world utility are needed if there is a desire to translate this technology to improved patient care.

Confocal Laser Endomicroscopy

Cystoscopy enables visualization of suspicious bladder lesions but lacks the ability to provide real-time histopathologic information. Confocal laser endomicroscopy (CLE) uses fiber-optic cables to transmit 488 nm wavelength laser light to tissues that have been exposed to fluorescent dyes. The technology is a probe-based optical technique that can provide real-time microscopic images of tissue and essentially characterizes cellular architecture. The technology is considered to have the highest resolution of any of the other enhanced diagnostic technologies incorporated into cystoscopy with a resolution of up to 2–5 μm and a depth of 240 μm [40]. As probes for CLE became miniaturized, it was feasible to study its utility during cystoscopy and ureteroscopy [47, 48]. Although very early in its development and its most useful clinical applications yet to be determined, CLE was studied in prospective trials examining accuracy for the diagnosis of urothelial cancer of the bladder and upper urinary tract using histopathology as the reference standard [49]. Investigators of this technology recently reported the results of a validation study for the diagnosis and grading of bladder cancer [50]. Seventy-three patients scheduled for TURBT were included in the study and CLE imaging was performed intra-operatively prior to

en bloc tumor resection and CLE images independently evaluated for tumor grade and likelihood of cancer by three separate observers. Low-grade urothelial cancer was most commonly associated with papillary configuration (100%), distinct cell borders (81%), presence of fibrovascular stalks (79%), cohesiveness of cells (77%), organized cell pattern (76%), and monomorphic cells (67%). However, high-grade urothelial cancer was associated with pleomorphic cells (77%), indistinct cell borders (77%), papillary configuration (67%), and disorganized cell pattern (60%). The study identified a concordance between CLE-based classification and histopathology in 76% and 70% of low-grade and high-grade tumors, respectively. The study also concluded that flat lesions were difficult to classify and greater improvements in the technology needed.

Real-Time Multispectral Imaging

Throughout this chapter, we have emphasized that various imaging modalities can be used in conjunction with WLC to improve detection of bladder cancer. However, each of the adjunct imaging modalities have unique limitations and possibly the most important is each modality is visualized separately and not in parallel with or overlaid with WLC necessitating repetitive switching between technologies during the procedure. Photodynamic diagnosis is dependent upon a substrate of heme metabolism leading to accumulation of protoporphyrin IX (Pp-IX-F) in tumors and emission of red fluorescence upon excitation with blue light. Narrow-band imaging is dependent upon lightspectra of defined wavelengths strongly absorbed by hemoglobin that lead to enhanced vascular contrast (EVC) that helps to identify tumors with increased or abnormal vasculature. Before the publication of a recent proof of principle study, endoscopic systems could not combine multiple imaging modalities such as PDD and NBI in one endoscopic platform [40]. However, a prior report suggested that real-time multispectral imaging (rMSI) allows for separate and simultaneous visualization of multiple spectral components and can extract information not visible in images exclusively reliant on white light [51]. Using the concept of rMSI, a recent study aimed to take advantage of the improved cancer detection properties of multiple imaging modalities and combine them into one platform to allow for multiparametric cystoscopy (MPC) [52].

The general setup for rMSI consists of a camera unit, a light source and a computer with a microcontroller board for both the camera and the light source. The study of Kriegmair et al. adapted rMSI technology for cystoscopy to allow not only simultaneous visualization (white light, PDD, EVC, Pp-IX-F, endogenous autofluorescence) but also combining or overlaying enhanced imaging modalities [52]. A color scientific complementary metal-oxide semiconductor camera was mounted to the cystoscope with a C-mount adapter. A modular LED light source with an optical multiband-pass filter was placed in front of the camera sensor and rMSI achieved by temporal multiplexing of white light, EVC and PDD illumination. A multiparametric image (MP) was obtained in real-time by digital fusion of the EVC and PDD image. Ten patients scheduled for TURBT of known tumor with HAL-assisted BLC were included in the study and 27 malignant lesions identified. At the time of MPC, each malignant lesion was visualized simultaneously by the five imaging modalities (Fig. 2.5). Following the procedure, two independent observers reviewed the recorded images and determined that single imaging modalities did not always raise high suspicion for malignancy when using the Likert-scale for assessment. However, the MP images were more likely to be suspicious for malignancy when compared to single modalities (Fig. 2.5). This study represents the first human application of MPC and not only was feasibility determined but also preliminary data suggest better cancer detection rates than single imaging modalities. The technology combined the individual benefits of each modality in a merged image that compensated for the limitations of the individual modalities.

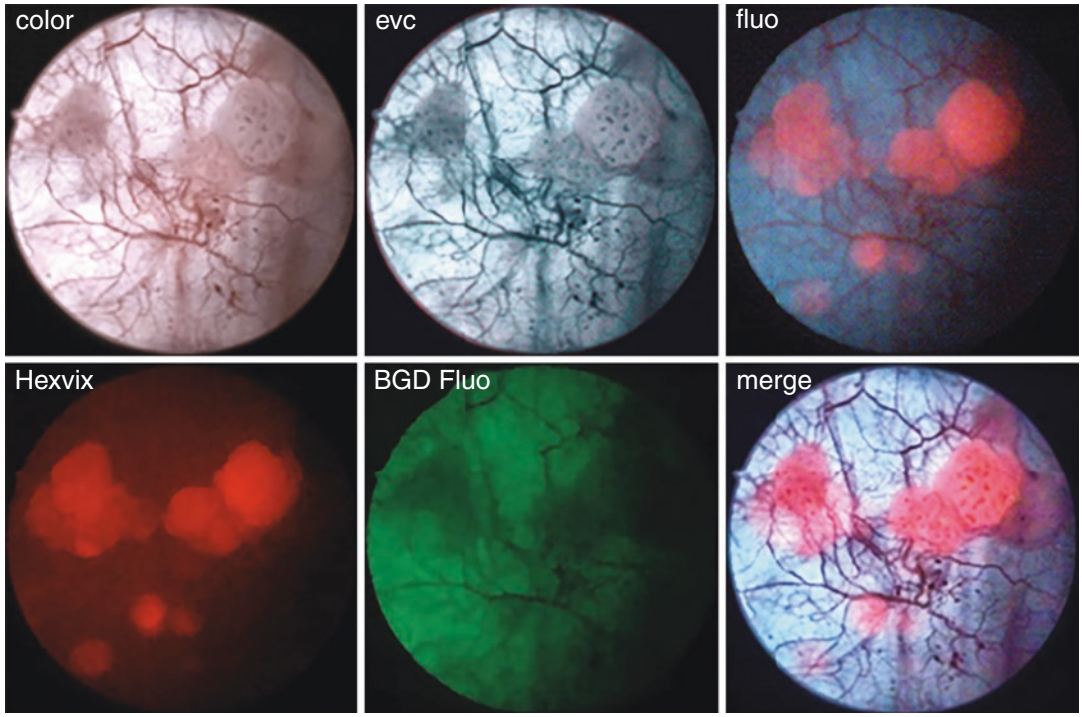

Fig. 2.5 Images obtained from multiparametric cystoscopy of multifocal papillary bladder tumors. Each of the modalities identified the tumors including white light cystoscopy (color), narrow-band imaging- like, enhanced vascular contrast (evc), protoporphyrin IX fluorescence (fluo), and hexaminolevulinate-assisted blue light cystoscopy (Hexvix). The tumors do not autofluoresce (BGD Fluo) and the multiparametric image (merge) overlays the modalities providing a clearer image. (Image kindly provided by C. Bolenz, M. Kriegmair, B. Grychtol, and N. Deliolanis)

Conclusion

Since its inception into clinical care, white light cystoscopy has evolved through a series of technologic innovations allowing for high-resolution images and a high sensitivity for detecting bladder cancer. However, several enhanced technologies applied to cystoscopy have irrefutably determined that white light cystoscopy may miss lesions of CIS and other low- and high-grade flat or subtle papillary tumors. In particular, fluorescence-based PDD and NBI demonstrate considerably higher sensitivity for detecting bladder cancer when compared to white light and when applied to TURBT reduced cancer recurrence rates. Given the growing number of promising or already approved enhanced technologies, the future of cystoscopy may incorporate multiparametric imaging as a means of improving patient care.

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3 Using Urinary Biomarkers in Urothelial Carcinoma of the Bladder and Upper Tracts

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Introduction

Bladder cancer has an estimated incidence of 80,470 new cases and mortality rate of 17,670 in the United States in 2019, and continues to be the fourth most common cancer in men and twelfth most common in women [1]. The initial presenting symptom is painless hematuria in the majority of patients, which should be investigated according to guidelines with imaging and cystoscopy, with or without cytology [2, 3]. While 70–75% of newly diagnosed patients have non-muscle invasive bladder cancer (NMIBC), these patients have around 50% risk of recurrence and up to 20% risk of progression in 5 years [4, 5]. Surveillance and early detection of recurrence in NMIBC are keys to prevent progression, and according to guidelines, routine cystoscopy and urinary cytology are necessary every 3 months in the first year in the surveillance of high-risk disease. Currently, risk-stratification is based on clinical and pathological features, such as tumor size, grade, stage, multifocality, and recurrence status [2, 4, 6] (WHO reference). Bacillus Calmette-Guerain (BCG) instilled intravesically is the treatment of choice for high-risk NMIBC. Despite the use of intravesical BCG, around half of these patients will recur, and the risk of progression remains high [7].

Historically, the most widely used form of cystoscopy is white light cystoscopy (WLC). However, WLC has limitations related to the poor visualization of some bladder tumors, particularly small papillary lesions and carcinoma in-situ (CIS) [8]. In high-risk NMIBC, it is recommended to re-resect the site of tumor within 4–6 weeks from initial transurethral surgery, as residual tumor is present in about 30–60% of cases, even if complete resection is assumed [9, 10]. Attempts to overcome these diagnostic technical limitations are being made with blue light cystoscopy using photoactive porphyrins, as well as narrow-band imaging [11–15]. On the other hand, urothelial malignancies of the upper tract will be missed by cystoscopic evaluation of the bladder alone. To overcome this anatomic barrier, cytology has been used traditionally as the first urinary marker to evaluate the presence of urothelial malignancies. Cytology has moderate sensitivity for high-grade disease but can miss up to 40% of high-grade tumors and most low- grade tumors [16]. The main advantage of urine cytology is a very high specificity and positive predictive value such that patients with a positive cytology are recommended to undergo bladder biopsies and upper tract imaging.

Contemporary investigative tools that urologists have been relying on for diagnosis of bladder cancer (cystoscopy and cytology) remain

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limited unfortunately. Cystoscopy often detects indeterminate findings that result in unnecessary invasive procedure such as bladder biopsy or transurethral resection for benign processes. On the other hand, cytology has not been reliable, particularly with the wide sensitivity and the false positives due to inflammation, urothelial atypia, and radiation-induced or BCG-induced cystitis. Urinary markers have been developed and investigated over several decades with an attempt to overcome these diagnostic limitations in bladder cancer. In this chapter, we review both historical and contemporary urinary biomarkers used in the realm of urothelial carcinoma. We discuss their molecular basis, the tests characteristics such as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and the utility in both initial diagnosis and surveillance following various therapies.

The Rationale for Urinary Markers

Bladder cancer is the most expensive cancer due to the costly diagnostic evaluation in hematuria patients, and expensive treatments and intensive surveillance that includes frequent cystoscopies in patients with NMIBC. Cystoscopy is an expensive, invasive procedure that causes patient discomfort and can be complicated by urinary infection. Furthermore, while adherence to protocols could be necessary in high-risk disease, cystoscopy in low-risk patients may be substituted with a cheaper noninvasive urinary marker with a high NPV. On the other hand, a urinary marker with high PPV could be used to further improve the detection rates of high-risk disease, which can potentially reduce the risk of progression of otherwise missed high-risk NMIBC.

In addition, indeterminate mucosal changes visualized on cystoscopy and atypical or suspicious cytology pose a challenge in management. While many of these are benign nonspecific changes, they often prompt the urologist to pursue a further invasive evaluation such as biopsy or transurethral resection of the lesion in the operating room, adding to the cost, discomfort, and medical risk to the patient. In this realm, a urinary marker with a high sensitivity and NPV could rule out bladder cancer and hence obviate the need for further investigation in the operating room.

Finally, patients with NMIBC who are treated with intravesical BCG require close surveillance because of the considerable risk of recurrence. The consequences of a missed recurrence can be major, with progression to muscle-invasive bladder cancer and potentially extravesical disease. A urinary marker that can accurately predict the risk of recurrence and the prognosis of patients in apparent remission following BCG can be valuable by guiding other subsequent therapy including an early radical cystectomy prior to progression.

Available Urinary Markers

NMP22

A member of the nuclear matrix protein family, NMP22 is abundant in cancerous urothelial cells. It is released in the urine following the apoptosis of malignant cells, resulting in higher concentrations than in benign conditions. The immunoassay to detect NMP22 is available as a qualitative point-of-care kit, and as laboratory-based enzyme-linked immunosorbent assay (ELISA). While the initially reported sensitivity was nearly 70% for low-grade and up to 93% for high-grade tumors, marker performance usually decreases in multicenter validation. In a large multicenter trial evaluating point of care NMP22 (BladderChek) and cytology in 1331 patients with hematuria, the overall sensitivity was 55.7% (95% confidence interval [CI], 44.1–66.7%) with 74% for high-grade or >T2 tumors and 47% for grades 1 or 2 and tumors <T2 [17]. The specificity of the NMP22 assay was 85.7% (95% CI, 83.8–87.6%) compared with 99.2% (95% CI, 98.7–99.7%) for cytology. In a prospective multicenter study of 668 patients with bladder cancer undergoing surveillance, the sensitivity and specificity of BladderChek were 49.5% (51/103; 95% CI, 39.5–59.5%) and 87.3% (493/565; 95% CI, 84.2–89.9%), respectively [18]. There are reports

showing lower sensitivity for smaller tumors which may explain worse performance in the surveillance setting [19]. There are also reports of ways to reduce false-positive results by excluding use in patients with inflammatory or infectious benign conditions [20]. The challenge is that many patients with hematuria who do not have cancer have other benign conditions such as inflammation and that patients with bladder cancer have had manipulation with cystoscopy with or without resection or recent intravesical therapy. Excluding these patients reduces the ability to use this assay broadly. The potential advantages of BladderChek are that it is point-of-care, does not require a lab, and is inexpensive.

BTA TRAK/BTA Stat

Bladder tumor antigen (BTA) tests exist as a qualitative ELISA-based assay (BTA TRAK) and a quantitative point-of-care test (BTA stat). These are designed to detect basement membrane elements released into urine as a result of tumor cell invasion of the underlying stroma [21]. The sensitivity and specificity of these tests in the surveillance setting are relatively modest, ranging from 54–61% and 74–86%, respectively [21]. In addition to the high rates of false-positive results, both BTA tests have failed to prove any association with recurrence-free and progression-free survival [22].

ImmunoCyt/uCyt+

ImmunoCyt/Ucyt+ (ImmunoCyt/Ucyt+ test, DiagnoCure, Saint-Foy, Canada) is an immunofluorescence assay applied to cytology specimens, using monoclonal antibodies against one form of the carcinoembryonic antigen and two other mucins that accumulate in urine following exfoliation of bladder cancer cells [23]. Similar to NMP22, ImmunoCyt has an improved sensitivity over cytology for low-grade urothelial tumors, and is higher with increased tumor grade, ranging from 79% in low-grade to 93% in high-grade [24, 25]. Sensitivity and NPV rates of ImmunoCyt vary between 62–85% and 74–93%, respectively [21]. Reported specificity was between 69 and 79%, which was lower than that for cytology, with high false- positive rates [26, 27]. ImmunoCyt has not gained popularity because of the need for special laboratory equipment with experienced technicians to analyze the test results.

UroVysion FISH

UroVysion (Abbott Laboratories, Abbott Park, Illinois) is a multitarget fluorescence in-situ hybridization (FISH) assay performed in specialized laboratories, designed to detect malignant urothelial cells in urine by identifying chromosomal aneuploidy in chromosomes 3, 7, and 17, or loss of the 9p21 locus in the p16 tumor suppressor gene [28]. It is FDA-approved for both detection and surveillance of bladder cancer. In the detection setting, UroVysion had a low sensitivity of 41% for low-grade cancers [29], while in a meta-analysis including 14 studies involving 2477 FISH tests, the pooled sensitivity and specificity of all studies were 72% (69–75%) and 83% (82–85%), respectively [30].

CxBladder

CxBladder test is a quantitative reverse transcription polymerase chain reaction (PCR) that measures the mRNA expression of five genes (IGFBP5, HOXA13, MDK, CDK1, CXCR2) in the urine to generate a composite CxBladder test score. It is designed in the form of three tests, a "CxBladder Triage" to rule out bladder cancer in low-risk hematuria patients, a "CxBladder Detect" to identify patients with probable bladder cancer diagnosis, and a "CxBladder Monitor" for the surveillance of bladder cancer patients after treatment. The initial study for detecting bladder cancer in hematuria patients revealed an overall sensitivity of 82%, reaching 97% in high-grade, and 100% in T1 tumors [31]. The surveillance test derived from the combination of the urine test with tumor-related clinical information had a

sensitivity of 93% (97% in high-grade and 85% in low-grade) and an NPV of 97% [32, 33].

Xpert BC Monitor

Another mRNA-based urine test, Xpert Bladder Cancer Monitor measures five mRNA targets (ABL1, CRH, IGF2, UPK1B, and ANXA10) using real-time PCR. This test is designed to detect NMIBC recurrences based on the overexpression of the aforementioned mRNAs. In the initial report, Xpert BC Monitor demonstrated an overall sensitivity and an NPV of 84% (100% for high-grade tumors) and 93%, respectively, compared to 33% and 76% for cytology [34]. Specificities were comparable at 91% and 94%, respectively. The prospective validation of 239 patients, however, reported an overall sensitivity and specificity of 74% and 80%, respectively, and a sensitivity and NPV in high-grade disease of 83% and 98%, respectively [35].

DNA Methylation Markers

AssureMDX test is a urine assay for DNA methylation-mutation of three genes (OTX1, ONECUT2, and TWIST1) along with mutations in three other genes (FGFR3, TERT, and HRAS) combined with clinical variables like age [36]. In this study of 154 patients, AssureMDX test was shown accurate with a sensitivity of 97%, specificity of 83%, an area under the curve of 0.93, and NPV of 99% in detecting bladder cancer, assuming a generous incidence of bladder cancer of 5–10%.

Another DNA methylation test is the *UroMark*, which consists of a biomarker panel of 150CpG loci, also designed for the detection of primary bladder cancer. This test has shown encouraging results with 98% sensitivity, 97% specificity, and 97% NPV in a proof of concept and validation cohorts of 116 and 274 patients, respectively [37].

Nucleix (EpiCheck) is a third DNA-methylation test involving the GDF15/TMEFF2/VIM promoter among several other genes in different combinations based on the clinical scenario. Recently, this marker has been prospectively studied in 440 patients (357 analyzable urine samples) undergoing surveillance for NMIBC in five institutions, and the test had a specificity of 88% (95% CI 84–91), an NPV of 94.4% (95% CI 91–97) for all cancers, and 99.3% for high-grade cancer. When added to clinical variables, the predictive ability of the test improved by 16% and 22% for all cancers and high-grade cancers, respectively [38].

Furthermore, the DNA-methylation combination tested by EpiCheck was found to have some use in upper tract urothelial carcinoma (UTUC). In a study of 57 patients from a single institution in Portugal, the sensitivity was 91% and specificity 100%, compared to a sensitivity of 26% for cytology in a subset of 19 patients. Interestingly, low VIM methylation levels carried an 18-fold increased risk of cancer-related death ($p < 0.001$) in the pT2–4 group [39]. In a more recent validation cohort of 473 patients from China, including 217 patients with urothelial carcinoma of the bladder and UTUC tested with a broader variety of genes, sensitivity was 82% for both bladder and upper tract tumors, while specificity was disappointingly low at 53% and 68%, respectively. Only in cases of gross hematuria, when combined with cytology, sensitivity and specificity rose to 91% and 92%, respectively [40].

When to Use Urinary Markers

Practical Considerations

When a clinician orders a test, there is an implicit understanding that there is a goal to use this test result to improve patient care by providing useful clinical information that will change an understanding of a condition or impact management. A clinician should know how to interpret and act upon a test if it is positive or negative. The PPV of a test determines how likely a condition is present when the test is positive. Similarly, the NPV is the likelihood that a condition is absent when the test is negative. Both of these results are impacted by the prevalence of disease. For

example, if you order chest imaging on a patient with known metastatic disease and find a nodule, then it is much more likely to be cancer than the same imaging in a patient who has no risk factors for cancer. A positive urine marker in a patient with a history of bladder cancer is much more likely to have a true-positive result than a patient with microhematuria even though the sensitivity and specificity of the assay are identical in both settings.

It is vital for a test to be useful for it to impact clinical care. Furthermore, a clinician needs to know what they will do with a test result before they order the test. If the answer to the questions "what will I do if test is positive?" and "what will I do if test is negative?" is unknown then a test should not be used because it will only add cost, confusion, and anxiety.

What to Do with a Positive Urine Marker?

As noted above, the PPV is the critical characteristic that determines the action that is merited based on a positive test. This is impacted by prevalence of disease, so a clinician needs to consider the clinical scenario where markers may add value. Cytology is commonly used and clinicians know that if there is a positive cytology they should evaluate the upper tracks and perform biopsies of the bladder and prostatic urethra. This is supported by the high PPV of cytology due to rare false-positive results. On the other hand, the PPV of most urine markers is 10–20% [17, 32], which makes them less actionable in general settings. The reason most markers have a low PPV is due to issues related to specificity. The high rate of positive tests when no tumor is seen cystoscopically is a challenge and most markers have a specificity that is less than 90% and some less than 80%. To add to the confusion, it is not always clear that every positive test with normal cystoscopy is a "false" positive. It is possible the marker is more sensitive than cystoscopy and it is known that white light cystoscopy is not as sensitivity as enhanced cystoscopy [41]. The question, is what a clinician will do with test result? At this time, the PPV is too low to justify a biopsy in the operating room due to risk of anesthesia and the low yield. One can consider a repeat cystoscopy sooner but how soon? In a high-risk patient, cystoscopy is performed every 3 months in most cases. Should it be done sooner? A multiinstitutional, retrospective study of patients with a history of urothelial carcinoma of the bladder identified 664 patients with a FISH assay and compared outcomes of FISH positive to FISH negative tests in patients with initial normal cystoscopy to test the concept of "anticipatory positive" [42]. In patients who were FISH positive, mean time to recurrence was 12.6 months, compared to 17.9 months if FISH was negative ($p = 0.03$). While, this suggests FISH positivity predicts a higher rate of recurrence, it does not demonstrate that there is need for an immediate action based on the FISH result. One other consideration with a positive urine marker is to perform enhanced cystoscopy in the office since flexible blue light cystoscopy is now FDA approved. This will avoid unnecessary anesthesia but does add cost and inconvenience so needs to be assessed in a prospective study.

If use of a urine marker is not justified for every patient in detection or surveillance, then what about in specific circumstances? There are settings where the prevalence of cancer is higher than baseline. This improves the PPV of urine markers and may justify their use. Examples of this are in patients with atypical cytology and equivocal cystoscopy. There are two prospective studies in patients with atypical cytology or equivocal cystoscopy evaluating the UroVysion FISH assay [43, 44]. In the first study including 120 patients with atypical cytology, the PPV of UroVysion in patients with a history of cancer was respectively 100%, 62.5%, and 43% if cystoscopy was positive, equivocal, or negative [43]. In patients with no prior history of cancer, the PPV was respectively 100%, 50%, and 50% if cystoscopy was positive, equivocal, or negative. In the prospective validation trial of these results, 216 patients were equally distributed between the detection and surveillance groups [44]. The PPV of UroVysion in both groups with equivocal cystoscopy was 100%, and there were no

false-negative results. In patients with negative cystoscopy, the UroVysion test detected all cancers but the PPV was 10% and 29% in patients with and without a history of cancer, respectively. A separate study evaluated the ImmunoCyt test in patients with atypical cytology and found that a reflex ImmunoCyt had a sensitivity of 73% and an NPV of nearly 80% in both low-grade and high-grade tumors [45]. One can conclude that these markers are actionable in the setting of an atypical cytology or equivocal cystoscopy. However, it really depends on the cystoscopic findings. If one sees a tumor then the marker does not add to the decision, since cancer is nearly always found. If there is an equivocal lesion (such as an erythematous patch) then the PPV is high and one should strongly consider a biopsy. If cystoscopy is negative, then upper track imaging should be considered if not recently performed and then a decision needs to be made whether to pursue a biopsy (ideally with enhanced cystoscopy) or repeat cystoscopy at a closer time interval. The evidence from these studies was strong enough to support consideration of urine markers like UroVysion and ImmunoCyt for evaluation of equivocal cytology in the AUA/SUO guidelines [2].

How to Use a Negative Marker?

This question is framed differently than "what to do about a positive marker?" because it is fairly implicit that a negative marker usually is not going to result in an action but rather a reassurance. The real question that most clinicians and patients have is whether a negative marker is good enough to avoid cystoscopy. At this time, according to guidelines, the answer to this question is "no". The concern is that the sensitivity of markers is too low to allow for patients to avoid cystoscopy. While most markers have a sensitivity for high-grade disease in the 80–90% range, missing 10–20% of high-grade tumors is deemed unacceptable [21, 27, 46]. There are potential roles for markers in different settings that need to be evaluated prospectively to assess for safety and efficacy.

In the surveillance setting, patients with high-risk disease get cystoscopy every 3 months due to high risk of recurrence and progression. Use of a marker to avoid cystoscopy in this setting is unnecessarily risky. Low-risk patients get infrequent cystoscopy and there is not much room to insert a marker into the surveillance schedule, since cystoscopy is already spaced out over a long interval. The potential setting for inserting a marker is in patients with low-grade but recurrent disease. The guidelines are less clear on how frequently a cystoscopy should be performed and missing a small low-grade tumor has little consequence to the patient in terms of progression, since low-grade cancers rarely progress or invade [2]. Most markers have a high NPV and some markers like CxBladder Monitor were designed specifically to maximize NPV so a negative marker very likely is associated with absence of disease. Prospective studies are needed to prove the veracity of this concept.

A second setting which is more controversial but perhaps more impactful is in evaluation of hematuria. The current AUA hematuria guidelines recommend evaluation of patients with three or more red blood cells per high-power field without known benign cause [47], but there are multiple studies demonstrating that these recommendations are frequently ignored [48–50]. A urine marker to improve risk stratification of patients into low and high risk could enrich patients getting referred for evaluation and avoid cystoscopy in the very low-risk patients with a negative marker, such as women less than 50 years of age with no carcinogen exposure. Incorporating a urine marker with clinical factors for detection has been evaluated and does improve prediction of cancer presence. For example, a cohort of 1272 hematuria patients who had NMP22 BladderChek testing was used to develop a nomogram to predict presence of bladder cancer [51]. Subsequently, a multicenter prospective study including 381 patients with hematuria was performed to validate this nomogram and found a predictive accuracy of the bladder cancer detection nomogram was 80.2% [52]. Prospective randomized trials are needed to

confirm the safety and efficacy of marker-based approaches for evaluation of hematuria.

Can a Marker Predict Outcomes?

A potential role for urine markers is in predicting outcomes and response to therapy. The gold standard initial treatment for high-risk NMIBC is BCG. However, not only do half of these patients recur, but also patients with recurrences tend to have a worse outcome. The ability to predict recurrences and risk of progression in BCG-treated patients has been examined in the past two decades. Several retrospective studies and one prospective single-institution trial have examined this hypothesis. In a small study of 37 patients of whom 25 patients had recurrences, the hazard ratios for recurrence and progression to muscle-invasive disease were 4.6 and 9.4, respectively [53]. In another study of 65 patients with high-risk NMIBC, a positive post-BCG UroVysion was associated with 2.7-fold increase in risk of recurrence, while the increased risk of progression was not statistically significant [54]. Kamat and colleagues, in a prospective single-institution trial, examined 126 patients with NMIBC using UroVysion FISH at baseline prior to BCG therapy, at 6 weeks from initiation of treatment, at 3 months, and 6 months. A positive FISH test results at any time-point correlated with higher hazard of recurrence (3–5 times) and a higher hazard of progression (5–13 times) [55]. While these results are intriguing, they still need validation through a multi-institutional prospective trial, the results of which have not yet been published. It is worth mentioning that in this clinical scenario, the PPV of UroVysion has been shown consistently high; however, it is challenging to interpret the relatively common false-negative results in order to change management on a per-patient basis. Whether the FISH tested negative prior to recurrence or missed detecting the tumor, or whether the recurrent tumor is less aggressive than the positive-FISH counterpart, is speculative, and has been described as "molecular BCG failure" [56]. There may be a role for Urovysion to improve stratification into clinical trials. The use for changing management for individual patients may be more challenging.

Urinary Markers in Upper Tract Urothelial Carcinoma

The evaluation and management of urothelial carcinoma of the bladder and UTUC share several common concepts due to the common histologic origin of the tumors. The molecular biology of both cancers is broadly similar, although some are differences in genetic (microsatellite instability) and epigenetic (hypermethylation) exist between some UTUC and bladder cancer [57]. The performance of urinary markers in isolated UTUC has not been studied widely. In a study of 326 patients examining the performance characteristics of cytology in patients who underwent a nephroureterectomy or segmental ureterectomy for UTUC revealing 47% with muscle-invasive tumor and 67% with high-grade disease, urinary cytology had a sensitivity and PPV of 56% and 54% in high-grade disease, and 62% and 44% in muscle-invasive disease, respectively. After inclusion of atypical cytology, sensitivity improved to 74% and 77% and PPV was 63% and 45% for the respective categories. When selective ureteral cytology was examined, PPV was higher than 85% [58]. In another study of 82 patients suspected to have an abnormality of the UTUC, washing from upper tracts for cytology and FISH were performed along with further imaging or endoscopic procedure. In this cohort, cytology had sensitivity and specificity of 52.6% and 91.4%, respectively while FISH had sensitivity and specificity of 84.2% and 91.1%, respectively. The combination of both allowed the identification of 19 tumors with sensitivity of 100% and specificity of 83.6% [59]. Furthermore, a recent study examined the performance of several markers such as cytology, FISH, NMP22, and immunocytology in 758 urine samples collected from the bladder (n = 373) or selectively from upper tracts (n = 385), where sensitivities were 74.6, 79, 100, and 100%, while specificities were 66.6, 50.7, 5.9, and 66.7%, respectively for upper tracts urine samples. In bladder-derived

samples, sensitivities were 59.3, 52.9, 62.5, and 50% whereas specificities were 82.9, 85.0, 31.3, and 69.8% [60]. While the urine marker tests demonstrated better sensitivities for urine collected from the upper tracts, specificities were lower. In light of the few studies performed and the inconsistent performance characteristics with a tendency for poorer prediction in UTUC compared to bladder, there is no clear utility of urinary markers in the realm of UTUC.

The Guidelines

Despite many years of research to identify clinically useful urinary biomarkers in the diagnosis and surveillance of bladder cancer, guidelines require a high level of evidence to recommend utilization. At this time, the currently available tests are insufficiently accurate to replace cystoscopy. In fact, the American Urological Association/Society of Urologic Oncology guidelines strongly recommend against using urinary biomarkers in place of cystoscopy in the surveillance of NMIBC (Evidence Strength: Grade B), including in patients with low-risk cancer (Expert Opinion), while they allow for the use of UroVysion FISH in the response assessment to intravesical BCG, and allow the use of UroVysion FISH and ImmunoCyt/Cyt+ in cases of equivocal cytology (Expert Opinion) [2]. The European Association of Urology guidelines state that none of the urinary molecular tests are accepted for diagnosis or follow-up of bladder cancer [3].

The Optimal Trials for Use of Urinary Biomarkers

In order to change practice and guidelines, appropriate trials are needed to generate the evidence to justify utilization of markers. Urinary biomarkers have failed to become part of routine clinical practice due to low specificity, high cost, and practical challenges of performing the tests. The potential areas for use of urinary biomarkers are as a rule-out test in patients with hematuria, as an adjunct to cystoscopy to better diagnose a patient with a positive assay, in surveillance following therapy, and in assessing the risk of recurrence or progression following initial response to intravesical treatment, namely BCG, in order to offer a second-line therapy or a radical surgery.

The attempt to identify the perfect urinary biomarker has faced many barriers. An alternative approach to answering such questions and to designing clinical trials should be undertaken.

Urinary biomarkers should be designed, studied, and used according to the characteristics that serve the particular indication. The design of studies to demonstrate a clinical benefit is necessary and a study has been published which outlines potential study designs [61]. Biomarkers with high NPV are ideal in scenarios in which identifying a tumor is unlikely, such as diagnostic cystoscopy for asymptomatic microhematuria or surveillance of low-risk patients. As such, a biomarker with an NPV approaching 100% can obviate the need for cystoscopy in this setting, regardless of the reduced specificity [33]. In such a case, a low-risk patient with a positive test would represent an outlier yet would not be missed, while high-risk patients with positive test will have their cystoscopies expedited [61]. In the surveillance setting, a high sensitivity is desired in order to identify recurrences; however, an acceptable specificity is also needed to allow the biomarker positive result to add to the decision-making. Trials that mandate biopsies are needed, similarly to the blue light cystoscopy studies [11, 12, 15], with enough power to detect a 10% improvement in sensitivity, or alternatively be powered to detect the significant improvement in quality of life and costs from avoiding cystoscopies after the second year of surveillance of intermediate-risk tumors [61]. Conversely, relying on urinary biomarkers to substitute cystoscopy in high-risk disease, particularly in patients at high-risk to fail BCG, might be too ambitious. A more focused approach would integrate urinary biomarker tests in the clinical model, which includes enhanced cystoscopy whenever needed to achieve the best available outcome for patients including a clinical trial, if optimal treatment is not obvious.

Conclusion

The current role of urinary biomarkers is limited because of their test characteristics and the study designs. Their use at this point is specialized and best thought of as a component of the overall clinical picture that only occasionally affects the decision making. Prospective trials that mandate biopsies are needed to demonstrate the benefit and long-term oncological safety of relying on urinary biomarkers in lieu of cystoscopy for low-grade disease. Similarly, prospective trials could demonstrate that markers have a role to play as an additional tool to cystoscopy and clinical algorithm for intermediate- and high-grade NMIBC. Until then, searching for the ideal marker that suits all scenarios will probably face similar recurrent barriers.

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Pathology

4

Eva M. Compérat and Hikmat Al-Ahmadie

Introduction

The urinary tract from the renal pelvis to the proximal portion of the urethra is lined by a multilayered epithelial lining called *urothelium* (formerly referred to as transitional epithelium). The thickness of the urothelium varies depending on the extent of bladder distention and can therefore range from 4 to 7 cells thick. A number of conditions can alter the thickness and the shape of the urothelium such as inflammatory and reactive conditions and may make the histologic evaluation of bladder tissue more challenging.

Approximately 98% of malignant tumors arising in the urinary bladder are of epithelial (urothelial) origin, of which the overwhelming majority, approximately 90%, is "usual" urothelial carcinoma (formerly referred to as transitional cell carcinoma). Most urothelial carcinomas (UCs) at initial diagnosis are papillary and superficial and in approximately 70% of cases, multiple recurrences following local resection without tumor progression will develop. Pathologic features that have been reported associated with recurrence and progression include the depth of invasion, if any at presentation, multifocality, a history of prior urothelial tumors, tumor size, and grade [1–3].

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, loss of nuclear polarity, loss of cohesion, and frequent mitotic activity, that may be atypical and extends to the upper portion of the urothelium. Loss of cellular cohesion contributes to the higher rate of detecting these high-grade lesions on urine cytologic examination compared to other papillary neoplasms. CIS is often relatively straightforward to diagnose, although a number of morphologic variants may be challenging due to their rarity [4].

Papillary Neoplasms

Papillary (exophytic) neoplasms of the bladder, based on their cellularity and degree of atypia, may be either benign (urothelial papilloma) or malignant (papillary urothelial neoplasms of low-malignant potential - PUNLMP, low-grade

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papillary urothelial carcinoma - LGPUC, and high-grade papillary urothelial carcinoma - HGPUC) [5]. Generally, the highest grade component of the papillary lesion is assigned to the neoplasm with the exception that if the high-grade component is minimal (<5%), an overall low-grade can be assigned with a note referring to the presence of a focal high-grade morphology.

Urothelial Papilloma

Urothelial papilloma is a rare, benign condition typically occurring as a small, isolated growth seen primarily (but not exclusively) in younger patients. Morphologically, it is a discrete, exophytic papillary growth with a central fibrovascular core lined by urothelium of normal thickness and cytology with prominent umbrella cells [5, 6]. Inverted urothelial papillomas are similarly rare and benign neoplasms, differing only in that the epithelial cords are endophytic and consequently more closely packed. Both exophytic and inverted papillomas generally follow a benign course and have recently been reported to harbor activating RAS pathway alterations (primarily activating *KRAS* and *HRAS* mutations) and lack the more common genomic features of urothelial carcinoma [7].

Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

PUNLMP is a papillary urothelial neoplasm with an orderly papillary proliferation of urothelial cells with minimal architectural abnormalities and minimal nuclear atypia. Generally, the papillae are lined by thickened urothelium [5]. When strictly defined, PUNLMP does not progress to invasive disease but recurrence is common [8, 9].

Low-Grade Papillary Urothelial Carcinoma (LGPUC)

LGPUC is characterized by an overall orderly appearance but have variability in architecture or cytologic features such as variability in nuclear polarity, nuclear size, shape, and chromatin texture. Mitotic figures may be frequently identified but are generally not atypical and are limited to the lower half of the neoplastic urothelium [5]. The majority of these lesions will recur, but progression is not common (ranging from 2.4% to 8%) [8, 9].

High-Grade Papillary Urothelial Carcinoma (HGPUC)

HGPUC is characterized by disorderly appearance due to marked architectural and cytologic abnormalities typically in the form of nuclear pleomorphism, clumped chromatin, increased mitosis, including atypical forms, and apoptosis [5]. They are commonly associated with invasive disease at the time of initial presentation. The adjacent mucosa may show evidence of CIS, and in some cases, prominent cellular discohesion and denudation may be present. Tumor recurrence occurs in the majority of cases and disease progression may occur in up to a third of cases [10, 11].

Invasive Urothelial Carcinoma

The histopathological features of invasive UC can be variable, except when a specific variant histology is present (see more details about variant histology later in the chapter). Most invasive UC show cohesive irregular nests or solid sheets of cells with moderate to abundant cytoplasm. The nuclei are generally large hyperchromatic and pleomorphic commonly associated with irregular nuclear contours and occasionally prominent nucleoli. Mitotic figures are generally readily identifiable. Changes in underlying stroma (of the lamina propria and beyond) can aid in assessing the presence of invasion. Such changes include retraction, desmoplastic reaction, fibrosis, or inflammation. Once invasion is established, assessing the depth and extent of invasion becomes very important. A very important finding in this regard is the presence of invasion into the detrusor muscle of the bladder (muscularis propria) which would in general

determine if the patient should be offered conservative/localized or more radical surgical treatment. The terminology applied in this setting, such as "muscle invasion" without further qualification may be misleading as it does not distinguish between invasions of the muscularis mucosae (a component of the lamina propria) or the muscularis propria. Also, the term "superficial bladder cancer" is not precise and does not reflect a uniform disease state as it refers to biologically different lesions in noninvasive flat (in situ) or papillary (low or high grade) urothelial carcinoma and carcinoma with lamina propria invasion. Therefore, invasion into the muscularis propria should be reserved to when tumor infiltrates thick and organized smooth muscle bundles, which should be distinguished from the generally thin, loose, wispy, and sometimes branching muscle fibers of the muscularis mucosae.

There are useful morphologic criteria that can be applied to determine invasion of lamina propria invasion, which include the presence of: (1) urothelial nests, clusters, or single cells within the lamina propria, (2) prominent retraction artifact, (3) abundant eosinophilic cytoplasm of the infiltrating tumor, and (4) the presence of desmoplastic or inflammatory stromal response to the tumor.

When tumors invade the lamina propria (pT1), it is recommended to provide details about the extent of invasive disease. A number of methods have been studied and attempts to subclassify pT1 tumors based on their depth of invasion have been successful only in some cases and provided predictive or prognostic value for disease progression. This includes measuring the depth or width of the invasive disease, or whether invasion of the muscularis mucosae is present [12–14].

Lymphovascular invasion (LVI) is an important histological finding that should be reported when present. It is defined by the presence of tumor within endothelium-lined spaces. Numerous studies have documented the clinical importance of LVI as an important prognostic marker of upstaging, lymph node involvement, recurrence, and decreased overall survival, underscoring the importance of identifying and reporting such finding [15–18].

Pathologic Features of Invasive Urothelial Carcinomas (Including Divergent Differentiation)

The microscopic features of invasive UC are variable and nonspecific, consisting of cohesive nests of cells with moderate to abundant cytoplasm and large hyperchromatic nuclei, nuclear pleomorphism, irregular nuclear contours, and occasionally prominent nucleoli. Urothelial carcinomas, however, may show divergent differentiation (Table 4.1), particularly high-grade tumors, can be seen in approximately one-third of cystectomy specimens, but less frequently in transurethral resection specimens (approximately 7%). Although divergent differentiation/variant histology is commonly associated with locally advance disease, it can be identified in a subset of lamina propria-invasive tumors which may impact treatment selection and require a more radical surgical approach [19]. It is recommended to report variant histology anytime it is identified regardless of specimen type (biopsy, TUR, cystectomy) or tumor stage (NMIBC or MIBC) [20] [20].

The most frequently encountered variant histology is invasive UC with divergent differentiation, most commonly in the form of *squamous* and *glandular differentiation.* **Squamous differentiation (SqD)** is the most common variant histology identified in UC occurring in up to 40% of cases [21, 22]. *Glandular differentiation* is less common ranging from 8% to 18% [21, 23–25] and morphologically includes areas that

Table 4.1 WHO classification of tumors of the urothelial tract

Invasive urothelial tumors
Infiltrating urothelial carcinoma (with divergent differentiation)
Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid/signet ring cell/diffuse
Sarcomatoid
Giant cell
Poorly differentiated
Lipid-rich
Clear-cell

Adopted with modification from reference [38]

resemble adenocarcinomas of other organs such as enteric/colonic, mucinous, or a variety of mixed types.

Nested (including large nested), small tubular, and microcystic variants have been grouped under the heading of deceptively bland carcinomas due to their appearance and low-grade features, which can sometimes be difficult to distinguish from benign entities especially when examining superficial biopsy samples where frank invasion may not be easy to establish. It is debatable whether to grade these variants knowing that they tend to present at an advanced stage despite their deceptively bland histopathologic features. These tumors generally consist of well-demarcated medium-sized to large nests closely resembling von Brunn nests but they typically infiltrate the *lamina propria* or deeper within the bladder wall [26–29]. Mitoses are generally rare, and the nuclei show minimal or no atypia particularly in the superficial component of the tumor, but may display more atypia in the deeper and more invasive part of the tumor.

Lymphoepithelioma-like carcinoma is another variant that is sometimes difficult to recognize due to the presence of a dense immune cell infiltrate surrounding and infiltrating nests of, or single, tumor cells. It is important to recognize this variant as it may be mistaken for lymphoma and when present in pure form (i.e., not associated with classic urothelial carcinoma), may follow a less-aggressive clinical course [30, 31].

Micropapillary UC (MPUC) is a rare variant whose diagnosis requires the application of strict morphologic criteria. The tumor is characterized by the presence of small and tight tumor clusters lacking true fibrovascular cores and located within clear "lacunar" spaces. This arrangement is likely due to reverse cellular orientation or polarization and lack of cohesion between the tumor and the adjacent stroma [21, 32, 33]. These tumors have strong propensity for lymphovascular invasion [34]. Despite the increasing recognition of MPUC, there is generally lack of good interobserver agreement, particularly when strict diagnostic criteria are not applied [35]. This has significant clinical implication particularly that some clinicians advise early cystectomy for patients with MPUC even in the absence of invasion into the muscularis propria [36, 37].

Plasmacytoid UC is a rare and aggressive variant that exhibits a diffuse and infiltrating pattern of discohesive, individual, or small clusters of cells, generally with minimal stromal reaction. Tumor cells contain eccentrically located nuclei resembling plasma cells and in the vast majority of cases, tumor cells contain intracytoplasmic vacuoles that give the appearance of signet ring cells [39–41]. Of all the variants of UC, PUC is most likely to be encountered in its pure form, but can occasionally be seen in association with usual UC or other variants [38]. Clinically, PUC is characterized by advanced stage at presentation, high mortality rate, high propensity for relapse, and frequent peritoneal carcinomatosis despite sometimes the apparent initial response to chemotherapy [39–43]. Recent analysis by next-generation sequencing identified the presence of *CDH1* truncating mutations, and less frequently CDH1 promoter hypermethylation, as the defining molecular feature of PUC [39]. Truncating somatic *CDH1* mutations were identified in 84% of PUC and were specific to this histologic variant.

The sarcomatoid variant of UC, formerly known as carcinosarcoma, is rare and generally presents at advanced stage. Despite morphological similarities with sarcomas, molecular analyses have shown a common clonal origin for the carcinomatous and sarcomatous components, suggesting that these spindle cell areas strictly derive from the underlying epithelial malignancy. Giant cell, undifferentiated, clear cell, and lipid-rich variants are exceedingly rare and have poor outcome [38]. Tumors with pure non-urothelial features include squamous cell carcinoma and adenocarcinoma, in which no urothelial component (invasive of in-situ) should be recognized. Primary small cell carcinoma of the bladder is an uncommon neoplasm and resembles small cell carcinoma of any other organ. Neuroendocrine immunohistochemical markers, such as synaptophysin and chromogranin, may aid in the diagnosis if needed. These tumors seem to correspond to the neuronal tumors described recently in the molecular

classification and display frequently loss of wild-type *TP53* and *RB* [44, 45].

En Bloc Resection

The role of transurethral resection of the bladder tumors (TURBT) is to remove the visible tumor (therapeutic) and provide tissue to establish diagnosis and stage (diagnostic). It is crucial for diagnostic histopathologic interpretation that there be minimal to no artefacts. One of the major criticisms of TURBT is that when cutting the tumor, a dissemination of the tumor material is possible. Instead of resecting with an electrical wire-loop, the en bloc resection (EBR) has been suggested. This technique allows to resect the entire tumor including the detrusor muscle, limits tumor scattering, and displays no cautery artefacts. EBR is supposed to improve the resection quality, lowering perioperative complication rates, and decreasing recurrence rates and might even lower the frequency of second resections [46]. This technique is especially useful in case of smaller tumors <1 cm, as it has been suggested by the NMIBC panel of the EAU [47]. Several recent studies demonstrated that EBR is a safe technique associated with high rates of recurrence-free survival after 2 years (85%) [48]. In many of the more recent publications, detrusor muscle was found in 100% of the specimens, which allows for correct staging [49]. Nevertheless, ERB cannot be performed for every bladder cancer. Not all patients are suitable for ERB, as some might harbor big tumors (>3 cm), tumors in locations that are difficult to reach or resect (anterior wall, bladder neck, etc.), or tumors which have an endophytic and infiltrating growth [46, 50].

Upper Urinary Tract Biopsies

Confirming the diagnosis of an upper tract tumor can be readily achieved by ureteroscopic biopsy of the ureter or renal pelvis and can be complemented by urine cytology from upper tract in select cases [51]. Contrary to the bladder, ureteroscopic biopsy can be more difficult to obtain, and the material may be sparse, superficial, and with crush or thermal artefact. Although interpretation of the small amounts of tissue may be challenging to pathologists, evaluation of ureteroscopic biopsies can provide accurate assessment of grade and stage in the majority of cases, especially by combining biopsy and cytology material [51, 52]. As biopsy techniques continue to evolve, the quality and quantity of biopsy material obtained ureteroscopically continue to improve as a result, as has been shown in a number of recent studies comparing standard versus newer biopsy forceps and basket devices [53, 54]. The challenge that remains, however, is how representative these small ureteroscopic biopsies are of the entire upper tract tumor especially when the tumor is large and may be heterogeneous. An alternative to ureteroscopic biopsy may be a CT-guided percutaneous approach to sampling upper tract tumors, which has been shown to be safe and provided high diagnostic yield and concordance [55].

Pathology Report

Several items need to be mentioned in a pathology report. The International Collaboration on Cancer Reporting (ICCR) produces common, internationally validated, and evidence-based pathology datasets for cancer reporting with the aim to encourage uniform pathology reporting standard across the world and utilize these reports as a guide to improve cancer patient outcomes and management worldwide [20]. Not only does it ensures that the same histological elements are reported, it also allows for more accurate comparison of different studies conducted in different institutions or countries. The American Urological Association (AUA) and Society of Urologic Oncology (SUO) published guidelines that provide risk stratification, and clinical framework for the management of nonmuscle-invasive and muscle-invasive urothelial bladder cancer [56, 57]. Similar guidelines are also provided by the European Association of Urology (EAU) [58, 59]. However, for standardized reports to provide meaningful information, clear and reproducible

histological criteria defining different elements should be strictly followed. The World Health Organization (WHO) classification provides detailed description of different entities and histological elements and is regarded as a very useful guide [22]. Elements to be included in pathology report can be required or recommended. Required elements are those which are prognostically important and on which clinical management is based. These elements are mandatory reporting items that should be included in every pathology report. In comparison, recommended elements are clinically important and reporting them is considered to be good practice but are not yet validated or regularly used in patient management.

These guidelines generally agree on including the following elements in pathology reports: Clinical information, specimen site, additional specimens submitted, operative procedure, histological tumor type, the presence and extent of variant histology, presence of noninvasive carcinoma, associated epithelial lesions, histological grade, extent of invasion, the presence of muscularis propria (in TURBT specimens), tumor focality, substaging T1 disease (when possible) and lymphovascular invasion. In cystectomy specimens, additional elements may be included such as response to neoadjuvant therapy, margin status, lymph node status, and pathologic stage.

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5 Risk Stratification of Patients: Risk Tables and Assessment – NMIBC and MIBC

James Douglas, Werner Struss, and Stephen Williams

Introduction

When caring for patients with bladder cancer (BC), it is important to be able to clarify their optimal management in terms of both surveillance schedules and adjuvant or radical treatments. As detailed in the previous sections, the tumour should have been characterised histologically with the key factors being the grade and stage. In non-muscle invasive bladder cancer (NMIBC), statistically independent factors influencing decision-making include size, number and location of tumours within the bladder.

To be able to fully risk assess a bladder cancer, it is essential to be able to determine whether or not the disease is organ confined, metastatic or if concurrent upper tract tumours are present. As such, all new bladder cancers require a degree of radiological staging. We currently stage bladder cancer using the updated eighth edition (2017) of the TNM (*t*umour, *n*odes, *m*etastasis) classification approved by the Union International Contre le Cancer (UICC) [1] (Table 5.1). The TNM classification addresses the extent of tumour involvement with the bladder wall and local progression. In addition, metastatic disease is classified according to involvement of the (non)-regional lymph nodes or remote sites. Ideally, in order to stage patients adequately, the histopathologic and radiographic TNM classifications are used conjunctively. Preoperatively, a cystectomy specimen in BC is not available and staging is based on the imaging assessment and histopathology from the transurethral resection of bladder tumour (TURBT).

In practice, the imaging modality is usually a CT-urogram for organ confined non-muscle invasive disease with the addition of a CT-chest for muscle invasive bladder cancer (MIBC). Some centres with less resource may opt for an ultrasound scan to assess the upper tracts for patients with low-risk NMIBC. For patients with tumours around the trigone, the presence of a synchronous upper tract TCC is 7.5% compared to 1.8% overall [2]. In addition, a higher grade and the number of tumours also increase the risk of concurrent upper tract involvement [3].

With the tumour characteristics, the patient requires detailed assessment. Compounding factors may influence decision-making and management options significantly. To this extent, comorbidities can substantially limit any treatment options available for an individual. Ideally, shared decision-making with the patient aims to weigh best practice management options with tolerability and quality-of-life expectations. Multiple studies have investigated possible pre-operative indicators influencing surgical outcomes. Some

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Table 5.1 2017 TNM classification of urinary bladder cancer

T – Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary tumour
Tis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades sub-epithelial connective tissue
T2	Tumour invades muscles
	T2a tumour invades superficial muscle (inner half)
	T2b tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
	T3a microscopically
	T3b macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
	T4a tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b tumour invades pelvic wall or abdominal wall
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)
N2	Metastasis in a multiple regional lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)
N3	Metastasis in common iliac lymph node(s)
M – Distant metastasis	
M0	No distant metastasis
	M1a non-regional lymph nodes
	M1b other distant metastases

Table 5.2 Charlson Comorbidity index

Calculation of the Charlson Comorbidity Index	
Number of points	Conditions
1 point	50–60 years Myocardial infarction Heart failure Peripheral vascular insufficiency Cerebrovascular disease Dementia Chronic lung disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2 points	61–70 years Hemiplegia Moderate to severe kidney disease Diabetes with organ damage Tumours of all origins
3 points	71–80 years Moderate to severe liver disease
4 points	81–90 years
5 points	>90 years
6 points	Metastatic solid tumours AIDS

Table 5.3 Approximate 5 year OS according to stage of disease

Bladder cancer stage and prognosis				
Stage	TNM		Approximate 5-year overall survival	Occult-positive lymph nodes
0	Ta/Tis	N0M0	95%	5%
I	T1	N0M0	70%	5%
II	T2a-b	N0M0	55%	25%
III	T3a-4a	N0M0	30%	45%
IV	T4b	N0M0	20%	45%
	Tany	N + M0	15%	
	Tany	N any M+	Median OS <9 months	

authors have shown pre-operative serum albumin levels as a predictor of poor overall survival (OS), cancer-specific survival (CSS) and disease recurrence for radical cystectomy. Similarly, publications have demonstrated that elevated age-adjusted Charlson comorbidity index scores (Table 5.2) increase the risk for post-radical cystectomy complications [4–8].

The bluntest method we have for risk stratification of bladder cancers is to divide them into NMIBC, MIBC and metastatic disease. Categorising patients accordingly is of critical importance. The role of re-resection TURBT in ruling out understaging is covered elsewhere in this book. Table 5.3 summarises the 5-year overall survival rates for patients diagnosed with bladder cancer according to TNM classification. Outcome is proportionate to the extent of disease burden at the time of diagnosis. The table also highlights the risk of concomitant unidentified nodal metastasis.

NMIBC

RISK Groups

Non-muscle invasive bladder cancer represents a very heterogeneous disease with vastly different levels of risk at each end of the spectrum. The

Table 5.4 Comparison of EAU, AUA and NICE guidelines

Risk groups	EAU	AUA	NICE
Low	New solitary pTa low grade (G1/2) <3 cm PUNLMP	Solitary Ta low grade ≤3 cm PUNLMP	Solitary pT1 low grade (G1/2) <3 cm
Intermediate	All others	Recurrence within 1 year, LG Ta Solitary LG Ta > 3 cm LG Ta, multifocal HGc Ta, ≤3 cm LGT1	Solitary pTa low grade (G1/2) <3 cm Multifocal pTa low grade (G1/2) pTa high grade (G2) Any pTa g2 (unspecified) Any low risk with recurrence <12
High	Any pT1, pTa high grade (G3) pCIS Multiple recurrent & >3 cm Ta low grade (G1/2)	HGT1 Any recurrent HGTa HGTa, >3 cm or multifocal Any CIS Any BCG failure in HG patients Any variant histology Any LVI Any HG prostatic urethral involvement	Any pT1 pTa HG (G3) CIS Aggressive variants/nested micropapillary

most accepted method is to divide the disease into low-, intermediate- and high-risk. The EAU, AUA and NICE guidelines broadly agree (see Table 5.4) utilising tumour grade (histologic variants and presence of lymphovascular invasion), stage, size, number and recurrence rate to place the patients into the three groups based upon their risk of recurrence and progression. This allows a consensus for surveillance schedules and recommendations for adjuvant therapies.

Risk Scoring

EORTC (European Organisation for Research and Treatment of Cancer)

The EORTC genito-urinary cancer group developed a scoring system and risk tables based upon data from seven EORTC trials. This included individual patient data from 2596 patients with Ta or T1 tumours. Concurrent CIS was recorded, but pure CIS patients were excluded. 78% of these patients had intravesical treatments with the majority of this being chemotherapy. Key points with this dataset are that patients did not undergo a re-resection TURBT and only a minority of patients (n = 171) received induction BCG. No patients were treated with maintenance BCG. Table 5.5 shows the factors, how they are weighted and how the score can be used to predict future recurrence and progression. The EORTC risk stratification has found application in the EAU and AUA risk groups.

CUETO (Club Urologico Espanol de Tratamiento Oncologico)

It is worth noting again that the EORTC risk of progression, for the high-risk group of patients, is calculated from a cohort where maintenance BCG was not administered. Comparatively intravesical administration of immunotherapy (intravesical BCG) has proven to be superior in the reduction of disease recurrence to TURBT alone [9–12]. BCG therapy also demonstrates a preventative benefit in disease progression [13]. As such, the Club Urologico Espanol de Tratamiento Oncologico (CUETO) have developed a risk calculator to predict the short- and long-term risk of recurrence and progression in BCG-treated patients. The CUETO score is based upon the data from 1062 patients from four CUETO trials that compared different intravesical BCG treatments. However, there were numerous unconventional treatment schedules that raise the question of outcome-based applicability when compared to patients treated according to usual guidelines [14]. In addition, no patients in this

Table 5.5 European Organisation for Research and Treatment of Cancer (EORTC)

EORTC: Disease recurrence and progression scores		
Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2–7	3	3
>8	6	3
Tumour diameter		
<3 cm	0	0
>3 cm	3	3
Prior recurrence		
Primary	0	0
<1 recurrence/year	2	2
>1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	2	2
Yes	4	2
Grade [15]		
G1	0	0
G2	1	0
G3	2	5
Total score	**0–17**	**0–23**
Probabilities (95% CI)		
	At 1 year (%)	At 5 year (%)
Recurrence		
0	15 (10–19)	31 (24–37)
1–4	24 (21–26)	46 (42–49)
5–9	38 (35–41)	62 (58–65)
10–17	61 (55–67)	78 (73–84)
Progression		
0	0.2 (0–0.7)	0.8 (0–1.7)
2–6	1 (0.4–1.6)	6 (5–8)
7–13	5 (4–7)	17 (14–20)
14–23	17 (10–24)	45 (35–55)

cohort received postoperative instillations of chemotherapy (MMC) or re-resection TURBT. Finally, in both studies, the exclusion of carcinoma in situ (CIS) further reduces clinical applicability.

The CUETO prognostic factors not only include prior recurrence status, number of tumours, tumour stage, associated CIS, tumour grade, similar to the EORTC score, but also include gender and age (see Table 5.6). The risks of recurrence and progression are less in the BCG-treated cohort CUETO calculator (see Table 5.7).

Table 5.6 Comparison between the risk factors for recurrence and progression between the EORTC and CUERTO risk calculators [16]

EORTC – predict recurrence and progression in pts with stage Ta, T1 bladder cancer	CUETO – predicts risks of recurrence and progression for BCG-treated pts
Number of tumours	Sex
Size	Age
T category	Prior recurrence status
Grade	Number of tumours
Presence of CIS	T category
	Associated CIS
	Tumour grade

Recently, merged data of 1812 patients from two EORTC randomised phase 3 trials in intermediate- and high-risk NMIBC were interrogated to determine prognostic factors in NMIBC patients treated with 1–3 year of BCG after initial TURBT. In addition, the study aimed to derive nomograms, stratify risk groups and identify high-risk patients who should be considered for early cystectomy. In multivariable analyses, Cambier et al. identified a prognostifier using prior recurrence rate, number of tumours at recurrence and tumour stage and grade to show progression and death due to BC. In particular, patients with G3pT1 disease do poorly and show progression at 1-year of 11.4% and 19.8% at 5-years. Noticabley, 1- and 5-year disease-specific death rates in this subgroup are 4.8% and 11.3%. Study limitations were the lack of repeated transurethral resection in high-risk patients and exclusion of patients with carcinoma in situ, leaving additional unaccountable variables [17]. Conclusively, the study surmised that currently recommended bacillus Calmette-Guérin maintenance schedules for NMIBC patients at high risk of recurrence and/or progression still do relatively poorly. The authors suggest alternative treatment options are urgently required.

The Molecular Landscape of Non-Muscle Invasive Bladder Cancer

In recent years, progressive sequencing techniques allowing the interrogation of urine, tissue

Table 5.7 Comparison between the risk of recurrence at 1 and 5 years between the EORTC and CUERTO risk calculators [59]

	Recurrence rate at 1 year (95% CI)		Recurrence rate at 5 year (95% CI)	
Recurrence score	Risk tables	Author's results	Risk tables	Author's results
EORTC				
0	15 (10–19)	0	31 (24–37)	0
1–4	24 (21–26)	3 (1–5)	46 (42–49)	15 (10–21)
5–9	38 (35–41)	28 (23–34)	62 (58–65)	49 (41–56)
10–17	61 (55–67)	80 (66–89)	78 (73–84)	96 (80–99)
CUETO				
0–4	82 (5.9–10.5)	1.4 (0–2.9)	21 (17–25)	4.9 (1.6–8)
5–6	12 (8–16)	17 (10–24)	36 (29–42)	34 (24–44)
7–9	25 (20–31)	46 (37–55)	48 (41–55)	84 (74–91)
10–16	42 (28–56)	74 (57–84)	68 (54–82)	96 (79–99)

CI confidence interval, *EORTC* European Organisation for Research and Treatment of Cancer, *CUETO* Spanish Urological Club for Oncological Treatment

and blood samples for molecular alterations have led to rapid advances in our understanding of the genomic profile of NMIBCs. Subsequently, this has led to characterisation of distinctive molecular subtypes. Genomic classification enables us to risk stratify patients more readily and move from prognosis to prediction, guiding individualised patient care.

Recent literature suggests that NMIBC shares molecular characteristics with MIBC, although research to this extent, currently, more readily focuses on metastatic bladder cancer. Regardless, a unified molecular classifier for NMIBC has not been established to date. The three most current studies by Hedegaard et al., Hurst et al. and Tan et al., respectively, propose quite different sub-classification signatures. Notably, though, all studies have identified high- and low-risk subtypes. More aggressive subtypes present with higher-grade disease, greater risk of progression and worse recurrence-free survival, therefore requiring more frequent monitoring, and may necessitate more aggressive treatment. Conversely, subtypes associated with less aggressive disease show significantly better survival outcomes and may require less frequent surveillance and therapies [18–20].

Despite these efforts, present limitations of the research investigations involving molecular characterisation include the lack of standardisation regarding tissue preparation, extraction of epigenomic material and implementation of sequencing techniques, thus, to a certain extent, limiting reproducibility and validation of results across multiple studies. In addition, the clinical impact of perioperative treatment on molecular classifiers (e.g. immediate post-TURBT instillations of chemotherapy, repeated TURBTs, subsequent courses of intravesical chemotherapy or immunotherapy) has not been investigated in the current studies [21].

Genomic profiling has found clinical application in numerous FDA-approved urinary tests. None of these urinary tests have been accepted for diagnosis or follow-up in routine practice or clinical guidelines. Conclusion drawn regarding the existing tests is that sensitivity is usually higher at the cost of lower specificity, compared to urine cytology. It is important to note that sensitivity and specificity of a urinary marker test depend on the clinical context of the patient (screening, primary detection and follow-up). Also, benign conditions (e.g. urinary tract infection and stones) and intravesical bacillus Calmette-Guérin (BCG) impact the results of these investigations often causing false positives. Nonetheless, positive results in patients with negative cystoscopy and upper tract workup may identify patients more likely to experience recurrence and possible progression earlier than conventional investigations do to date.

Shared expert opinion emphasises the necessity for clinical application of molecular classifiers that risk stratify NMIBC, notably to determine which patients may benefit foremost from surveillance, intravesical BCG treatment, immediate cystectomy or alternative intravesical targeted therapies.

In conclusion, the utilisation of risk stratification tools in NMIBC, to date, has shown some

promise in determining the best surveillance strategy for patients after primary diagnosis or recurrence of disease. Limitations in both the EORTC and CUERTO risk stratification tools have been discussed extensively, highlighting the heterogeneous mix of tumours in the realm of NMIBC addressed in these studies, which associates with a broad spectrum of risk for recurrence and progression. The more recent publication by Cambier et al. [17] appears to shed more light on the natural history of patients with intermediate- and high-risk NMIBC. These patients conceivably have the most to gain from these models. Ideally, a new risk model for NMIBC would include the entire spectrum of disease (including CIS) and would incorporate some additional pathologic parameters such as limited versus extensive lamina propria invasion, lymphovascular invasion and accurate grading as discussed in a recent review article [22]. These parameters are mostly relevant for high-grade T1 disease, which Cambier et al. highlighted as a particularly high-risk group. With our understanding of the molecular biology of non-muscle invasive bladder cancer advances in the current genomic era, future improvements in risk stratification are likely to be based on biomarkers rather than conventional clinical and pathologic parameters.

MIBC

Approximately 25% of patients with BC present with muscle invasive disease (T2-T4) [23]. The diagnosis of MIBC is confirmed after pathological interrogation of the transurethral resection biopsy specimen of the bladder tumour. Full staging is achieved with the addition of radiological imaging in the form of CT imaging of the chest, abdomen and pelvis. Some centres are now considering the use of a standardised approach to imaging and reporting of multi-parametric magnetic resonance imaging (mpMRI) for BC. The Vesical Imaging-Reporting And Data System (ViRADS) aims to locally stage the disease. This imaging may compliment pathology, reduce radiation-based imaging and ultimately avoid time delays to radical treatment associated with TURBT [24].

All patients with muscle invasive disease are considered high risk with the hazard of occult nodal disease ranging between 18 and 45% (see Table 5.3). Despite providing excellent local control, surgery alone only provides a 5-year OS of around 50% when combining all stages and this drops even further for non-organ confined disease (Table 5.3). As expected, OS declines with worsening local and nodal staging (Tables 5.8 and 5.9).

Since level 1 evidence demonstrated a 5% Overall Survival improvement (from 45% to 50%) over 5 years, neoadjuvant cisplatin-based chemotherapy (NAC) has become the standard of care for those patients with advanced bladder who have adequate performance status and renal function [31, 32]. This meta-analysis of the advanced bladder cancer (ABC) collaboration in 2003 and 2005 showed that on average, 27% of patients achieve a complete pathologic response (i.e. stage pT0) after receiving NAC [33]. Interestingly, the advantage was most pronounced for patients with clinical locally advanced (T3-T4a) disease in the NAC arm of the SWOG 8710 trial [34].

Table 5.8 Five-year OS after radical cystectomy alone for pT3b–T4 bladder cancer [25–28]

Survival after radical cystectomy alone for pT3b–T4		
Study, year	No. of patients	Five-year survival
Dalbagni, 2001	129	26%
Stein, 2001	254	44%
Maderbacher, 2003	111	38%
Herr, 2003	353	42%

Table 5.9 Five-year OS after radical cystectomy alone for N2–3 bladder cancer [25–30]

Survival after radical cystectomy alone for N2–3 patients		
Study, year	No. of patients	Five-year survival rate
Dalbagni, 2001	39	13%
Stein, 2001	86	24%
Zincke, 2002	24	15%
Mills, 2002	60	29%
Maderbacher, 2003	44	26%
Herr, 2003	108	28%

Risk with Clinical Parameters

At radical cystectomy, around 30–40% of patients will have achieved a complete response after TURBT and neoadjuvant chemotherapy compared to around 10% with TURBT alone. With such a significant difference, one would expect a larger survival benefit than just 5%. It is reasonable to assume that this is accounted for by some patients having chemo-resistant disease and progression through chemotherapy. As such, many urologists are still reticent to administer neoadjuvant chemotherapy. Some authors have attempted to risk stratify their patients to determine neoadjuvant therapies. In a prospective trial of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) chemotherapy, Millikan et al. first described the utilisation of risk stratification to select patients for NAC or adjuvant chemotherapy. They considered high-risk features to include three-dimensional mass on examination under anaesthesia (EUA), involvement of adjacent organs (e.g. prostatic stromal invasion on transurethral biopsy of the prostatic urethra or direct invasion into the vagina) and the presence of lymphovascular invasion (LVI) [35].

More recently, a risk-stratification model developed at M.D. Anderson Cancer Center (MDACC) specified criteria for clinical staging and patient selection for NAC. This study by Culp et al. aimed to determine which patients would benefit the most from NAC prior to RC. Patients were divided into high or low risk depending on whether or not they presented with hydronephrosis, clinical T3b-T4a disease, LVI or aberrant histology (i.e. micropapillary or neuroendocrine/small cell features) [36]. The investigation surmised that high-risk patients exhibited a decreased 5-year overall survival (47.0% vs 64.8%) and decreased disease-specific (64.3% vs 83.5%) and progression-free (62.0% vs 84.1%) survival probabilities compared to low-risk patients. This led them to administer neoadjuvant chemotherapy to the high-risk group and reserve adjuvant or palliative chemotherapy to the low-risk group if they relapsed or had adverse features at final pathology. A revalidation study by von Rundstedt et al. demonstrated similar results using the modified MDACC clinical risk-stratification model applied in their study cohort and showed that the high-risk category was associated with lower CSS and OS [37].

Risk with Imaging

Progressive imaging techniques are improving pre-treatment staging of MIBC. Although PET/CT is currently not recommended as routine staging, it has proven prognostic value in MIBC. In fact, FDG PET/CT has proven superiority in detecting more malignant disease than conventional CT/MRI in 20–40% of patients [38, 39] Initially, small studies demonstrated positive PET/CT scans prior to planned cystectomy in patients with no evidence of metastatic disease by conventional staging methods have been associated with poor survival [40, 41]. A meta-analysis of FDG PET/CT by Lu et al. for the staging and restaging of bladder cancer found that the pooled sensitivity was 82%, the pooled specificity was 89% and the global accuracy was 92% [42]. Mertens et al. investigated the ability of 18F-fluorodeoxyglucose (FDG)–PET/CT to detect extravesicular lesions and their association with overall survival [43]. 98 of 211 (46.4%) patients with MIBC had one or more extravesicular lesions on PET/CT. Conclusively, patients with a positive PET/CT had significantly shorter overall and disease-specific survival: 14 vs. 50 months and 16 vs. 50 months, respectively. In another study, patients with organ-confined disease diagnosed on CT were found to have more extensive disease on FDG-PET/CT. As a result of the findings on FDG-PET/CT, patients scheduled for curative treatment with radical cystectomy had their surgery cancelled and instead were treated with systemic chemotherapy for more advanced disease [44]. In fact, Apolo et al. argued FDG PET/CT may change the clinical management in up to 68% of the patients [38]. In summary, new imaging modalities are proving to be useful tools to identify higher risk and progressive disease. Sensitivity and specificity are superior to conventional imaging techniques, not only by allowing for a more accurate staging but

also by guiding changes in clinical management of patients with MIBC.

Risk Via IHC

It is clear that bladder cancer comprises a heterogeneous group of diseases beyond conventional histopathology. Elaborative immunohistochemistry (IHC) investigations have aimed to risk stratify patients with bladder cancer to aid in gauging prognostic significance of selected histopathologic characteristics.

Overexpression of vascular endothelial growth factor (VEGF), Her2, EGFR (human epidermal growth factor receptor), FGFR3 and mutations, copy number alterations or RNA expression changes affecting the PI3K/Akt/mTOR pathway are common in bladder cancer, which has led to the investigation of these markers as diagnostic tools [45–53]. Multiple trials are investigating possible clinical implications of these markers: a single-arm, phase II study involving bevacizumab (a monoclonal antibody targeting VEGF-A) in combination with ddMVAC prior to radical cystectomy was unable to discern role of bevacizumab on OS [54] and targeted agents for Her2 have not found clinical application [55, 56]. A phase II trial (TUXEDO) of cetuximab (monoclonal antibody against EGFR) in combination with concurrent chemoradiation therapy with either mitomycin C and 5-FU or cisplatin in MIBC is underway in the United Kingdom and unfortunately, an open-label phase II trial of dovitinib (a FGFR3 inhibitor) in patients with advanced urothelial carcinoma did not demonstrate a clinical benefit [57]. mTOR has not found clinical trial implementation to date.

Risk Via Genomic Classifiers

Molecular classification of MIBC has potential implications for the clinical management of bladder cancer patients. There are five popular molecular subtyping schemes that utilise differing genomic platforms; however, they share many similarities [53, 58–61] (Table 5.10). At the highest level, there are basal and luminal types with further sub-classification according to the individual classifier used.

Table 5.10 Molecular subtype classification of bladder cancer

Bladder cancer subtypes					
Basal-like	Luminal				UNC
Basal-like	Non-basal-like				CURIE
Basal	p53-like	Luminal			MDA
UroB	SCC-like	Infiltrated	Genomically unstable	UroA	LUND
Cluster III	Cluster IV	Cluster II	Cluster I		TCGA

Color bars represent subtype classifications made by each institution. Subtype groupings were made independently and associations were assigned on the basis of the MD Anderson Cancer Center (MDA) classifier. CURIE, Institut Curie; UNC, University of North Carolina. Adapted from Kamat et al.

This body of work has identified deletions, mutations and aberrant methylation of tumour suppressor genes such as *PTEN, TP53*, *RB1*, and *CDKN2A* and activation, mutation or overexpression of oncogenes such as *ERBB2*, *CCND1 and FGFR3*. Recent work has suggested that specific mutations, particularly in ERBB2, ERCC2 and DNA repair genes, may predict response to neoadjuvant chemotherapy [50, 53, 61, 62].

The basal subgroup appears to respond best to cisplatin-based chemotherapy, but when fully interrogated, it appears that those with EMT and immune infiltrated tumours seemed to not do as well with neoadjuvant chemo as those without.

The prognosis of patients who fall into the luminal subgroup has been shown to have the best prognosis regardless of the administration of neoadjuvant therapies; however, again, there is a difference in survival between the luminal and the luminal infiltrated subgroups [62].

More recently, Kamoun et al. have presented their work attempting to combine the published molecular subtypes and create a 'consensus' classification. This international collaboration of experts has agreed a system comprising six subtypes. This now needs to be tested prospectively in well-designed randomised controlled trials (Fig. 5.1) [63].

Future clinical trials are being planned where neoadjuvant treatments are being tailored based upon a tumour's genomic classification.

In summary, multiple studies investigating the genomic landscape of MIBC demonstrate disease complexity. Gene expression profiling has identified several subtypes of muscle invasive bladder cancer. The aim of a consensus system offers a robust framework that will enable testingand validate predictive biomarkers in future clinical trials. This in turn will aid the understanding of response to various treatment modalities and identify potential targeted agents for personalised cancer management.

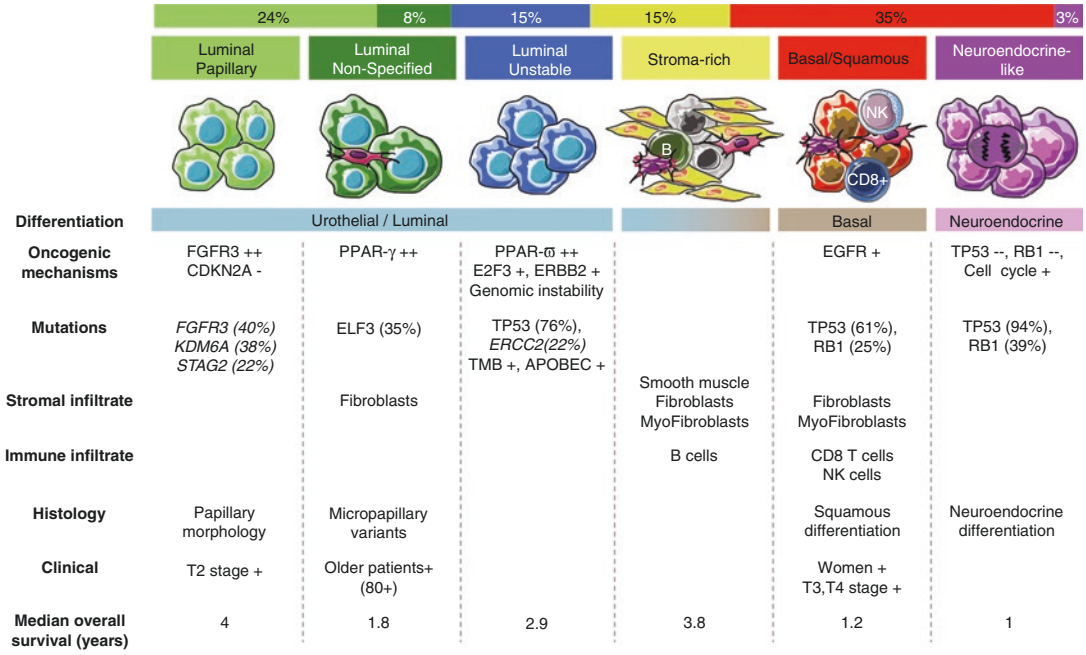

Fig. 5.1 Summary of consensus classification

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6 Perioperative Preparation and Management of Cystoscopy Patient

Farzin Goravanchi

There are approximately 1050 surgical cases of cystoscopy performed per year at the UT MD Anderson Cancer Center operating rooms. Majority of these cases are performed in the outpatient surgical suite which is separated from the main hospital; Mays operating rooms. Focus on patient safety as well as efficiency of the operating room is addressed. The limiting factor for having patients at the Mays OR is BMI greater than 45. Patients who are ASA I-IV may have their surgery performed at our center. Cystoscopy is performed on patients who have a history of bladder cancer or other type of abdominal cancer which has affected the bladder. These patients often come to the operating room for an initial screening, biopsy(s), and/or resection(s). Majority of the patients with bladder cancer are over 70 years of age, have a long history of tobacco use, hypertension, CAD, COPD, diabetes mellitus, and other chronic diseases. Due to the comorbidity of these patients, all patients are evaluated preoperatively by the anesthesia preoperative clinic.

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Preoperative Assessment

The anesthesia preoperative assessment clinic does screen patients, address risk factors, and reduce the time needed on the day of surgery to evaluate the patient.

Preoperative clinic does assessment on patients, order pertinent labs as well as order consultations including pacemaker/AICD check, insulin pump management, and pulmonary evaluation [1]. Instructions regarding the medications on day of surgery and NPO instructions are also given to the patient.

Preoperative laboratory Basic CBC, liver enzymes, Cr, Electrolytes (more significant in patients on diarrheic or chemotherapy). Coagulation labs when indicated. We do not routinely Type and Screen blood type due to the very low rate of blood transfusion.

Cardiopulmonary evaluation EKG for patients who are over age 65 or history of hypertension or cardiac disease. Routine Echocardiogram and stress test performed only if indicated by cardiologist. For patients with coronary stents, American Heart Association guidelines are used. We may postpone elective surgery for 1 year, and if surgery cannot be deferred, we continue aspirin during the perioperative period in high-risk patients with drug-eluting stents [2]. All cardiac pacemaker/AICD

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devices are evaluation preoperatively in cardiology clinic. They are evaluated for battery life, functionality, and functional parameters. A recommendation of intraoperative and postoperative management of the device is also provided by the cardiologist.

All patients with insulin pumps also have a consultant to evaluate the device and provide guidelines for management.

NPO guidelines Use ASA recommendations. Patients may have clear liquid diet up to 2 hours prior to surgery check in time. This allows the surgery schedule to be more flexible; allowing OR space for patients who are delayed for any reason to be replaced by patients who are present in the hospital.

Preoperative medications Instructions of what medications specifically cardiac medications are given to patients. Include hypertensive medications, diabetic, inhalers, antithrombotic, anxiety, pain, and antibiotics. ACE inhibitors and ACE antagonists are avoided morning of surgery and other antihypertensive medications are taken.

Patients are given a prescription for antibiotics prior to surgery. This has helped reducing the time needed in the surgical holding area to administer antibiotics. Patients take Ciprofloxacin 500 mg orally on the evening prior to surgery and a second dose after surgery. High-risk antibiotics from the IV to home oral administration have improved our compliance on time antibiotic administration from 15% to 95%; in addition of reducing the time needed to administer the medication.

OR Management

The holding area nursing is educated on the special and the management of the cystoscopy patients. The nurses check for labs, NPO guidelines, consent, and potential needs of the patient. The nurse places an IV catheter on the patient and gives any potential medications instructed to the patient. Majority of cystoscopy procedures are performed under general anesthesia.

Airway management Approximately 95% of the airways are secured using a Laryngeal Mask Airway (LMA) device. Patients are screened for airway management and the best technique has been experienced to be the LMA. It is less invasive and reduces the amount of narcotics and other level of anesthesia needed for the procedure. We do have multiple devices addressing difficult airways including Fiberoptic, Airtraq by Teleflex, and C-MAC by Karl Storz.

Muscle relaxation Bladder tumor resections may involve tumors which may have invaded the bladder muscle wall. This would require a deep level of anesthesia with muscle relaxation for safe and adequate tumor resection. Due to a limited number of anesthesia providers, variability of intraoperative management of these patients has been limited. The surgeon will often ask for a short period of complete muscle relaxation when electrocautery is used. This would help the surgeon by decreasing spontaneous movement caused by stimulation of the obturator nerve causing adduction of leg, which may cause bladder perforation. Because of the long duration of reversal with neostigmine/glycopyrrolate, patients are usually given lower doses of muscle relaxant, which increases the risk for bladder perforation. By using Sugammadex, the anesthesiologist may improve the surgical condition by providing a deeper level of muscle relaxation with a standardized dose of muscle relaxant. A more predictable reversal of muscle relaxation will be provided. We only use muscle relaxants mainly when a surgeon asks for it. When asked, rocuronium 0.45 mg/kg of ideal body weight is given. Sugammadex reversal dose of 4 mg/kg is used when adequate spontaneous recovery of the muscle strength has occurred.

Pain medications The induction dose of narcotics is limited to 25 mcg for induction with small incremental addition if needed. Majority of patients do not require more than 50 mcg of fen-

tanyl for an average procedure. Benzodiazepines are avoided for majority of patients. Acetaminophen 1000 mg and celecoxib 200 mg are given orally in holding area. Multimodal therapy depending on patient medical history is used. Patients with hepatic or renal dysfunction do not receive acetaminophen and celecoxib.

Pain from bladder spasm is treated with Hyoscyamine (Levsin/SL) 0.125 mg tablet and Belladonna-Opium (B&O Supprettes) 16.2 mg Suppository. Lidocaine 2% jelly is also used when patients complain of pain at cystoscope insertion site.

Antiemetic Routine ondansetron 4 mg is used prior to emergence from anesthesia. Dexamethasone 4–8 mg IV is also used at the beginning of the procedure. For more extensive procedures requiring large dose of narcotics, promethazine 6.25 mg IV is also given.

Positioning Most of the procedures are performed in lithotomy position. This gives the best access to the perineum and the indicated procedures. By placing the legs into the lithotomy position, the venous return to the chest area is increased; increased venous return to the chest. This also decreases the lung capacity and compliance for patients. This may be significant for patients who have significant cardiopulmonary compromise. As a result and large wedge is placed under the head and upper chest to compensate for the elevated leg positon.

Common peroneal nerve injury is the most common nerve injury in the lithotomy position [3]. If a patient has arthritis, limited joint mobility, or has prior injury, patient is positioned awake in order to reduce the chances of injury.

Pacemaker/AICD Follow cardiology recommendations; if possible use a bipolar cautery (Gyrus scope), which reduces interference with the cardiac device. We also perform a postoperative check on the device if required.

Sedation (MAC) anesthetics This is reserved for patients with severe cardio-pulmonary-neurological compromise. Mild sedation with fentanyl and 2% lidocaine jelly may be used for a limited procedures.

Postoperative

We have the capability of monitoring patients overnight in our extended recovery rooms and discharging them the following morning. Patients may go home on the day of surgery if specified by the surgeon and if they meet the following criteria: have pain under comfortable degree, no nausea, able to eat and drink, able to urinate unless has an indwelling catheter, have stable vital signs and glucose level, and ambulate in order to be discharged home for outpatient surgery. Nursing will also monitor for signs and symptoms of bladder perforation or any other surgical or anesthetic complications.

PACU nursing will also contact the patients by phone on postoperative day 1–3. Questions regarding potential complications of surgery, anesthesia, and nursing are addressed. Focusing on pain, bleeding, infection, nausea, activity, and any potential concerns that patients have. If there are findings during the call, the faculty will be notified of the findings.

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Transurethral Resection of Bladder Tumors (TURBT)

7

Tilman Todenhöfer and Arnulf Stenzl

Introduction

Transurethral resection of bladder tumors (TURBT) is one of the most common procedures in urology with 300.000 TURBT performed per year in the European Union. It is both a diagnostic and therapeutic procedure. Its quality has been shown to have a significant impact on the outcome of patients with bladder cancer [1]. By cutting through the tumor as it is done with the most common resection technique, at least one of the principals of oncological surgery is disobeyed. Furthermore, two thirds of the costs of all bladder cancer cases are due to the large number of TURBTs and cystoscopies. This chapter will therefore not only look into various aspects of the actual tumor resection but also focus on measures to increase visibility of suspicious areas. Furthermore, ways to improve the quality of the specimen in order to allow more accurate pathologic staging will be discussed (en bloc resection).

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Indications

The most common indication for performing a TURBT is the presence of a suspicious lesion or papillary tumor during cystoscopy. Further indications for TURBT include a positive cytology in the absence of any suspicious finding in cystoscopy. These quadrant biopsies can be performed by a cold-cup biopsies or loop resections.

After TURBT, as significant risk exists for the presence of a residual tumor [2], this risk is increased in patients with T1 tumors or TaG3 tumors [3]. Approximately 30% of patients with T1 tumors in initial resection will be found to have muscle-invasive disease. Therefore, a second resection is recommended in patients with pT1 tumors or high-grade tumors in initial resection or patients with incomplete initial resection who are not planned for immediate cystectomy. The second resection has been shown to have a potential positive impact on recurrence-free survival and progression-free survival of patients with NMIBC [4]. This positive impact seems to be particularly present in patients without muscle in the initial resection [5]. The second resection should be performed within 2–6 weeks after the initial resection as a further delay may negatively impact RFS and PFS [6].

The use of a bladder diagram during cystoscopy may help to improve the detection of lesions during TURBT [7].

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Patient Preparation

Coagulation lab and hematology should be performed to rule out coagulopathies. Patients who receive anticoagulants or platelet aggregation inhibitors due to concomitant diseases (such as atrial fibrillation or coronary heart disease) should consult with the prescribing physician to check whether these drugs can be discontinued temporarily. In patients with small papillary tumors, discontinuation of these drugs is usually not necessary and bleeding can be avoided by thorough coagulation after resection of the tumor. Postoperatively, the weighting of the risk of bleeding and clot formation to determine the optimal time point to resume these drugs may be challenging. Urine culture should be performed in all patients prior to surgery. Patients with active urinary tract infection should receive antibiotic treatment and should have a documented sterile urinary culture before undergoing surgery. Guidelines differ regarding their recommendations on the use of antibiotics in patients receiving TURBT [8, 9]. The American Association of Urology (AUA) recommends the use of Fluoroquinolones or Trimethophrim-sulfamethoxazole in all patients receiving cystourethroscopy with manipulation (including TURBT) [10]. In contrast, the current EAU guideline panel concluded that a weak recommendation to use antibiotic prophylaxis for patients undergoing TURBT who had a high risk of suffering postoperative sepsis would be appropriate [11].

TUR-BT can be performed in both general anesthesia and regional anesthesia. The choice of the optimal form of anesthesia is dependent on the patient and the anesthesiologist. In patients with large tumors at the lateral wall, general anesthesia allows the application of a systemic muscle relaxant in order to reduce the risk of rapid leg adductions caused by irritation of the obturator nerve (with increased risk of perforation). In patients receiving regional anesthesia, an obturator block can be performed in order to reduce the risk leg adductions leading to perforation or bleedings.

Patients scheduled for TURBT should have physical conditions compatible with lithotomy position. Pads should be used in order to reduce the risk of nerve injury, e.g., of the sciatic, femoral, or common peroneal nerve.

In patients with large tumors, irrigation fluid should be warmed preoperatively in order to prevent hypothermia.

Basics of Standard TURBT

The surgeon should be aware of all known details of the disease before performing the surgery. This includes the medical history and the findings of the last cystoscopy. The awareness of the urinary marker results including cytology may help to predict the risk of the presence of high-risk NMIBC.

The main steps of a TURBT are digital rectal examination and/or bimanual palpation (Fig. 7.1), cystoscopy using white with or without blue light cystoscopy of the entire urethra and bladder, resection of tumors, and biopsies of normal appearing mucosa (in the case of positive cytology without tumor evidence) or the prostatic urethra.

Before performing cystoscopy with subsequent TURBT, a digital rectal examination and (in the case of female patients) bimanual examination are recommended (Fig. 7.1). However, due to the low accuracy of these examinations, they cannot replace imaging in patients with advanced tumors. For TURBT, the use of a 24–28 Fr Resectoscope is recommended. The resectoscope sheath can be inserted in combination with a 0 degree lens for optimal visualization of the urethra. In female patients, an obturator can be used in combination with the resectoscope sheath. Atraumatic passage of the urethra is essential for preventing urethral strictures. For inspection of the bladder, the use of a 30 or 70 Degree cystoscope lens is recommended. In case the whole bladder cannot be visualized using these standard lenses, the use of a 120 degree lens should be considered (Fig. 7.2). This can be particularly helpful for the visualization of tumors at

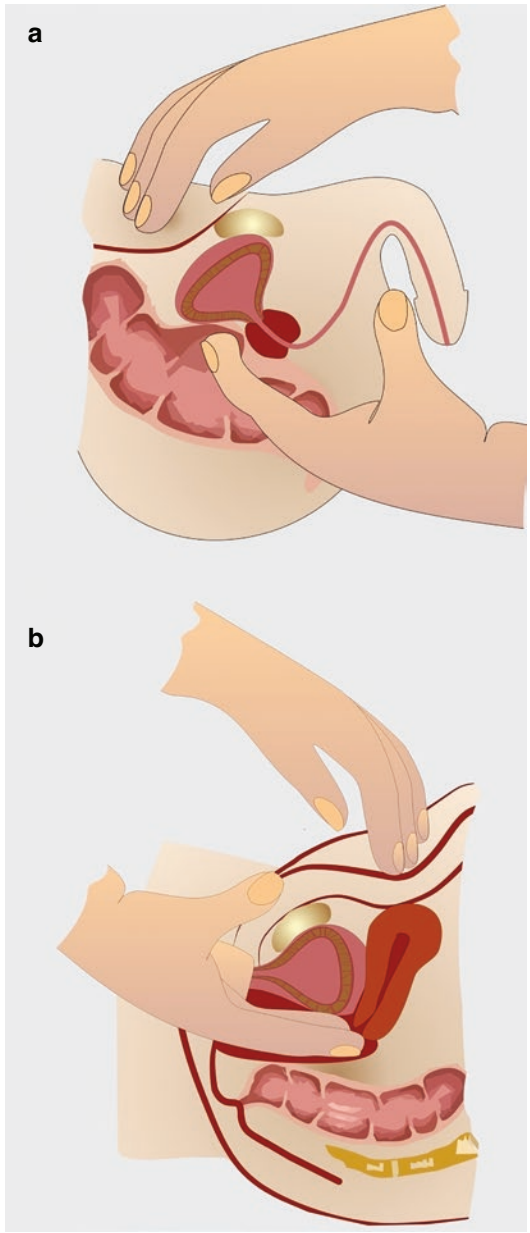

Fig. 7.1 Principles of bimanual palpation in male (**a**) and Female patients (**b**)

the bladder neck, anterior wall, or bladder dome or in cases of large middle lobes (Fig. 7.2). The entire bladder should be inspected for the presence of papillary tumors or abnormal lesions. As with cystoscopy, the use of a standardized map can help to facilitate the documentation of the lesions and the correct assignment of specimens.

Resection should be performed using a 30 degree lens. The ultimate goal of TURBT is to completely resect all visible tumors in the bladder. Tumors with distinct locations should be sent to the pathologist as separate specimens. After complete resection of a papillary lesion, a deep biopsy should be performed to improve clinical staging by resecting tissue of the muscularis propria. In cases of multiple papillary tumors, there is no clear recommendation whether a deep biopsy has to be performed at all tumor sites. The risk of understaging should always be weighted against the risk of perforation by a deep biopsy. In this context, it is important to consider the patient's medical history. In patients with a previous history of high-grade tumors, the priority of performing a deep biopsy is much higher than in patients without history of BC who present with a typical papillary lesion.

Resection can be performed using either a monopolar or bipolar cutting loop. Currently, there are conflicting data whether a bipolar resection is able to significantly reduce the rate of complications during TURBT [12, 13]. Whereas monopolar TURBT requires the use of a nonconducting solution such as glycine or sorbitol, saline use is possible with bipolar TURBT. The use of saline may prevent the development of TUR syndrome, which is most frequently a result of bladder perforation with subsequent fluid absorption by the peritoneum. In contrast to the TUR syndrome caused by TUR-P, the nadir of serum sodium levels is usually later due to the different pathophysiology (TUR syndrome caused by TUR-P is most often the result of fluid that is absorbed across open venous sinuses).

Especially for very small papillary lesions, there is a significant risk of preventing sufficient pathologic evaluation by excessive use of cautery. This can be prevented by performing cold cup biopsies. Moreover, the use of bipolar resection has been shown to impact the degree of cautery artifacts [13].

After resection, cauterization of all resection areas should be performed. This is particularly important in patients receiving TURBT under anticoagulant therapy or platelet aggregation inhibitors. After resection, the ureteral orifices

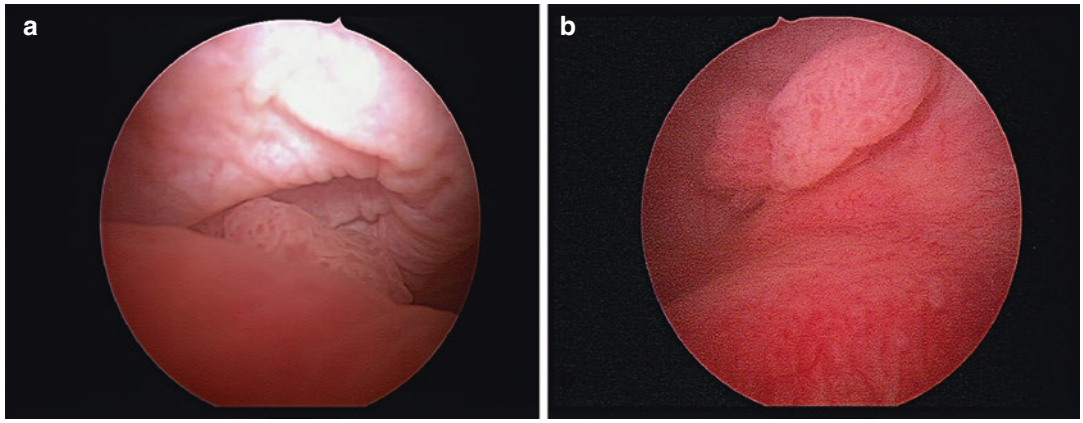

Fig. 7.2 Use of a 120 degree lens (**a**) in a patient with a large middle lobe, leading to decreased visibility of the tumor (**b**)

should be visualized in order to make sure they have not been affected by resection or cauterization. The insertion of a two-channel indwelling irrigation catheter is recommended in case the patient develops postoperative hematuria. The degree of hematuria should be inspected before finishing the procedure. In the case of significant gross hematuria, further coagulation is required.

Blue Light TURBT

The identification of flat nonpapillary tumors and carcinoma in situ (cis) can be challenging using white-light cystoscopy. Moreover, the inaccurate determination of tumor margins using white light may limit the efficacy of white light TURBT. This may contribute to the high rate of residual tumors after initial TURBT (up to 40%). Photodynamic diagnosis (PDD) has been introduced to facilitate the identification of flat lesions not visible during white light cystoscopy [14]. For PDD, preoperative intravesical application of photosensitizing agents is essential. These photosensitizing agents are prodrugs that are metabolized into protoporphyrin IX. Photoactive protoporphyrin IX is especially accumulated in malignant urothelial cells [15]. Blue light exposure (380–480 nm) leads to the emission of a red fluorescence by cells accumulating photoactive porphyrins (Fig. 7.3).

Either 5-aminolevulinic acid (5-ALA) or hexaminolevulinate (HAL) has been used and approved as PDD agents for patients with BC. The use of 5-ALA has been limited by its low bioavailability and the relatively short duration of tissue fluorescence. This phenomenon is a result of the relatively low fat solubility of 5-ALA.

Prospective trials and meta-analyses including a high number of patients have shown that the use of PDD increases the sensitivity for tumor detection, in particular, carcinoma in situ [16, 17]. However, false positive lesions are a concern in the context of PDD, which can be caused by inflammation or BCG therapy [18]. In a recent trial including patients with positive urine cytology, the detection rate was not affected by the use of PDD [19]. Whereas strong evidence exists showing that the use of PDD reduces recurrence rates in patients with NMIBC, mixed results have been reported regarding the impact on the progression rates compared to white light cystoscopy [20]. Grossman et al. reported no significant difference in the rate of development of T2–4 bladder cancer in 551 patients enrolled in a prospective randomized trial comparing white light and fluorescence cystoscopy for Ta or T1 bladder cancer [21]. Using a new definition of progression of NMIBC introduced by the international bladder cancer group (IBCG), Kamat et al. recently reported a longer time to progression in

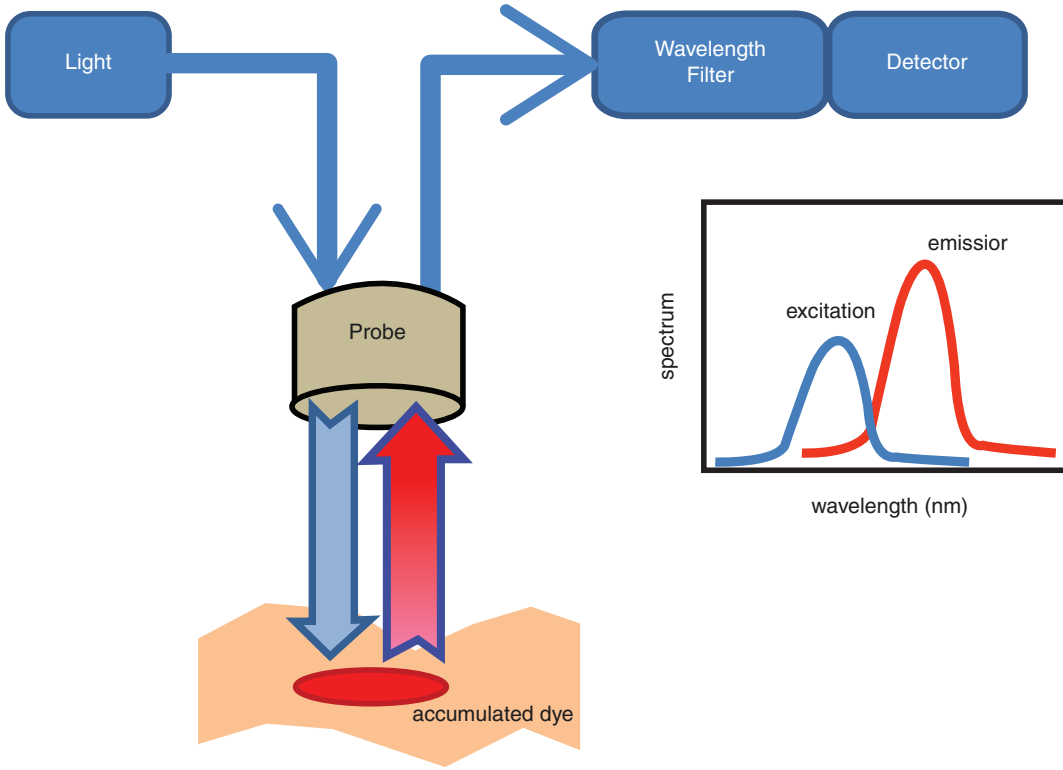

Fig. 7.3 Principle of Photodynamic diagnosis (PDD)

patients included in a phase III randomized trial comparing blue light cystoscopy vs. white light cystoscopy [22]. The use of PDD during TURBT has also been shown to have a positive impact on costs and quality-adjusted life years [23].

When using blue light cystoscopy, it has to be taken into account that the angle of the cystoscope has a significant impact on fluorescence. In most cases, the trigonum and the areas around the ureteral orifices appear fluorescent, which changes by altering the insertion angle of the cystoscope and is not demarcated. Such a "false-positive" fluorescence may lead to unnecessary biopsies/resections.

When using PDD, the photosensitizing agent HAL should be applied via a sterile catheter at least 60 minutes before TURBT in order to achieve a sufficient fluorescence. TURBT should be performed 60–120 minutes after instillation to prevent photobleaching. A regular check of the technical equipment is essential to ensure optimal performance of PDD. One potential cause of inefficient PDD is the use of a light cable with suboptimal technical performance or the defect of the cystoscopy lens.

Figure 7.4 shows the potential of identifying tumor lesions hardly visible by white light cystoscopy.

Narrow Band Imaging

The detection of tumors can also be improved by the use of a high resolution wide field imaging that improves the contrast between normal urothelium and hypervascular cancer. This is achieved by using two light spectra that are preferentially absorbed by hemoglobin, which enhances the contrast between blood vessels and normal urothelium. The narrow-band imaging (NBI) technique is available for both rigid and flexible endoscopes. In contrast to PDD, no patient preparation and instillations are required. The use of NBI has been shown to improve detec-

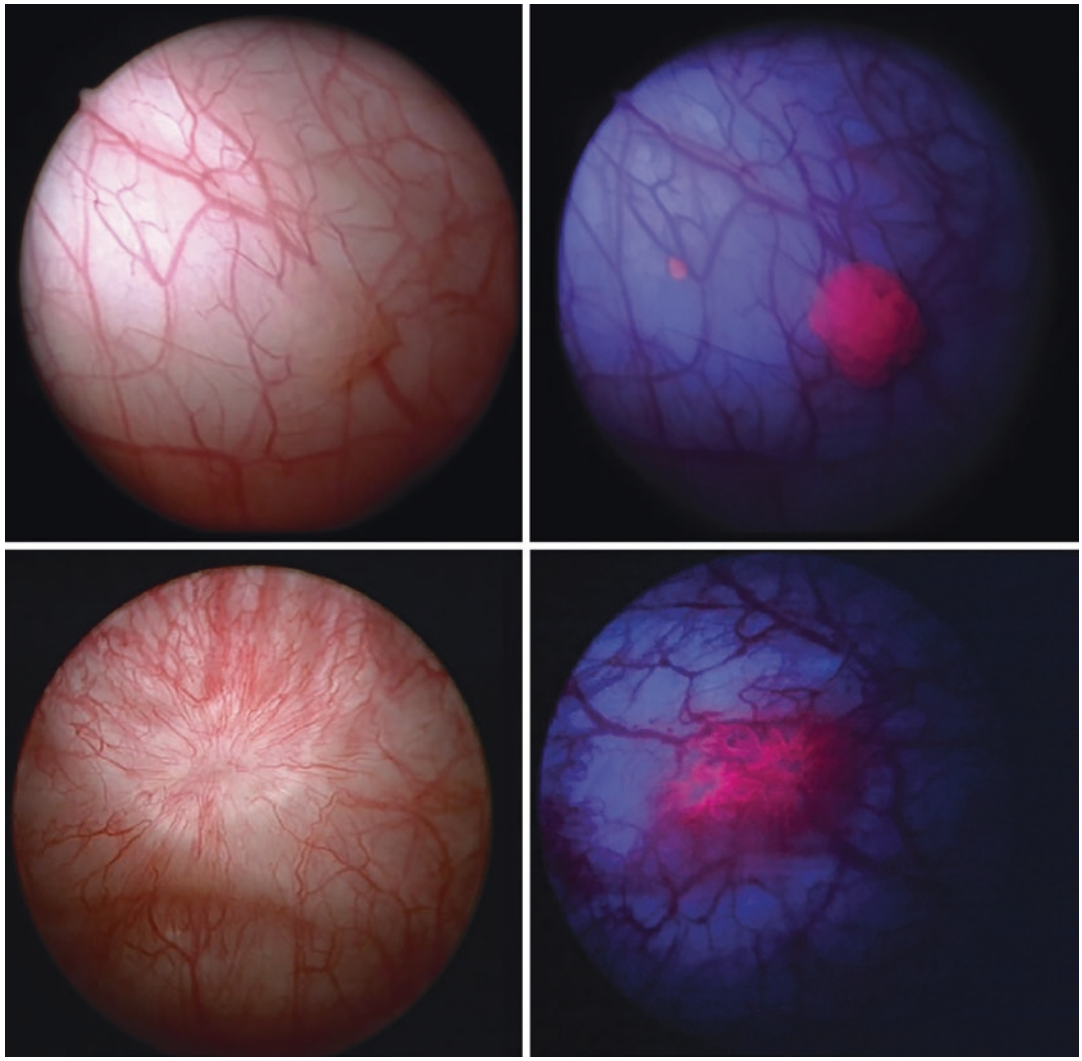

Fig. 7.4 White and corresponding blue light cystoscopies of patients with urothelial carcinoma

tion of urothelial carcinoma, in particular, cis, in a meta-analysis including 1022 patients [24] and prospective randomized trials [25]. No final conclusions can be made on the impact of NBI on recurrence rate and recurrence-free survival. In a prospective randomized trial of the Clinical research office of the Endourological society (CROES), no difference in recurrence rates after 12 months was observed in patients undergoing TURBT for a primary tumor [26]. However, in patients with low-risk tumors, a significant reduction of tumor recurrences by the use of NBI has been reported in this trial [26]. The impact of NBI on progression rates and progression-free survival remains to be determined.

Image1 S

The company Karl Storz (Tuttlingen, Germany) has developed the Storz Professional Image Enhancement system (IMAGE1 S). This is a technique similar to narrow band imaging using visual enhancement of filtered light. The concept is based on the use of four different enhancement/visualization modes. To increase

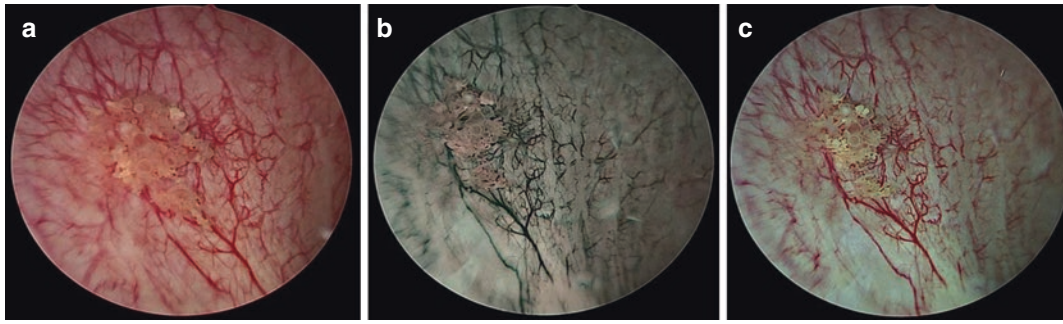

Fig. 7.5 Image1 S (**a**) Clara and Chroma modes combined to enhance brightness and contrast. (**b**) Spectra A mode. (**c**) Spectra B mode

contrast, the modes Spectra A and B use tone shift algorithms (Fig. 7.5b, c). The sharpness of the image is increased by the mode chroma (Fig. 7.5a). Local brightness adaptation is used in the mode clara to improve visibility of darker regions.

The four different modalities can be used according to the specific clinical situation, e.g. the Spectrum B is suggested in the case of interfering factors such as hematuria. The technique is currently in multicenter trial initiated by the Clinical Research Office of the Endourological Society (CROES).

En Bloc Resection

The stepwise resection of papillary tumor has risen significant concerns of tumor cell spillage during TURBT. Whether such a tumor cell spillage is the cause of the high recurrence rate of NMIBC has not been elucidated yet. Performing en bloc resection of tumors aims to reduce the rate of tumor cell spillage during TURBT and potentially allows a better pathologic evaluation of the tumor specimen. The fragmentation of the tumor specimen by a common stepwise resection challenges the performance of the pathologist especially with regard to the subepithelial layer and the exact staging of T1 tumors.

En bloc resection can be performed using different sources of energy, including monopolar/bipolar energy (Fig. 7.6), holmium/thulium lasers, or hybrid techniques (water jet plus monopolar incision). Regardless of the source of energy, the healthy mucosa close surrounding the tumor is incised circumferentially (Fig. 7.6a–c). This is followed by a lifting of the tumor basis within the incision borders (Fig. 7.6d, e) and removal of the whole tumor and the underlying muscle layer (Fig. 7.6e, f). This lifting can be done bluntly or by the use of energy sources for incision of attaching fibers. Using hydrodissection, the tumor basis is lifted by injecting saline under the tumor followed by incision using monopolar energy.

The extraction of the specimen represents a significant challenge of en bloc resection, especially in cases of big tumors. Several techniques have been used to extract the en bloc specimens including graspers, irrigation syringes, and endoscopy retrieval bags.

The optimal technique with regard to reduction of tumor cell spillage has not been defined yet. Several trials have been performed to assess the feasibility of en bloc resection. In summary, these trials have shown that en bloc resection is feasible in selected exophytic tumors. The rate of presence of detrusor muscle in the specimen is high in the majority of studies (up to 96–100% of cases) [27]. En bloc resection does not seem to have a negative impact on resection time [28]. The effect of en bloc resection on rates of recurrence and progression is unclear and is currently investigated in prospective trials such as the Hybrid Blue Study comparing standard TUR-BT with hydrodissection followed by en bloc resection.

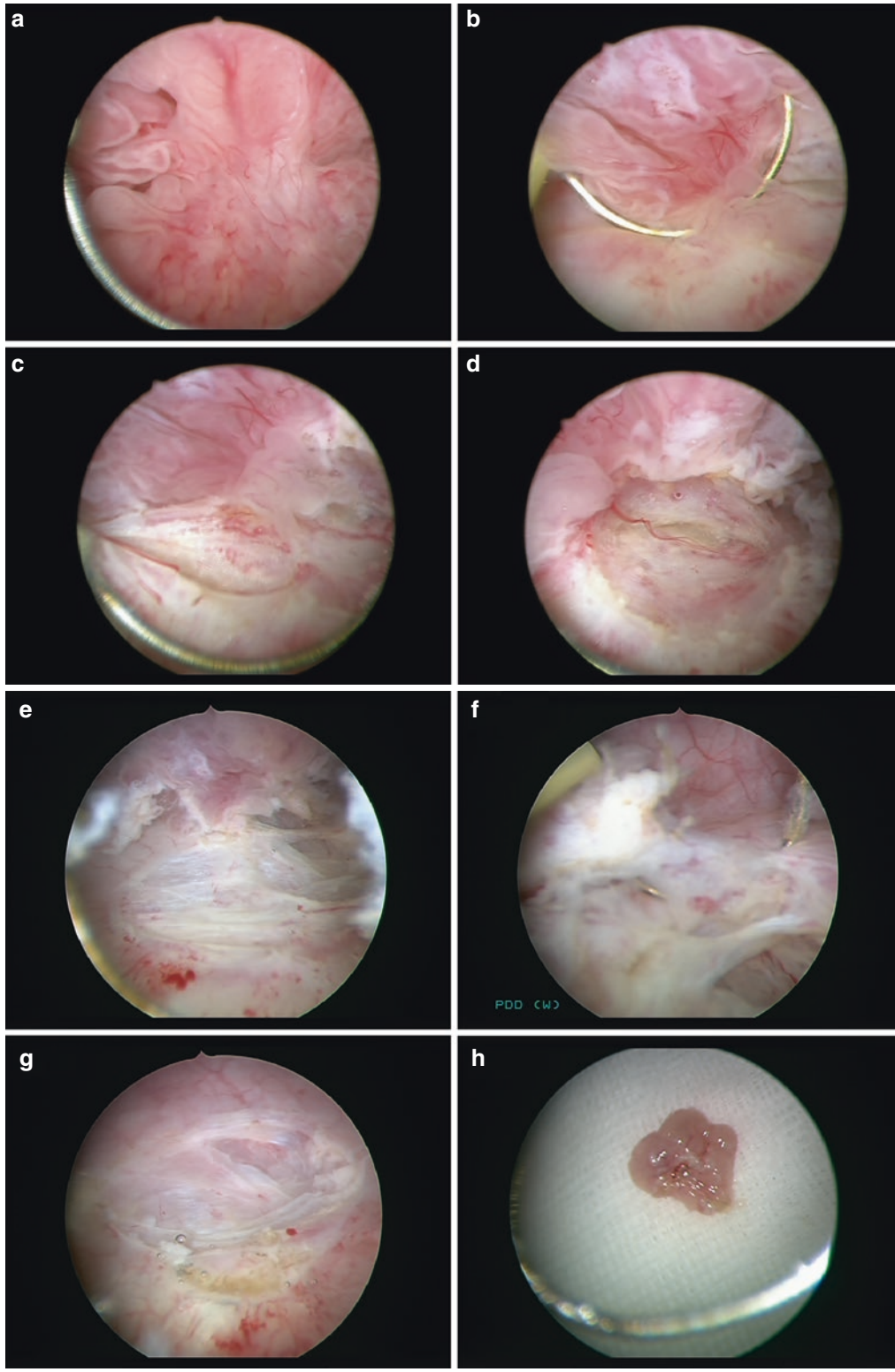

Fig. 7.6 Step-by-step en bloc resection of the tumor shown in Fig. 7.2. The healthy mucosa close surrounding the tumor is incised circumferentially (Fig. 7.5a–c) followed by a lifting of the tumor basis within the incision borders (Fig. 7.5d, e) and removal of the whole tumor and the underlying muscle layer (Fig. 7.5e, f). The resection bed (Fig. 7.5g) displays muscle fibers, and the tumor specimen is complete (Fig. 7.5h)

Handling of Specimens in the OR

Tumor specimen of different locations should be submitted in separately labeled containers to the pathology department. The location should be clearly defined on the pathology requisition form. Deep biopsies should be submitted separately for each location. Sterile gauze pads can be used to catch tissue specimens after removal of the resectoscope. After resection of a large tumor, irrigation syringes may be used to make sure all parts of the tumor are removed before resection of another tumor (to prevent confusion of the specimens of different locations).

Special Circumstances

Tumors at the Anterior Wall

The resection of tumors located at the anterior wall can be facilitated by external suprapubic pressure using the nondominant hand (Fig. 7.7). Alternatively, a nurse or other physician can be asked to apply external pressure on the bladder. If the tumor is hard to reach, the bladder should be further emptied to allow access to the tumor. In tumors located near the bladder dome, care should be taken not to perforate the dome as the proximity to the peritoneum may lead to injury of the bowel.

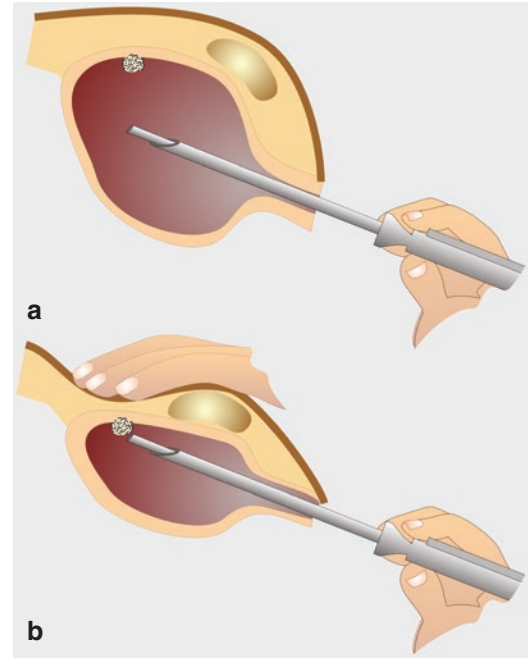

Fig. 7.7 Facilitating resection of anterior wall tumors (**a**) by pressure on the suprapubic area using the nondominant hand (**b**)

Tumors Located near the Ureteral Orifices

In tumors located near the ureteral orifices without involvement of the orifice, care should be taken not to apply excessive coagulation in order to prevent scar formation and obstruction of the orifice. In tumors that require resection of the orifice, a clear cut using a purely cutting current without excessive subsequent coagulation may help to prevent hydronephrosis [29]. Insertion of ureteral stents should be avoided whenever possible due to the high rate of irritative voiding symptoms of patients with stents. In most cases, cystoscopy allows the evaluation of urine flow out of the ureteral orifices after resection. If a clear urine flow out of the orifice is present, no stenting is required. Patients developing symptoms due to ureteral obstruction can be treated by subsequent stent insertion. The oncologic impact of vesicoureteral reflux caused by resection or insertion of a stent has been discussed controversely. Whereas some studies suggest a higher risk for upper tract urothelial carcinoma (UTUC) in patients with reflux, others found no difference of UTUC incidence in patients with and without reflux [30–32].

Tumors Located at the Lateral Wall

The resection of tumors located at the lateral wall is associated with a significant risk of obturator nerve reflex, leading to rapid adduction of the ipsilateral leg and increased risk for perforation and bleeding. In patients with preoperatively known tumors at the lateral wall, general anesthesia should be considered as neuromuscular blockade using muscle relaxants reduces the risk of

obturator nerve reflexes. In patients who receive regional anesthesia, an obturator nerve block can be applied to reduce the risk for obturator nerve stimulation.

Tumors Located at the Bladder Dome

The resection of tumor at the bladder dome can be challenging due to the potential distance of the bladder dome to the resectoscope. This distance can be reduced by emptying the bladder in order to facilitate resection. The close proximity to the peritoneum and bowel should lead to particular attention not to perforate the bladder during resection.

Tumors Located in Bladder Diverticula

Tumors located in bladder diverticula are often difficult to resect. In contrast to a normal bladder wall, diverticula usually do not contain a muscularis propria layer. This absence increases the risk for perforation during TURBT and makes the pathologic evaluation of tumors resected from bladder diverticula challenging. As pathologic staging may not be accurate in these tumors, imaging using cross-sectional techniques is important. In patient with infiltrating tumors, a complete diverticulectomy (consider importance of negative margins at the orifice) or radical cystectomy may provide better oncologic outcome compared to a resection [33].

Management of Common Complications

Although TURBT can be considered as safe procedure with low major complication rates, appropriate management of these complications is essential for patients' safety. The most common complications of TURBT include postoperative bleeding with hematuria, bladder perforation, urinary tract infection, and hydronephrosis.

Bladder Perforation

Heterogenous results have been published on occurrence rates of bladder perforations during TURBT. A prospective trial including 36 patients undergoing TURBT and postoperative cystography reported perforation in more than half of the patients (58.3%) [34]. In the majority of studies, the prevalence of perforations is <5% of patients [35, 36]. The risk of bladder perforations is increased in elderly patients, especially women, with low body mass index [35, 37, 38]. Moreover, the risk of perforation is affected by the tumor size and extent of invasion by the tumor [35]. Tumors located at the lateral wall are associated with an increased risk of obturator nerve reflex, leading to bladder perforation. Bladder perforations may result in tumor cell spillage, peritoneal carcinosis, bleeding, and TUR syndrome. Usually, bladder perforations are extraperitoneal and do not require surgical repair. As soon as a perforation of the bladder is noted by the surgeon, the surgery should be finished as soon as possible and care should be taken to reduce irrigation fluid in order to prevent extravasation of significant amounts of irrigation fluid. In patients with extraperitoneal perforations, the catheter should remain in place for at least 7 days and a cystography should be performed before removing the catheter. Irrigation should be avoided. Moreover, the patient should receive prophylactic antibiotics (such as fluoroquinolones). In the case of a significant amount of extraperitoneal irrigation fluid, placement of drainage should be considered. Intraperitoneal perforations lead to a significant risk of bowel perforations and sepsis. In the case of small intraperitoneal perforations, attempts of conservative management in accordance with the management of extraperitoneal perforations can be considered. In the case of relevant intraperitoneal lesions, laparoscopic or open surgery with bladder repair is necessary. The impact of bladder perforation on the occurrence of extravesical recurrences has been discussed controversely. Results of retrospective series have shown inconsistent effects of perforation on occurrence of extravesical disease [36,

38, 39]. Of note, postoperative instillation therapy has to be avoided in patients with suspected bladder perforation [40].

Bleeding

Relevant bleeding is the most common complication of TURBT [41]. However, transfusion rates are low with series reporting perioperative blood transfusions in 1.0–1.5% of patients [42, 43]. Interestingly, the continuation of antiplatelet or anticoagulant therapy has been reported to have no significant impact on perioperative bleeding in retrospective cohorts [43–45]. Bleeding can be prevented by meticulous coagulation of the resection bed following resection of the tumor. In the case of a postoperative bleeding, the first step is to extract potential clots of the bladder using an irrigation syringe. This can prevent the formation of larger clots. In the case of resections in the area of the bladder neck leading to postoperative bleedings, traction can be applied on the balloon catheter to reduce bleeding. If conservative measures fail and the patient experiences prolonged gross hematuria, presents with formation of significant clots or shows a significant decrease of hemoglobin, the patient should undergo Re-TURBT with coagulation. For patients showing hemodynamic instability due to significant bleeding of the bladder, immediate endoscopy should be performed. Reoperation rates after TURBT are low and have been reported to be in the range of 1–2% [42].

Postoperative Hydronephrosis

In the case of an asymptomatic or mildly symptomatic hydronephrosis after resection of a tumor located near the ureteral orifice, conservative treatment with antiphlogistic drugs (e.g., diclofenac) can be performed. In the case of severe symptoms, infection, or renal failure, insertion of a ureteral stent or nephrostomy is recommended. As discussed above, insertion of a ureteral stent has been discussed critically in the perioperative setting of a TURBT. Therefore, some centers prefer to use a nephrostomy instead.

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8 Single Immediate Intravesical Instillation of Chemotherapy-Rationale and Practical Considerations

Max Burger

What Is the Rationale of Single Immediate Instillation of Chemotherapy?

TURBT is no radical surgery per se. It scatters tumor cells circulating through the bladder despite repeated rinsing; residual cells have been shown to persist and to implant into normal bladder mucosa spurring tumor recurrence at site of implantation [4, 8]. In addition, small tumors can be overlooked by TURBT and may also grow and lead to tumor recurrence (Burger). Both phenomena are thought to be susceptible to immediate intravesical chemotherapy, since it may destroy tumor cells circulating in the wake of TURBT thus preventing implantation, and since it may ablate small residual tumors overlooked [4, 8]. Given these assumptions, timely application of chemotherapy following TURBT and sufficient dwell-time of an adequate dose need to be achieved. Also, limited impact of single immediate instillation has to be suspected in case of greater loads of scattered tumor cells or inherent propensity to develop novel recurrence, i.e., adverse constellations of nonmuscle-invasive bladder cancer, i.e., in multiple, large, and poorly differentiated tumors.

What Is the Current Evidence for the Use of Single Immediate Instillation of Chemotherapy?

Is Single Immediate Instillation of Chemotherapy Effective Per Se?

The effect of single immediate instillation of chemotherapy is level 1a evidence [1]. E.g., Gudjónsson et al. found recurrence rates after some 4 years of 62% with versus 77% in a randomized controlled trial studying some 200 patients with low- to intermediate-risk nonmuscle-invasive bladder cancer ($p = 0.016$) [5]. This has been confirmed by further data. To date, five meta-analyses each comprising at least 1500 patients have assessed single immediate instillation of chemotherapy following TURBT versus TURBT alone; all demonstrated significant reduction of recurrence rate in the single instillation arms [1]. Sylvester et al. recently assessed individual data of over 2000 patients demonstrating significant reduction of recurrence rates after 5 years by 14%, i.e., from 59% in patients without versus 45% in patients with single immediate instillation [9]. The authors report a feasible number-needed-to-treat; seven treatments applied prevented one prevent one recurrence within 5 years.

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Are there any Differences Between Chemotherapeutic Agents?

To date, no randomized clinical trial has been reported; mitomycin C, epirubicin, pirarubicin, and gemcitabine have been assessed with largely comparable effects [1]. In one study by Böhle et al., continuous irrigation with saline for 24 h was used in both the gemcitabine and the control arms; no differences in recurrence rate were found [2]. Great effect of continuous saline irrigation has been discussed. A retrospective analysis of the effect of single immediate instillation of chemotherapy, continuous bladder irrigation with saline or none of these found a benefit for single immediate instillation of chemotherapy, but difference between the two latter [6].

Which Patients Profit Most?

In the trial by Gudjónsson et al., a subgroup analysis found the greatest effect in primary, solitary, and smaller tumors, and significant effect in patients with a European Organization for Research and Treatment of Cancer (EORTC) risk score of 0–2 versus no effect in patients with a risk score of ≥3 [5]. In the meta-analysis by Sylvester, a significant effect was only found in patients with a prior recurrence rate of a maximum 1 per year and those with an EORTC recurrence score < 5 [9]. A recent large randomized controlled trial with over 2000 patients by Bosschieter et al. showed an effect of single immediate instillation also in intermediate- and even high-risk nonmuscle-invasive bladder cancer [3]. The further schemes of instillation therapies did not adhere to more recent guideline recommendations; however, and thus cannot be finally interpreted yet [1]. So, taken together, the EAU guidelines state: "In patients with non-muscle-invasive bladder cancer and a prior low recurrence rate (to one recurrence per year) and in those with an EORTC recurrence score < 5, a single instillation (SI) significantly reduces the recurrence rate compared to transurethral resection of the bladder alone" [1]. The EORTC recurrence score is computed from clinical and histopathological parameters; naturally, on the former can be assessed during TURBT and thus be used for the decision on single immediate chemotherapy instillation. As an orientation, the EORTC attributes a recurrence score of 3 to a number of tumors between 2–7, and also to a tumor size of 3 cm and up, and also to a number of prior recurrences of a maximum 1 [1].

How Is Current Single Immediate Instillation of Chemotherapy Administered?

Firstly, it is important not to administer early instillation, whenever extravasation has to be considered, i.e., in case of perforation during TURBT; cases of severe adverse events have been reported [7]; duration of chemotherapy dwell-time in the bladder is related to adverse events rate. While the optimal dwell-time of chemotherapy within the bladder has not been defined, 1 hour is a duration commonly assessed in respective trials [5]. To assure no overly lengthy duration of chemotherapy dwell-time, the EAU guidelines strongly recommend to give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation [1].

Secondly, propensity of continuous bleeding following TURBT has to be considered, since continuous saline irrigation will likely be required conflicting the idea of single immediate instillation of chemotherapy. So, the EAU guidelines strongly recommend to omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation [1].

Thirdly, all trials on single immediate instillation of chemotherapy have administered the dose at once within 24 hours following TURBT. While the optimal timing has not been defined, instillation likely should be administered within 2 hours [1].

In-a-Nutshell: A Practical Guide on Single Immediate Instillation of Chemotherapy

- When performing TURBT, consider the potential use of single immediate instillation of chemotherapy and assess the patient accordingly for clinical parameter; also refer to the TURBT chapter XY.
- Consider single immediate chemotherapy in patients with a tumor number of a maximum of 7, a tumor size with maximum of 3 cm, and a number of prior tumor recurrences per year of a maximum of 1.
- Assure lack of perforation and lack of propensity of hemorrhage following TURBT, such as insufficient coagulation or persistent hemorrhage despite sufficient coagulation.
- Place an indwelling permanent transurethral catheter; use any model you usually apply.
- Use any chemotherapy agent you are familiar with for intravesical instillation; mitomycin C and epirubicin have been reported most commonly.
- A common schedule is 40 mg of mitomycin C.
- Apply single immediate instillation of chemotherapy within the first 2 hours following TURBT as a single dose via the indwelling catheter; close the catheter by a respective clamp.
- Assure removal of the clamp and unaffected discharge of the chemotherapy after 1 hour.
- Assure lack of lower abdominal complaints in the first 6 hours following TURBT.

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9 Adjuvant Intravesical Therapy: Bacillus Calmette-Guerin

Gautier Marcq and Wassim Kassouf

Introduction

Albert Calmette, a bacteriologist, and Camille Guerin, a veterinarian, were working together at the Pasteur Institute in Lille (France) and discovered Bacillus Calmette-Guerin (BCG) in 1908. They isolated a virulent strain of Mycobacterium bovis from the udder of an infected cow [1]. The demonstration of BCG as a cancer therapy was made by Lloyd Old at the Sloan-Kettering Institute in New York during the 1950s [2]. It was until 1976 that Alvaro Morales, an urologist in Canada, was the first to test topical BCG in the bladder: the first use of intravesical BCG against nonmuscle-invasive bladder cancer (NMIBC) [3].

Since then BCG remains one of the most successful immunotherapy against cancer. The mechanism of BCG still remains unclear, but involves cellular immune response through T cells, macrophages, and complex cytokines cascade.

From what we know, BCG mechanisms can be divided into a direct antitumoral effect and an immune response-mediated antitumoral effect [4]. Briefly, fibronectin allows BCG to attach to urothelial cells and enters the cells via macropinocytosis (i.e., bladder cancer cells internalize BCG) which depends on GTPases Rac1 and Cdc42, upstream of Pak1 [5]. Oncogenic aberrations, deletion of PTEN, or activating mutation in the RAS family of oncogenes, can modify the BCG uptake in cell lines such as PC3, HeLa, MCF-7, UM-UC-3, and MGHU4 [6, 7]. Once in the cells, BCG has a direct cytotoxic effect [8]. The immune system is then activated through antigen presentation and a release of cytokines by the bladder cancer cell. This step requires the Major Histocompatibility Complex or MHC II, intercellular adhesion molecule (ICAM-1), and secretion of IL-6, IL-8, GM-CSF, TNF-α to present antigen to the CD4 lymphocyte. This mechanism recruits additional immune cells such as granulocytes, more CD4+ T cells, CD8+ T cells, NK cells, and macrophages. Cytokines (such as IL-1, IL-2, IL-6, IL-8, IL-10, 1L-12, tumor necrosis factor-alpha, and interferon) are secreted, which recruit cytotoxic cells (natural killer cells, cytotoxic T cells, neutrophils, and macrophages) that specifically target the tumor cells. These cytotoxic cells are then directed against bladder cancer cells and help to prevent recurrences.

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Indications

Oncological Outcomes: Recurrence

BCG is currently recommended by international guidelines for intermediate- and high-risk NMIBC in order to decrease the risk of tumor recurrence and progression [9–12].

BCG decreases recurrences at 3 years by 70% compared to TURBT alone in a meta-analysis pooling 8 RCT [13]. A different group reported another meta-analysis with data from six RCT [14]. Results were assessed with a population of 585 patients. The weighted mean log hazard ratio for the first recurrence was −0.83 (95CI [−0.57; −1.08], $p < 0.001$). The authors reported a 56% reduction of recurrences in the BCG-treated group. Further 4 meta-analysis pooling data from RCT comparing BCG to other intravesical therapies reported that BCG was superior to TURBT alone (without additional intravescial therapies) regarding tumor recurrence [15–18].

Adjuvant instillations are keys in NMIBC management. Over the years, many studies investigated and compared different agents and regimens. A meta-analysis using individual patients data (IPD) from 9 trials included 2820 patients to compare the efficacy between BCG and mitomycin C (MMC) [15]. They reported no difference in the time to first recurrence ($p = 0.09$) between BCG and MMC; however, in the trials with BCG maintenance, the use of BCG was associated with a 32% reduction in risk of recurrence compared to MMC ($p < 0.0001$) [15]. Interestingly, there was a 28% recurrence risk increase ($p = 0.006$) with the use of BCG without maintenance.

BCG was also proved to decrease recurrences when compared to epirubicin in a European Organization for Research and Treatment of Cancer (EORTC) multicenter RCT 30911 [19]. This trial included 957 patients with intermediate- or high-risk stage Ta T1 NMIBC and excluded CIS patients. Patients were randomized to receive six weekly instillations of epirubicin, BCG, or BCG plus isoniazid followed by three weekly maintenance instillations at months 3, 6, 12, 18, 24, 30, and 36. After a median follow-up of 9.2 years, the two BCG arms had significantly a longer time to first recurrence ($p < 0.001$) compared with epirubicin.

A meta-analysis by Shang et al. included 1111 patients from 5 trials, confirmed these findings. A total of 35.5% (195/549) in the BCG group and 51.4% (289/562) in the epirubicin group had tumor recurrence ($p < 0.05$). Furthermore, the members of the Urothelial Cancer Group of the Nordic Association of Urology reported a RCT with 250 primary T1 G2-G3 NMIBC patients [20]. They randomized patients between BCG and combination of epirubicin and interferon-alpha2b. At 24 months, the BCG-treated patients had significantly less recurrences ($p = 0.012$).

Oncological Outcomes: Progression

Regarding this risk of progression, two meta-analyses reported specifically data on progression for NMIBC patients who received BCG treatment compared to other regimens [21, 22]. First, Sylvester et al. included 4863 patients from 24 trials with progression information [22]. They reported a reduction of 27% in the odds of progression with BCG if BCG maintenance is used (OR 0.73, $p = 0.001$) when comparing transurethral resection plus intravesical BCG to resection alone or resection plus another treatment other than BCG. In addition, no statistically significant difference was found between treatments for overall survival or death due to bladder cancer [22]. Second, Böhle et al. reported a pooled analysis of 9 individual studies with 1277 patients were treated with BCG and 1133 with MMC [21]. They found no statistically significant difference in risk of progression between the BCG- and MMC-treated groups (combined OR = 0.77; 95% CI 0.57–1.03; $p = 0.081$) when pooling the results of all studies with or without BCG maintenance. However, in the subgroup with BCG maintenance, they reported a statistically significant superiority of BCG over MMC (OR = 0.66; 95%CI [0.47; 0.94], $p = 0.02$). They did not analyze the risk of death. Third, Malmström et al. compared BCG to MMC with pooled 2820 individual patients data (IPD) analysis from 9 RCT

[15]. IPD analyses are considered statistically stronger than meta-analysis [23]. After a median follow-up of 4.4 years, the authors reported an overall 12% progression rate in NMIBC patients with about 13% of patients with concomitant CIS. In the subset of 1880 patients for whom data on progression were available, they found no significant differences even in the subgroup of patients who underwent maintenance.

The EORTC trial 30,911, detailed in the above section, reported no difference on progression when comparing BCG or BCG plus isoniazid (with 3 years maintenance) to epirubicin but reported a longer time to first recurrence ($p < 0.001$), less distant metastases ($p = 0.046$), better overall survival ($p = 0.023$), and better disease-specific survival ($p = 0.026$) in the BCG groups after a median follow-up of 9.2 years [19]. However in this study, it is important to highlight that (i) CIS patients were excluded, (ii) only about 20 progressions were reported in the 3 arms which decreased the statistical power of the analysis, and (iii) a second-look TURBT was not routinely done where some patients may have been upstaged to T2 disease rather than true progression.

To conclude, BCG is superior to TURBT alone or TURBT followed by intravesical therapies such as MMC, epirubicin, or epirubicin and interferon-alpha2b to decrease recurrences. Compared with TURBT alone, BCG with maintenance decreases progression of disease in intermediate- and high-risk NMIBC. Inconsistent results regarding progression comparing BCG with intravesical chemotherapy can be related to differences in patient selection, follow-up, and adherence to BCG maintenance schedule.

BCG for Carcinoma In Situ

For carcinoma in situ (CIS), intravesical BCG significantly reduces the risk of short- and long-term treatment failure compared with intravesical chemotherapy (MMC, epirubicin, adriamycin, or sequential MMC/Adriamycin) in a large meta-analysis pooling 9 RCT with 700 patients [24]. After a median follow-up of 3.6 years, authors reported a reduction of 59% in the odds of treatment failure with BCG and a 26% reduction in progression risk in favor of BCG. Other studies confirmed these results and also reported that adding MMC to BCG did not led to improved oncological outcomes of patients with CIS [24, 25]. All of the data above strongly support the systematic use of BCG for CIS patients.

Factors Influencing BCG Outcomes

BCG Strain

Different strains are available on the market. In 2002, the EORTC group performed a meta-analysis including all randomized trials in patients with superficial bladder cancer (stages Ta, T1, or carcinoma in situ) that compared transurethral resection plus intravesical BCG to either resection alone, resection plus intravesical chemotherapy or resection plus immunotherapy other than BCG [22]. From the 24 trials included, 20 trials used maintenance BCG. After a median follow-up of 2.5 years, their analysis showed no differences across 5 different strains of BCG: Tice, Connaught, Pasteur, RIVM, and A. Frappier. A prospective, open label, randomized, and comparative study including 129 pTa, pT1, and pTis NMIBC patients found no difference in recurrence-free survival between the Tokyo and the Connaught strains after a median follow-up of 2.4 years [26]. The latter study did not use any BCG maintenance. Despite the randomization in this study, there were significantly more CIS patients allocated to the Tokyo group. In addition, this study had to end prematurely since the manufacturer of BCG Connaught stops the production while the study was still recruiting.

Recently, a prospective randomized single-institution trial with 142 high-risk NMIBC patients aimed to compare Connaught and Tice strains [27]. After a median follow-up of 4 years, authors reported that treatment with Connaught strains conferred a better recurrence-free survival at 5 years compared with BCG Tice ($p = 0.0108$) [27]. Similarly, no BCG maintenance was used after the BCG induction courses. Using flow

cytometry, the authors demonstrated that BCG Connaught induced stronger T-helper cell 1-based responses, greater priming of BCG-specific CD8+ T cells, and more robust T-cell recruitment to the bladder compared with BCG Tice.

Gender

Although BCG is efficacious in women, studies reported controversial results regarding impact of gender on BCG efficacy. Two large multicenter retrospective series of 1021 patients (with multiple or recurrent high-grade Ta, T1, and/or CIS) [28] and 2451 patients (T1 high-grade only) [29] did not find gender to be associated with recurrence or progression on multivariate analysis. Another study from the SEER database with 7410 high-grade NMIBC patients reported no influence of female gender on recurrence but only on progression at 2, 5, and 10 years (HR = 1.23, 95CI [1.12;1.36], $p < 0.01$) [30]. In contrast, the CUETO group pooled the data from 3 randomized control trials and analyzed the data of 1062 patients [31]. They reported that female gender was associated with an increased risk of recurrence (HR = 1.7, 95CI [1.3; 2.3], p = 0.0006) but not progression after a follow-up of 5.7 years. Similar results were also found in a multicenter retrospective series of 916 patients with high-grade NMIBC [32]. However, in another single-institution retrospective analysis of 146 patients with primary stage T1 high-grade NMIBC, female gender was associated with an increased rate of recurrence, progression, and death from bladder cancer [33].

Age

Regarding the effect of patient age, a report from the SEER database including 23,932 NMIBC patients showed that patients older than 80 years old are less likely to receive BCG (HR 0.88, 95CI [0.79;0.98]) for patients from 80 to 84 years old and HR 0.51, 95CI [0.45;58] for those ≥85 y.o.0 [34]. In a multivariable analysis after adjusting for sex, race, grade, stage, comorbidities, and socioeconomic status, age was predictive of disease-specific survival and overall survival. Moreover, BCG may be less effective in the elderly [35]. In one of the EORTC study with 957 patients with intermediate- or high-risk Ta T1, Oddens reported that patients older than 70 years old had a shorter time to progression ($p = 0.028$), and NMIBC-specific survival ($p = 0.049$) after adjustment for EORTC risk scores in the multivariate analysis. Moreover, to assess the impact of age on the response to BCG, a team analyzed the data from a national phase II multicenter trial for BCG plus IFN-α intravesical therapy for superficial bladder cancer ($n = 1106$ patients) [36]. They reported a 22% difference in cancer-free survival rates at a median follow-up of 24 months in patients 61–70 years old versus those older than 80 years (61% vs. 39%, $p = 0.0002$). The log rank test for trend between all age groups was significant ($p = 0.0342$). Aging is related to a significant reduction in BCG efficacy and these findings are recurrent among trials.

Smoking

Only retrospective cohorts have looked specifically on the effect of smoking during BCG therapy [37–39]. The largest study included primary NMIBC patients across 16 centers; a total of 2043 patients were used for the analysis with a median follow-up of 4 years [37]. In multivariable analysis, smoking status was associated with the cumulative incidence of disease progression ($p = 0.003$). Among patients with a smoking history (current or former), cumulative smoking exposure was associated with disease recurrence ($p < 0.001$), progression ($p < 0.001$), and overall survival ($p < 0.001$) in multivariable analyses that adjusted for age, gender, stage, grade, multifocality, tumor size, and the use of intravesical therapy. However, smoking cessation over 10 years reduced significantly the risk of disease recurrence (HR = 0.66; 95CI [0.52; 0.84], $p < 0.001$) and progression (HR = 0.42; 95CI [0.22; 0.83], $p = 0.036$). As such, all bladder cancer patients should be counseled for smoking cessation.

Genetic Variations

Genetic variation based on genomic studies may be associated with BCG response [40].

Genes related to BCG response were mainly involved in single-nucleotide polymorphisms of inflammatory genes such as IL-6 (−174 C/C), TNF-α (rs1799964 C/C), IL-8 (rs4073 A/A), or copy number variations such as loss of heterozygosity (LOH) in the IFN-a (chromosome 9p21) [41], and gene methylations such as methylation of tumor suppressor genes (STK11, MSH6, BRCA1, PAX5A, MGMT, and CDH13) [42]. Interestingly, some authors reported a nomogram of changes in urinary cytokine levels to predict patient response to BCG based on a prospective clinical trial with 130 patients [43]. This nomogram called CyPRIT was constructed using urinary levels of nine inducible cytokines (IL-2, IL-8, IL-6, IL-1ra, IL-10, IL-12 [p70], IL-12[p40], TRAIL, and TNF-α) predicted the likelihood of recurrence with 85.5% accuracy (95% CI 77.9–93.1%). Further validation and cost effectiveness studies are needed.

BCG Administration: Pre-, Peri-, and Post-Instillation Management

BCG instillations are usually performed 2–4 weeks after TURBT. No data are available regarding the optimal timing of the first BCG instillation; however, BCG instillation too early after TURBT will increase risk of systemic adverse effects.

BCG Contraindications

Leukocyturia, nonvisible hematuria, or asymptomatic bacteriuria are not contraindications for BCG therapy [44, 45]. Absolute contraindications for BCG administration are: BCG instillation during the first 2 weeks after TURBT, macroscopic hematuria, symptomatic UTI, pregnancy/lactation, hypersensitivity to BCG, traumatic catheterization (blood on the foley catheter or iatrogenic bleeding from the urethra), and active tuberculosis [9–12].

Immunosuppression is a relative contraindication. Some authors have reported successful and safe BCG therapy in renal transplant patients, lymphoma or chronic lymphocytic leukemia patients, or patients receiving chronic steroids (oral or inhaled) [46–48]. However, some authors reported cases of TB or BCG sepsis reactivation in immunocompromised patients [49, 50]. Herr et al. reported retrospective results of BCG therapy in 45 immunosuppressed patients with high-grade NMIBCs (including 12 patients with organ transplants) [51]. A total of 9 out of 12 transplant patients and 32 out of 33 other immunosuppressed patients (under chemotherapy for another cancer or under steroids) responded completely to BCG after a 40 months median follow-up. The role prophylactic antituberculosis therapy in these patients is not known.

BCG Schedule

Induction BCG is performed as Morales et al. described it in 1976: a weekly instillation for a 6-weeks period. Based on the randomized trial by Lamm et al., BCG maintenance is strongly recommended to improve oncological outcomes [52]. This trial included patients with intermediate- and high-risks NMIBCs who underwent induction BCG. Three months after induction, 550 patients were randomized to receive BCG maintenance or not. Maintenance therapy consisted of intravesical BCG each week for 3 weeks given 3, 6, 12, 18, 24, 30, and 36 months from initiation of induction therapy. After a median of 8 years follow-up, the estimated median recurrence-free survival was 35.7 months 95CI [25.1; 56.8] in the control arm and 76.8 months CI95 [64.3; 93.2] in the maintenance arm ($p < 0.0001$). Currently, the recommended BCG maintenance schedule is still the one defined by Lamm et al.

EORTC 30962 trial is a prospective, randomized trial comparing full-dose versus 1/3-dose BCG and 1-year versus 3-year maintenance BCG in 1355 patients with intermediate- and high-risk NMIBC [53]. In high-risk NMIBC, full-dose

BCG with 3 years of maintenance yielded optimal oncological outcomes. For intermediate- risk disease, there was no difference in recurrence-free survival between 1-year versus 3-year maintenance with full-dose BCG.

As such, for intermediate patients, 1-year BCG maintenance is recommended. Details about dose reduction are explained in a dedicated paragraph below. Grimm et al recently reported the NIMBUS trial results: a phase III randomized study with HG, recurrent or primary NMIBC in the BCG-naïve setting (including CIS patients) [54]. The study compared standard Lamm protocol versus a reduced frequency BCG therapy, in which induction was delivered with once-weekly BCG instillations at weeks 1, 2 and 6, and maintenance was delivered with single instillations at weeks 1 and 3 of months 3, 6 and 12. This trial was stopped early due to an inferior efficacy of the reduced schedule. After a median follow-up of 12 months, the authors reported a relative risk reduction for recurrence of 60% favoring the Lamm protocol.

BCG Dose

BCG standard full dose depends on the strain used: BCG Connaught full dose is 10^9 unit forming colony (UFC) (reconstituted dose is 81 mg), BCG Pasteur is 10^9 UFC (150 mg), BCG Tokyo is 80 mg, BCG Danish 10^9 UFC (120 mg), BCG Oncotice is 5.10^8UFC (about 50 mg), and BCG RVIM is also about 5.10^8 UFC [55]. Proper reconstitution is important to insure proper dose delivery [56].

In order to find an optimal dose-response efficacy of BCG treatment, many studies have questioned the BCG full dose. In a prospective randomized trial, the CUETO group compared full dose (81 mg) versus one-third dose of BCG Connaught (27 mg) for NMIBC patients (Ta,T1 or Tis) [57, 58]. After a median follow-up of 61 months, the recurrence rates between the two groups were similar after adjusting for grade and CIS. However, for patients with multifocal tumors, the standard dose was more effective against recurrences ($p = 0.0151$) and progression ($p = 0.048$) than the reduced dose. The reduced dose group had significantly less side effects (absence of local toxicity in 45% vs. 33%, and systemic toxicity in 84% vs. 68% of patients) and less treatment dropout rates (9% vs. 4%).

The previously mentioned EORTC 30962 trial showed no significant differences in toxicity between one-third dose and full dose; however, full dose for 3 years had improved recurrence-free survival compared with one-third dose for 1 year of BCG maintenance (HR = 0.75; 95CI [0.59–0.94]; $p = 0.01$) [53, 59].

The CUETO group performed a multicenter, randomized prospective trial comparing three regimens; low-dose BCG (1/3 of dose, 27 mg) versus very low-dose BCG (1/6 of dose 13.5 mg) versus MMC (30 mg) for intermediate-risk NMIBC [60]. They found a significantly longer disease-free rate in favor of BCG one-third dose versus MMC ($p = 0.006$) and no significant difference between the two BCG groups. No statistically significant difference among the three groups was found regarding disease progression.

For intermediate-risk NMIBC, a 1-year schedule at full dose is recommended; for high risk patients, a 3-year schedule at full dose is recommended [9–12]. A reduced dose can be offered in patients who developed local toxicity to decrease BCG drop out. The reduced dose of choice should be one-third of the dose since one- sixth of the dose does not decrease side effect further and may be associated with lower efficacy.

Peri-Instillation Medical Therapy

A randomized controlled trial compared 200 mg ofloxacin versus placebo following each instillation of induction BCG therapy in 115 patients with primary or recurrent NMIBC (Ta/T1, CIS, G1-G3) [61]. The first and second doses of ofloxacin (200 mg) were given 6 hours and 10–12 hours (or in early next morning) post-BCG instillations. The study reported that the use of prophylactic ofloxacin decreased the percent of patients with at least 1 class II adverse effect from 83.3% to 61.1% ($p = 0.017$). The percent of patients with class III adverse effect also decreased in the ofloxacin treated group from 75.9% to 54.4% during instillations 1–9 ($p = 0.019$). The use of ofloxacin did not impact recurrence rate; however, more patient in the pla-

cebo group did not have the full BCG induction. The effect of long-term use of ofloxacin on BCG efficacy needs further evaluation.

The use of prophylactic isoniazid does not reduce the side effects of BCG. A phase III multicenter trial randomized 957 patients with Ta and T1 NMIBC (excluding Tis) between 3 groups: epirubicin, BCG, or BCG plus isoniazid (300 mg of isoniazid given orally the day before, same day, and day after instillation) [62]. While BCG outperformed epirubicin, the addition of isoniazid did not reduce local or systemic side effects.

The use of anticholinergic may help with bladder spasms. If the anticholinergic fails, premedication with Percocet 2 tablets (oxycodone 5 mg – acetaminophen 325 mg) and 10 mg of valium about 1 hour prior to each instillation treatment may be considered [63].

BCG Instillation and Dwell Time

An infection should be ruled out by history, physical examination, and a measure of temperature. Proper manipulation and care is required while manipulating BCG. Bleaching toilets are mandatory for patients after voiding for up to 6 h postinstillation. Male patients also need to be aware to wear a condom during sexual intercourse when receiving BCG.

The SIU-ICUD reviewed the optimal way for BCG administration [63]. First, an atraumatic catheter placement is mandatory (i.e., without observing blood or severe pain). In case of traumatic placement or severe pain, instillation should not be administered. In case of difficulty of catheter placement due to a suspected stricture, a urethral dilatation should be avoided during instillation. Second, BCG should be instilled with low pressure, ideally dripped under gravity alone.

The dwell time used is 2 hours which is the same dwell time described in 1976 [3]. Only one retrospective study reported results with modification of the dwell time [64]. In 51 patients with pronounced BCG side effects, the dwell time was reduced to ≤30 minutes. Decreasing dwell time significantly reduced rates of fever, chills, dysuria whereas urinary frequency and hematuria were not affected. The authors did not report any analysis on oncological outcomes. They only provided similar complete response rate at 8 months.

In order to increase adherence to the BCG protocol, the SIU-ICUD reviewed tips and tricks for patient management based on expert opinion [63]:

- To help patients who have trouble to maintain BCG for the appropriate dwell time, they should be advised to avoid caffeine and decrease fluid intake before the instillation. However, after the appropriate dwell time and the first postinstillation void, patients are encouraged to increase fluids intake.
- If patient have a small bladder capacity, a split-dosing can be used. For example, half of BCG dose can be instilled for half of the time then the bladder is emptied and the process is repeated with the remaining half dose and half dwell time. However, there is no available data regarding the impact on oncological outcomes of this method; the BCG dose delivered to the bladder might differ from the regular administration.
- If patient reported pain or spasticity during instillation, the use of 40 cc of 2% lidocaine can be mixed with 4 cc of sodium bicarbonate 8.4% instilled 10 to 15 minutes prior to BCG can be considered.

Management of Side Effects

BCG Side Effects Rate

Studies comparing intravesical chemotherapy versus BCG reported a better tolerance profile with the intravesical chemotherapy groups [15, 19, 22, 65]. Majority of local and systemic side effects occur at the time of the induction period and within the first 6 months of maintenance [59, 66]. A multicenter phase III trial reported that about 20% patients will stop BCG due to side effects [66]. In the same study, 15% stopped due to local BCG side effect such as cystitis or pain. Systemic BCG side effect (fever, malaise) was the related cause of BCG drop-out in 9%. Finally, after 6 months of maintenance side effects seem to decrease [66, 67].

Side effects are the main reason of the poor adherence to the full 3-years course of BCG maintenance. Earlier series revealed that around 16 to 19% of patients are able to finish the full BCG maintenance course [52, 68]. For example, in the Lamm trial, only 16% of patients received all of the 8 scheduled maintenance courses over 3 years [52]. However, this does not reflect our current practice as the majority of patients will complete BCG maintenance. Early recognition of side effects and their management improves BCG adhesion throughout the entire maintenance schedule. The EORTC 30962 trial more recently reported much better tolerability of BCG among their cohort of patients [53, 59]. In this trial, 62% (420/680) patients allocated in the 1-year arm of maintenance completed 12 months of treatment and 36% (246/675) patients allocated in the 3-year arm of maintenance completed all 36 months but most of BCG drop out patients were due to recurrence or progression and not side effects. In fact, only about 8% (n = 103) of patients stopped BCG maintenance due to local or systemic side effects [59].

BCG Local Side Effects

The very first BCG instillations are usually well tolerated. The main reported local side effects are frequency, urgency, and dysuria beginning shortly after the first 2-hour void that may worsen within 12 hours. Symptoms will resolve by 24 hours among most patients. Symptoms after every instillation may become worse and last longer than previous instillations. For example, about 50% of the patients complained of dysuria after first instillation versus 80% with subsequent instillations [69].

Asymptomatic granulomatous prostatitis occurs in about 40% of all local side effects cases and is mostly found after TRUS biopsy or TURP for BPH. There is no specific treatment for this side effect since no symptoms are usually reported [70]. The incidence rate of symptomatic prostatitis is much lower as this remains a rare side effect and may lead to systemic symptoms. Management for symptomatic prostatitis is reported in Table 9.1.

Table 9.1 Management options for side effects associated with intravesical Bacillus Calmette-Guérin (BCG)

Side effect type	Grade	Treatment/Comments
Management options for local side effects (modified from International Bladder Cancer Group)		
Symptoms of cystitis	1–2	Phenazopyridine, propantheline bromide, or nonsteroidal anti-inflammatory drugs (NSAIDs)
		If symptoms improve within a few days: continue instillations
		If symptoms persist or worsen: (a) Postpone the instillation (b) Perform a urine culture (c) Start empirical antibiotic treatment
		If symptoms persist even with antibiotic treatment: (a) if positive culture: adjust antibiotic treatment according to sensitivity (b) if negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary)
		If symptoms persist: antituberculosis drugs + corticosteroids.
		If no response to treatment and/or contracted bladder: radical cystectomy.
Hematuria	1–2	Perform urine culture to exclude hemorrhagic cystitis, if other symptoms present.
		If hematuria persists, perform cystoscopy to evaluate presence of bladder tumor.
Symptomatic granulomatous prostatitis	>2	Perform urine culture.
		Quinolones.
		If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for 3 months.
		Cessation of intravesical therapy.
Epididymo-orchitis	>2	Perform urine culture and administer quinolones.
		Cessation of intravesical therapy.
		Orchiectomy if abscess or no response to treatment.

Table 9.1 (continued)

Side effect type	Grade	Treatment/Comments
Management options for systemic side effects		
Infection-like		
General malaise, fever	1	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	≥2	Rare complication and considered autoimmune reaction.
		Arthralgia: treatment with NSAIDs.
		Arthritis: NSAIDs.
		If no/partial response, proceed to corticosteroids, high-dose quinolones, or antituberculosis drugs
Persistent high-grade fever (>38.5 °C for >48 h)	>2	Permanent discontinuation of BCG instillations.
		Immediate evaluation: urine culture, blood tests, chest X-ray.
		Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
		Consultation with an infectious diseases specialist.
BCG sepsis	4	Prevention: initiate BCG at least 2 weeks post-transurethral resection of the bladder (if no signs and symptoms of hematuria).
		Cessation of BCG.
		For severe infection: High-dose quinolones or rifampin 600 mg PO daily, isoniazid 300 mg PO daily, pyridoxine 50 mg PO daily, ethambutol 1200 mg PO daily for 6 months (except ethambutol 2 months only). Early, high-dose corticosteroids as long as symptoms persist. Consider an empirical nonspecific antibiotic to cover Gram-negative bacteria and/or *Enterococcus*.
Noninfection-like		
Allergic reactions	1–2 up to 3–4	Antihistamines and anti-inflammatory agents.
		Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
		Delay therapy until reactions resolve.

Table modified and adapted from EAU guidelines [11]

The duration of cystitis is usually from 2 to 48 hours but can last from 48 hours to 7 days in about a third of patients or even more than 7 days in about 12% of patients [68]. First line treatments of cystitis are phenazopyridine, propantheline bromide, or nonsteroidal anti-inflammatory drugs (NSAIDs) [63]. In case of severe cystitis with poor response to first line treatment fluoroquinolones (for a 3 to 12 weeks duration) or oral isoniazid are therapies of choice [63]. Patients with severe cystitis can also be treated with oral steroid doses such as prednisone starting at 20 mg daily for 3 weeks with a 3-week taper. Higher doses can be used in very troublesome cases [71, 72].

In addition to local side effects, there are also optical changes into the bladder. Some granulomas can be seen generally up to 6-weeks postinstillation but may require 6 months or more to disappear after the therapy ends [73, 74]. These lesions may resolve themselves after longer follow-up and do not require specific treatment.

The managements of local and systemic side effects are reviewed in Table 9.1. Based on World Health Organization recommendations for grading the toxic effects of drugs as a guide, some authors reported a grading applied to BCG therapy [75]:

- *Grade 1*: Moderate and <48 h (usually requires no modification of BCG therapy)
  Burning, frequency, hematuria, fever
- *Grade 2*: Severe and/or >48 h (suspension of BCG instillations until resolution of symptoms)
- *Grade 3*: Local, regional, systemic, and immunoallergic (suspension of BCG instillations until resolution of symptoms)
  Skin rashes, joint pain, and rheumatoid arthritis with or without ocular involvement
- *Grade 4*: Systemic BCG reactions (cessation of BCG therapy required).
  Multiple organ failure: no bacteriological evidence of BCG is necessary to start treatment

This grading system allows to easily stratifying patient risk and subsequent patient management.

BCG Systemic Side Effects

Regarding systemic side effect of BCG, they can be divided into infection-like and noninfection-like (Table 9.1).

BCG infection is a rare entity that generally occurs just after bladder instillation and has usually diurnal pattern (i.e., in the early evenings) following the cortisol cycle. Noninfection-like systemic side effects do not have any diurnal pattern.

Grade 1 systemic side effect (less than 48 h) can be overcome with the use of a NSAIDs before the next BCG instillation and/or reduced BCG dose [63]. BCG sepsis is defined by the presence of skin mottling, chills, rigors, high temperatures (over 39 °C); hypotension and severe sepsis can occur in worse cases scenario. Sepsis related to BCG is a rare entity since the reported incidence is less than 0.5% of all BCG-related side effects; however, some cases may be fatal [76–78].

For systemic side effects with over grade 2 complications (more than 48 hours persistent symptoms) appropriate measure should be taken promptly including fluid resuscitation, antipyretics, anti-TB, antibiotics, and systemic steroids [63]. Antibiotic treatment of choice is rifampin 600 mg PO daily, isoniazid 300 mg PO daily, pyridoxine 50 mg PO daily, ethambutol 1200 mg PO daily. Ethambutol can be stopped after 2 months while the rest of the drugs continue for a total of 6 months. Systemic steroids treatment with prednisolone 40 mg IV daily can be administered in case of severe sepsis and tapered over a 2- to 3-week period after the sepsis has resolved.

Noninfection-like systemic side effects are usually related to immune hypersensitivity such as arthralgia and skin rash [9–11]. Some authors have also reported Reiter's syndrome that includes urethritis, arthritis, conjunctivitis associated with BCG therapy or even grave anaphylactic reactions [76, 79, 80]. Such grave side effect requires BCG termination and steroid therapy.

Defining and Evaluating Recurrence

Definitions of recurrence after or during BCG courses have evolved with time (Table 9.2). An expert agreement has been reported to allow consensual definition for clinical and research practices [81, 82].

Table 9.2 Terminology for BCG-related oncological outcomes

Stratification of BCG failure	
Term	Definitions
BCG-refractory	High-grade disease progression after BCG induction cycle (at 3 months)
	Persistent of high-grade or progression (at 6 months) following: Two induction cycles or An induction cycle and a 3-week maintenance
	CIS at 3 months is not considered treatment failure and re-evaluate at 6 months
BCG-relapsing	No disease at 6 months with recurrence thereafter
Early relapse	Relapse occurring less than 12 months from last BCG exposure
Late relapse	Relapse occurring more than 12 months from last BCG exposure
BCG-unresponsive	Persistent or recurrent CIS within 12 months of completion of adequate BCG therapy Recurrent HG Ta/T1 within 6 months of adequate BCG therapy Persistent or new T1HG disease at first evaluation (3 months) following BCG induction Adequate BCG during the described period above: at least 5 of 6 induction doses and at least 2 of 3 maintenance doses
BCG-intolerant	Unable to complete induction therapy due to severe symptoms

aThe delay for unresponsive is currently challenged and for clinical trials sponsors have some flexibility in the use of 6 and 12 months to define BCG-unresponsive NMIBC. For more information: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM529600.pdf

Herr and Dalbagni described BCG-refractory NMIBC as a progressive disease after a single induction cycle at 3 month or persistent or progressive disease after two induction cycles or an induction cycle and a 3-week maintenance dose (at 6 months) [83]. More recently, the International Bladder Cancer Group added to the previous definition a notion of BCG exposure (i.e., adequate exposure to the number of instillations) [81]. They concluded that patients should have at least five of six induction doses and at least two of three maintenance doses.

BCG relapsing is a term dedicated to patients with a complete response at 6 months who underwent recurrences thereafter. BCG relapsing patients have a better prognostic compared to BCG refractory patients [84]. However, not all BCG relapsing patients share comparable outcomes. Gallagher et al. reported the impact of BCG failure on response to BCG plus IFN [85]. Results were collected from a subset of BCG failure patients included (n = 1106) in a phase II RCT [86]. After a median follow-up of 24 months, patients with BCG failure treated with BCG + IFN had a complete response rate of 45%. Patients with BCG late relapse within 12 to 24 months and longer than 24 months had complete response rate of 53% and 66%, respectively ($p > 0.05$). Moreover, these patients had similar response rate compared to BCG naïve patients ($p > 0.5$).

BCG-unresponsive NMIBC is defined by the combination of 2 groups: very early relapsers within 6–9 months of last BCG exposure and BCG-refractory patients. This category of BCG failure patients is presently often used for trials investigating agents in patients with BCG failure.

Regarding the management of BCG failure, one must first assess the upper tract and the prostatic urethra in order to make sure the patient has true failure and is not related to a missed tumor in the urothelial tract [9–12]. A retrospective analysis of 110 patients with high-risk NMIBC (median follow-up of 9.1 years) treated with at least two courses of intravesical BCG and diagnosed with disease recurrence showed that 52% had UTUC and/or urethral carcinoma (with or without intravesical recurrence) [87].

The presence of CIS alone at 3 months is not sufficient to conclude BCG-refractory disease [52, 81, 83, 88]. The majority of patients with CIS at 3 months following induction BCG will be rendered with no evidence of disease at 6 months with further BCG therapy.

A low-grade Ta recurrence in a patient with history of high-grade disease during the course of BCG is not a true BCG failure. A retrospective cohort (n = 917) from MD Anderson reported the oncological outcomes of NMIBC papillary recurrence at 3 months after BCG induction [89]. They showed that about 7% of the patient had a Ta recurrence at 3 months. Of those, 20% had a Ta low-grade (about 1.5% of the entire cohort). The recurrence rate for this Ta low-grade group was 33% at 1 year with a median follow-up of 66 months. The majority of these patients underwent bladder-sparing therapies. Moreover not a single patient had disease progression or required delayed cystectomy. Table 9.3 provides a brief summary on risk-stratified management of BCG failure. For more details on management of patients with BCG failure, refer to the appropriate chapter.

Table 9.3 Proposed management of BCG failure based from [9–12] and expert opinion

Stratification of BCG failure management	
Type of BCG failure	Proposed management [9–12]
Assess to rule out urothelial carcinoma in the upper tract and the prostatic urethra	
BCG-refractory or HG relapse within 12 months of last BCG dose	Require immediate reassessment to exclude a muscle-invasive bladder cancer or missed lesions [90]
	RC is the treatment of choice
	If patient refuses or not fit for RC: consider clinical trial, salvage intravesical therapy, or trimodal therapy
HG BCG-relapse after 12 months of last BCG dose	RC or "Re-challenge" with additional BCG courses if BCG maintenance was not performed [82]
	Consider other salvage intravesical therapy: Gemcitabine/docetaxel, BCG plus Interferon alpha, Mitomycin C
BCG-Intolerant	No clear definition of the best management method; Case by case basis
	Make sure that patient is truly intolerant (refer to BCG administration section above, tips and tricks notably for local side effects)
	In very high-risk NMIBC: consider RC
	In intermediate-/high-risk NMIBC: clinical trial, intravesical chemotherapy, trimodal therapy

CT computed tomography, *RC* Radical cystectomy, *NMIBC* Nonmuscle-invasive bladder cancer

Conclusion

BCG is the most studied immunotherapy for bladder cancer. Strong evidence supports the use of BCG for intermediate- and high-risk NMIBC. The appropriate schedule is mandatory to allow a maximum control of the disease. The major downside is local side effects and often a reason for treatment dropouts. A good management of side effects may help in treatment adherence. Treatment response is crucial since most of the patients are frail and too many may not undergo to RC. Identify and stratify BCG failure patients are mandatory to better select optimal patient care.

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10 Adjuvant Intravesical Chemotherapy

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Traditional Induction Intravesical Chemotherapy (Mitomycin C/ Epirubicin/Doxorubicin)

Multiple chemotherapeutic agents have been studied as induction intravesical chemotherapies for patients with NMIBC. Mitomycin C (MMC), epirubicin, and doxorubicin are the most studied drugs, although in clinical practice they are infrequently utilized in the setting of high-risk NMIOBC because of a large body of the literature suggesting inferior outcomes compared to induction BCG.

It has long been recognized in the literature that patients with low-risk NMIBC (PUNLMP or low-grade solitary Ta ≤ 3 cm on initial diagnosis or recurrence >1 year) do not benefit from further treatment after a complete transurethral resection, except for the possible addition of a single postoperative instillation of chemotherapy. Tolley et al. [2] showed that in a cohort of low-risk NMIBC patients, a single postoperative dose of MMC was largely equivalent to 5 instillations of MMC. Similarly, others reported no additional benefit of weekly instillations of epirubicin compared to a one-time postoperative dose [3–5]. The use of single instillation of postoperative intravesical chemotherapy will be further discussed later in this chapter. With this data in mind, induction IVT is not recommended in patients diagnosed with initial solitary small-volume low-grade papillary (Ta) lesions.

Patients with intermediate-risk NMIBC make up a heterogeneous group, and therefore, current AUA guidelines for this group are less definitive [6, 7]. This risk group consists of patients with predominantly low-grade pathology not meeting low-risk criteria and those patients with a first-time solitary high-grade Ta ≤ 3 cm. After reviewing the body of literature, the guideline committee provided a moderate recommendation regarding the use of IVT (chemotherapy or immunotherapy) in patients with intermediate-risk NMIBC. Because of varying tumor characteristics among these patients, IVT is utilized on a case by case basis considering both the benefit of disease recurrence/progression reduction weighed against the costs and side effects of therapy. For those with smaller solitary low-grade Ta recurrences, induction IVT does not confer benefit over single postoperative dosing and is therefore not recommended. If high-volume/multifocal disease is present, or if more frequent low-grade recurrences (within a year) are encountered, a course of induction IVT may be considered.

In the subgroup of intermediate-risk NMIBC patients with high-grade pathology that confers

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elevated risk of recurrence [8], induction IVT should more strongly be considered. Individual studies and meta-analysis show improved recurrence-free survival in this group with induction MMC, epirubicin, and doxorubicin compared to placebo after TURBT. However, most studies also demonstrate inferior disease recurrence and progression outcomes compared to BCG for both intermediate- and high-risk NMIBC patients, with inferiority more pronounced in the high-risk group [9–11]. One advantage of using IVC over BCG in intermediate-risk patients is the reduced side effect profile seen with most IVC compared to BCG. Furthermore, in the current climate of BCG shortage, the AUA has released a statement that recommends against use of BCG for intermediate-risk disease to reserve its use for high-risk disease. IVC should instead be used as the first-line option for intermediate-risk disease [12]. These recommendations are appropriate as the highest benefit to risk ratio for induction BCG is observed in high-risk NMIBC. In light of these considerations, ICV should be considered as a preferable to BCG in intermediate-risk disease. While MMC, gemcitabine, epirubicin, and docetaxel are all valid options with likely comparable efficacy for intermediate-risk disease, MMC is often preferred because it has the most extensive body of the literature to support its use in this setting. Induction IVC is generally begun around 2–3 weeks after TURBT once pathology is confirmed. The recommended solution of MMC is 40 mg in 20 cc of water administered for at least a 1-hour dwell time.

In high-risk NMIBC patients (those with cis, high-grade Ta > 3 cm, multifocal/recurrent high-grade Ta, high-grade T1, variant histology, lymphovascular invasion (LVI), or any high-grade prostatic urethral involvement), induction BCG is the gold standard if bladder preservation is attempted. Radical cystectomy remains an option for patients with particularly high-risk features such as LVI or variant histology due to the significant risk of understaging associated with these high-risk features [6]. MMC and epirubicin have been shown to be inferior to BCG in preventing tumor recurrence and progression in high-risk NMIBC [9–11] and are thus rarely indicated or utilized in this cohort of high risk NMIBC.

Improving MMC Efficacy

Methods to improve the efficacy of intravesical MMC have been explored with moderate success. These include alkalization of urine, dehydration to concentrate intravesical MMC, electromotive drug administration, and chemohyperthermia.

Urinary Alkalization & Dehydration

Urinary alkalization and dehydration are commonly used methods to increase efficacy of MMC. A large phase III randomized trial of 230 patients at high risk for recurrence (2 or more episodes of Ta, T1, or cis; multifocal disease; tumor size >5 cm; or high-grade pathology) reported a longer median time to recurrence (29.1 months vs 11.8 months) for induction MMC in the group that optimized MMC delivery [13]. The protocol involved having the optimized delivery group refraining from drinking fluids for 8 hours prior to instillation and taking 1.3 g of sodium bicarbonate the night before, the morning of, and 30 minutes prior to MMC instillation. The optimized delivery arm also received a higher dose of MMC of 40 mg in 20 mL of sterile water vs. the standard delivery arm that was given 20 mg in 20 mL. Both groups retained MMC in the bladder for 2 hours. Although the different doses used between arms make the relative impact or urinary alkalization and dehydration difficult to determine, this trial nonetheless has provided the best evidence to support optimization of MMC administration through urinary alkalization and dehydration. By extension of this trial, it is reasonable to consider alkalization of the urine during TURBT via intravenous bicarbonate if a single postoperative MMC dose is planned, even though the benefit of this practice has not been explicitly demonstrated in a prospective trial.

Electromotive Drug Administration

The use of electromotive drug administration (EMDA) has also been explored as a means to increase the efficacy of MMC. This intervention is defined as the instillation of a drug accompanied by electrical current to promote drug uptake. Di Stasi et al. [14] demonstrated increased MMC concentration in bladder tissue when compared to those with passive instillation. However, a 2017 Cochrane review of the current literature concluded that there was insufficient data to define its role in potentially reducing disease recurrence and/or progression at the expense of possibly increased rates of adverse events [15]. This review ultimately included 3 trials for analysis and did not find superiority of induction MMC-EMDA compared to induction BCG in regards to reduction in recurrence and progression. EMDA is not FDA approved in the USA presently and requires further study to clarify its toxicity profile and define its potential role in management of NMIBC.

Chemohyperthermia

The addition of heat has been proposed to improve MMC efficacy by enhancing drug absorption into bladder tumors by increasing permeability of cell membranes while also enhancing the cytotoxic effect of the chemotherapy [16]. The most extensively studied drug in this setting is MMC at temperatures warmed to 42 °C using the Synergo system, in which local hyperthermia is applied by a microwave transducer at the tip of a catheter with temperature regulation controlled by a computerized temperature system. MMC hyperthermia was shown to be superior to nonhyperthermic MMC in a cohort of 83 intermediate and high-risk patients of which 42% had exposure to prior intravesical therapy with a recurrence-free survival at 2 years of 83% vs. 43%. The trial did reveal a marginally higher rate of pelvic pain in the hyperthermia group [17]. Another randomized multicenter trial of 190 intermediate- and high-risk predominantly BCG-naïve patients with either intravesical hyperthermic MMC versus BCG showed a slightly improved 2-year recurrence-free survival with hyperthermic MCC of 78% vs 65% ($p = 0.02$). Although chemohyperthermia has shown promise, its role has yet to be determined and without a readily available commercial system in the USA, its use has primarily been limited to countries outside of the USA.

Maintenance Therapy with Intravesical Chemotherapy

As maintenance therapy with BCG has demonstrated improved outcomes vs. no maintenance in several large well-designed trials [18, 19], it means to seem logical that maintenance therapy with IVC would also provide added benefit. Evidence to support this hypothesis, however, is limited and at times conflicting. Interpretation of data on maintenance IVC is limited by the variability of the studies with most studies not directly comparing induction MMC to induction MMC plus maintenance, varying dosages and varying maintenance schedules, and varying tumor pathologies included across the studies. The best evidence supporting use of maintenance MMC comes from a large randomized 3-arm trial of 495 predominantly intermediate-risk NMIBC patients that compared 6 weeks of BCG, 6 weeks of MMC, and 6 weeks of MMC plus monthly instillations for up to 3 years. The investigators found a significantly improved 3-year recurrence-free survival of 86.1% in patients receiving MMC maintenance vs BCG induction (65.5%) and MMC induction alone (68.6%) [20]. In contrast, another prospective RCT comparing maintenance MMC therapy for 6 or 12 months found no difference in any end points [21].

Similar evidence supporting maintenance therapy does not exist for intravesical epirubicin. Okamura et al. [22] found no difference in 3-year recurrence-free survival comparing 6 weeks of epirubicin (40 mg) to 6 weeks induction and monthly maintenance for 1 year (75% vs. 77%, $p = 0.62$). Likewise, Serretta et al. [23] found no difference in 4-year recurrence rates (46% vs 50%, $p = 0.26$) with 6 weeks of epirubicin

(80 mg) and a 6-week course followed by monthly instillations for 1 year. Doxorubicin has limited data as a maintenance therapy, making conclusions difficult on its utility. One prospective randomized study [24] compared doxorubicin weekly for 6 weeks and doxorubicin weekly for 6 weeks and monthly for 2 years. They reported no difference in tumor recurrence and progression at 5 years of follow-up. In sum, there is limited evidence to support use of maintenance IVC in intermediate-risk patients who completely respond to IVC, which is reflected in the AUA's guideline of grade C evidence strength stating that clinician "may" utilize maintenance therapy [6].

BCG Shortage: New Chemotherapeutic Agents (Gemcitabine, Docetaxel, Gemcitabine/Docetaxel, Gemcitabine/MMC)

After the Connaught strain of BCG had its production halted by Sanofi in mid-2017, Merck's Tice strain of BCG became the only BCG strain available in the USA. This drop in supply along with the continual rise in demand has unfortunately led to BCG shortages and the need to substitute its use with chemotherapeutic agents. During the current shortage, the AUA has released a statement of recommendations for treatment modification which includes the provision that IVC should be first-line for intermediate-risk NMIBC and as an alternative to BCG if it is not available for high-risk NMIBC [12].

In the current climate of BCG shortage, induction therapy should be prioritized over maintenance therapy. If there is sufficient supply for maintenance therapy, it should be given at 1/3 strength a limited to 1 year. Patients with particularly high-risk features such as high-grade T1 with additional risk factors such as concomitant carcinoma in situ, lymphovascular invasion, prostatic urethral involvement, or variant histology who are not willing to additional oncologic risk with intravesical agents that are not validated in this setting should be offered initial radical cystectomy. It remains to be seen what intravesical chemotherapy or novel immunotherapy will emerge as a new standard of care in high-risk NMIBC patients who are BCG naïve.

Some of the agents that are now being used as initial treatment for high-risk disease (such as combination therapies of gemcitabine/docetaxel and gemcitabine/MMC) have been explored primarily as salvage therapies for BCG-unresponsive disease and hence will primarily be discussed in the salvage intravesical chemotherapy section. One such retrospective study from Johns Hopkins included a total of 33 patients who received combination induction gemcitabine/docetaxel, of whom 8 (24%) were naïve to BCG. With baseline demographic and clinicopathologic features comparable between the BCG-naïve and BCG-unresponsive/BCG-relapsing populations, they noted that BCG-naïve patients had a more favorable 1-year HG recurrence-free survival of 75% vs. BCG-unresponsive/BCG-relapsing patients with a 1-year HG recurrence-free survival of 49% [25]. The largest retrospective cohort of gemcitabine/docetaxel in 30 BCG-naïve patients was recently published by Thomas et al. of which 80% of patients had high-grade pathology. Results were impressive with complete response observed in 89% of patients at both 1 and 2 years with no patients progressing or requiring cystectomy [26]. Studies examining the combination of sequential gemcitabine and MMC have thus far largely been in the BCG failure population; however, one multi-institutional study of 52 patients included 10 BCG-naïve patients who were immunosuppressed and noted a nonsignificant difference in recurrence-free survival between BCG exposure groups of 48% at 1 year [27].

Single-Dose Postoperative Intravesical Therapy

Investigators began experimenting with single immediate postoperative instillations in the late 1980s with randomized trials of thiotepa [28], mitomycin C [29], and epirubicin [30]. The

rational for postoperative instillation of intravesical chemotherapy includes both destruction of residual microscopic tumor at the site of TURBT and destruction of tumor cells that are dispersed within the bladder during TURBT [31, 32]. Four separate meta-analyses concluded that a single postoperative instillation of chemotherapy significantly decreases tumor recurrence compared to TURBT alone [33–36]. In the most recent systematic review and individual patient data meta-analysis of 2278 eligible patients [36], a single immediate postoperative dose reduced the 5-yr recurrence rate from 59% to 45%. Only low-risk and intermediate-risk patients benefitted from a postoperative single-dose strategy. Based on these analyses, the AUA guidelines state that all known or suspected low- and intermediate-risk NMIBC patients should be considered for receipt of a single immediate instillation of intravesical chemotherapy after TURBT [6], while the EAU guidelines have a stronger recommendation that clinicians should administer a single postoperative dose within the first few hours after TURBT [37].

Postoperative Intravesical Agents

Mitomycin C and epirubicin are the two most widely studied intravesical chemotherapies in the postoperative setting, yet no study exists that directly compares efficacy of these two agents. The most recent meta-analysis by Sylvester et al. that used individual patient data found an overall absolute reduction in recurrence at 5 years of 14% (from 59% to 45%). MMC and epirubicin use, which accounted for 82% of all patients in the meta-analysis, were found to have similar hazard ratios of 0.63 and 0.58 compared to TURBT alone, respectively. This study also stratified patients by EORTC recurrence score and prior recurrence rate and found that a single immediate instillation was not effective in high-risk patients (defined in this analysis by having a prior recurrence rate of more than one recurrence per year or an EORTC recurrence score ≥ 5) [36]. Hence, it is not advisable to give a single postoperative instillation in patients with known or suspected high-risk disease.

In the large single randomized study of 2243 patients recently published that investigated an immediate postoperative dose ± induction mitomycin C depending on risk level versus only a delayed induction of Mitomycin C, Bosschieter et al. found an absolute reduction in the 3-year recurrence risk of 9% (from 36% to 27%, $p < 0.001$) in the group receiving immediate postoperative mitomycin C [29]. This finding supports the use of postoperative instillation even if an induction course of mitomycin C is planned. While prior studies comparing TURBT alone to postoperative instillation could not discern a difference in risk of progression because of the power required to detect differences in the overall low risk of progression in low- and intermediate-risk patients, this study showed a 3-year progression risk reduction from 5.5% to 2.7% ($p = 0.005$).

Gemcitabine has recently emerged as another viable single-dose postoperative agent after the SWOG randomized trial of 406 patients demonstrated a 34% reduction in the hazard ratio of tumor recurrence [38]. After 4 years of follow-up, patients in the saline group had a 47% recurrence rate vs. 35% in the treatment arm. Patients were eligible to receive 2 g of gemcitabine in 100 mL of saline or just 100 mL of saline alone within 3 hours after TURBT for a 1-hour dwell time if the surgeon suspected low-grade pathology based on tumor appearance. Among the 115 patients with confirmed low-grade pathology, a greater reduction in hazard of recurrence of 47% was observed (4-year recurrence rate reduction from 54% to 34%). Post hoc analysis did not find any benefit among patients with high-grade pathology, similar to other agents. Importantly, there were no grade 4 or 5 toxic events observed in this trial with similar distributions of grades 1–3 events between gemcitabine and placebo, solidifying this therapy as both safe and efficacious in patients suspected of having low-grade pathology. Although there has not been any study directly comparing gemcitabine with other agents in the postoperative instillation setting, the beneficial effect of gemcitabine versus placebo is comparable to MMC. The comparable efficacy,

availability, low side effect profile, and significant cost savings of gemcitabine have led to rapid diffusion of this agent as a clinical option in the USA. Illustrating its lower toxicity profile compared to MMC, a separate trial comparing gemcitabine and MMC induction therapy in patients with recurrent NMIBC found the incidence of chemical cystitis (21% vs 5.5%) and total incidence of adverse effects (72% vs 39%) significantly higher in the MMC group [39].

Toxicity

While the most common side effects of single instillation postoperative chemotherapy are temporary irritative lower urinary tract symptoms, severe complications ranging from bladder wall necrosis and fistula formation can occur after bladder perforation with extravasation of IVC and in particular MMC. Not uncommonly does it occur where perforation was not identified intraoperatively but only identified after CT confirmed suspicion of more severe postoperative symptoms than expected [40]. For this reason, besides avoiding postoperative instillation in cases of clear perforation, postoperative chemotherapy is avoided in cases with deeper resection into the muscle, extensive area of resection, or suspicion of an underlying thin bladder beyond the resection. Poor hemostatic control or prostatic bleeding is another contraindication to postoperative instillation. Immediate symptoms of extravasation range from the strong urge to urinate, abdominal/pelvic pain, and peritonitis in cases of intraperitoneal perforation. Severe pain occurring soon after instillation of intravesical chemotherapy should prompt concern for perforation and trigger immediate release of the chemotherapeutic agent followed by copious washout with saline. In a minority of cases, however, the patient may not become symptomatic until after catheter removal [41].

While most patients with a small extraperitoneal bladder perforation and epirubicin instillation will make a full recovery with conservative management with Foley catheter drainage [40], mitomycin C extravasation may have more devastating consequences. There are case reports of patients developing crippling symptoms of chronic pelvic pain, continued severe lower urinary tract symptoms, and fistula formation requiring reconstructive surgery after a single postoperative instillation of mitomycin C [42]. It is important to recognize that although rare, the risk of intravesical chemotherapy extravasation can lead to serious long-term morbidity and even mortality in some patients. Some argue that the therapeutic advantage of reducing the risk of recurrence of nonlife-threatening low-intermediate-risk NMIBC is not worth this risk, however small, and avoid its use altogether. This may factor into the wide variability of its use despite AUA and EAU guidelines, with European data showing a postoperative instillation rate around 40% among potential candidates and an American survey data reporting rates as low as 20% [43, 44]. It is likely that with appropriate patient selection and a low threshold to withhold therapy after more extensive resections, postoperative instillation of chemotherapy, in particular gemcitabine, can be a safe and effective adjunct to TURBT.

Practical Application of Single-Dose Postoperative Intravesical Chemotherapy

The urologist must use best judgment as to which patients have the highest benefit to risk ratio for postoperative intravesical chemotherapy instillation. In cases where a prior office cystoscopy clearly demonstrates low tumor volume and low-grade disease, the urologist can with reasonable certainty prepare for postoperative instillation prior to undergoing TURBT. In patients with suspected high-grade pathology, positive cytology, or high suspicion of CIS based on cystoscopic appearance, it is not likely that single-dose postoperative chemotherapy will benefit the patient. Furthermore, in patients with extensive resection beds >3 cm or significantly deep resection into the muscle or perivesical fat, it is recommended to avoid use out of concern for undiagnosed bladder perforation or potentially a delayed perfora-

tion that may occur in the setting of a weakened bladder wall that could sustain further insult from cytotoxic agents. As a result of these intraoperative uncertainties, for the vast majority of patients, it is wise to make a decision on intravesical instillation after concluding the resection. Our institution has increasingly utilized gemcitabine over mitomycin C because of its comparable efficacy, cost savings, and improved tolerability.

Regarding the timing of postoperative instillation, most trials have given the drug within 24 hours, and equivalent efficacy beyond that period of time has not been established. Although a randomized trial of immediate instillation versus the following day instillation of mitomycin C did not show any difference in efficacy [45], the immediate postoperative instillation is likely more suitable for patients and the healthcare system, saving the patient another trip at the cost of a negligibly longer outpatient hospital. During pharmacy preparation of the chemotherapy, the patient is afforded time to awake from anesthesia and can therefore register any pain out of proportion to that expected if an undetected bladder perforation occurred. With the drainage port either capped or clamped, the chemotherapy is instilled into the bladder and allowed to dwell for an hour. If significant postoperative bleeding is noted, the instillation is withheld. After 1 hour (or if patient cannot tolerate the full hour), the catheter is unclamped and the bladder is drained.

Salvage Intravesical Chemotherapy

Patients who have high-risk recurrences after BCG treatment represent a particularly challenging disease state to manage. The disease state has recently been termed "BCG-unresponsive" disease in order to focus on providing the treating urologist a clear definition for when further intravesical BCG is unlikely to provide benefit. It also serves to aide in trial design by establishing appropriate eligibility criteria for studies of novel salvage intravesical chemotherapy. BCG-unresponsive patients are comprised of those with high-grade recurrence within 12 months after two induction courses of BCG or high-grade recurrence after induction plus maintenance—these patients should be offered radical cystectomy [46]. While intermediate- or high-risk patients with persistent or recurrent Ta or CIS disease after a single course of induction BCG may benefit from an additional induction course of BCG, patients with high-grade T1 after a single BCG induction course are also deemed BCG-unresponsive and should be offered radical cystectomy [6].

As no intravesical treatment after BCG failure has been shown to have equivalent oncologic outcomes to radical cystectomy, BCG-relapsing patients who have high-risk recurrences within 6 months of the 2nd BCG induction treatment should also be offered radical cystectomy as the standard of care. Numerous studies have found that earlier high-risk recurrences after BCG carry a significant risk of progression, with salvage intravesical therapies having poor success rates in this setting [47, 48]. Comparisons among salvage intravesical regimens are challenging because of varying patient inclusion criteria used, but overall 1–2-year recurrence-free survival rates of various agents are modest at 18% to 43% [46]. Should patients either be unfit for radical cystectomy or refuse cystectomy once failing BCG, it is recommended that the patient enroll in a clinical trial if available. In the following sections, we detail salvage intravesical therapy options that are currently available as well as practical advice for employing salvage intravesical therapy.

Valrubicin

Valrubicin is the only US FDA-approved intravesical medication specifically for BCG-unresponsive CIS; however, this agent is infrequently used because of its unimpressive long-term results and poor tolerability. The original study that garnered the drug FDA approval was a single-arm 90 patient trial that found a 21% complete response rate at 6 months and an 8% disease-free rate with a median follow-up of 30 months [49]. Similar results with a poor long-term durability of 4% at 2 years were observed in

a secondary study of valrubicin. Furthermore, treatment with valrubicin was more irritative than most other agents with 86% of patients experience ≥1 local bladder symptom of frequency, dysuria, and urinary urgency [50]. For these reasons, valrubicin is generally not offered for CIS unresponsive to BCG.

Chemohyperthermia

Whereas chemohyperthermic MMC likely has a role in enhancing up-front efficacy of MMC, it has been less well studied in a patient population with BCG-unresponsive disease. One retrospective series of 111 "BCG failure" patients in which the exact definition of BCG failure was not specified found 1- and 2-year recurrence-free survival rates of 85% and 56%, respectively [51]. This study also found improved recurrence-free survival in patients who were able to complete a full 12-month maintenance course over those who did not. Another study in which 81% of patients had prior BCG found 1- and 2-year recurrence-free survival rates of 60% and 47%, respectively [52]. This study also included 12.5% of patients who received hyperthermic epirubicin because of a MMC allergy; this subgroup of patients had a nonsignificantly better 2-year recurrence-free survival of 55% vs 46% in the MMC group. Due to limited access of this technology in the USA and insufficient evidence in the BCG-unresponsive setting, chemohyperthermia is not administered as a salvage regimen outside of investigational studies.

Single-Agent Chemotherapy

Gemcitabine and the taxane class of chemotherapy have been the most widely studied chemotherapeutic agents in the salvage setting with moderate success. The SWOG S0353 phase II trial of intravesical gemcitabine enrolled 58 patients who all had recurrence after at least 2 prior induction courses of BCG with 89% of patients having high-risk disease at time of enrollment. This trial found an initial 3 month response rate of 47% with 28% remaining tumor-free by 1 year [53]. This was far inferior to a prior study investigating gemcitabine vs mitomycin in a population who were not strictly BCG-unresponsive that found 1-year recurrence-free rates of 72% [54]. The difference in outcomes is largely attributable to patient selection with the more recent SWOG criteria using a stricter definition of BCG unresponsiveness, highlighting the impact patient selection has on drug success.

Docetaxel was the prototypical drug of the taxane class first to be studied in a phase I trial in 2006 [55]. Long-term results of a cohort of 56 patients who received salvage docetaxel, all of whom received at least 1 prior BCG induction course (61% received more than 1 induction course), demonstrated an initial complete response rate of 59%. 1- and 3-year recurrence-free survival rates were 40% and 25%, respectively. Maintenance docetaxel was also observed to confer benefit in patients with initial complete response with maintenance therapy having a more durable median recurrence of 39 vs 19 months in the nonmaintenance group [56]. 17 (31%) patients underwent radical cystectomy at a median of 24 months, with only 4 showing progression to muscle-invasive disease. 5-year disease and overall survival rates were 85% and 71%, respectively. In comparison, patients with pT1 after radical cystectomy have 5-year overall survival rates of 78–85% [57]. After moderate success with salvage docetaxel, the same investigators also studied a nanoparticle albumin-bound paclitaxel and found comparable results with a recurrence-free survival of 18% at median follow-up of 41 months [58]. Notably, this population of patients was more heavily enriched with CIS (71%) versus the prior study that had 53% of patients with CIS at trial entry.

Multiagent Chemotherapy

Paralleling the increased efficacy of multimodal over single-agent systemic chemotherapy, it has been proposed that combination salvage intravesical therapies may have greater efficacy when given in alternating fashion than as single agents.

The combination of intravesical MMC and gemcitabine has been investigated at several institutions. The largest trial of 47 patients found a 1-year and 2-year recurrence-free survival of 48% and 38%, respectively [27]. The protocol employed a single postoperative dose of MMC followed by a 6-week induction of intravesical gemcitabine and MMC given as follows: 1 g of gemcitabine in 50ccs of sterile water instilled and retained for 90 minutes and then drained completely and then immediately following 40 mg of MMC in 20ccs of sterile water instilled and retained for 90 minutes. A monthly maintenance regimen was used for up to 12 months if the patient demonstrated an initial complete response. Importantly, this cohort was not comprised of solely BCG-unresponsive patients as 7 patients received no prior treatment and 10 patients were BCG-naïve. Another retrospective study of this combination regimen in 27 patients that included only those with prior intravesical failure (of whom 24 received prior BCG) found a 37% recurrence-free rate and a median time to recurrence of 15.2 months [59].

Sequential intravesical gemcitabine and docetaxel have also shown promise in several studies. Steinberg et al. reported on their experience of 45 patients of whom 4 were BCG-naïve [60]. Their protocol consisted of pretreating patients with 1300 mg or sodium bicarbonate the evening prior and morning of treatment to alkalinize the urine as alkalization is thought to reduce some of the side effects of the acidic gemcitabine as well as potentially enhancing the efficacy of MMC. Gemcitabine was administered as 1 g in 50 ml of sterile water and retained for 90 minutes. Following bladder drainage, 37.5 mg of docetaxel in 50 mL of saline was instilled. Patients were instructed to not urinate for 120 minutes after catheter removal. This induction regimen was administered weekly for 6 weeks, and monthly, maintenance was given for those patients found to be recurrence-free. Tolerability was adequate with only 5 patients unable to tolerate the full treatment course. Treatment success was 66% at first surveillance, 54% at 1 year, and 34% at 2 years after initiating induction. The Johns Hopkins' group found similar results employing the same protocol in 33 patients with a 42% 1-year and 24% 2-year recurrence-free survival rate [25].

Practical Advice for Salvage Intravesical Treatment Choice and Administration

Patients with high-risk NMIBC following BCG therapy who are unfit or refusing cystectomy remain a difficult patient population to treat. As there are no randomized trials comparing available salvage intravesical therapies and the majority of completed trials lacking comparator arms, it is difficult to compare the efficacy of one regimen versus another because of different patient baseline disease risk levels along with varying proportions of patients who are truly BCG-unresponsive. Thankfully, with a clear definition of BCG-unresponsive disease now in regular use, the inclusion criteria for future salvage intravesical chemotherapy should be more consistent. As there is a yet-to-be defined standard of care in this cohort of BCG-unresponsive patients refusing cystectomy, patients should be referred for clinical trials when available.

Should clinical trials not be available or practical based on patient geography or other limitations, combination salvage intravesical gemcitabine and docetaxel may be the salvage intravesical chemotherapy option of choice. To date, it is the only nondevice-assisted salvage therapy to demonstrate a 1-year recurrence-free survival of >50% with good tolerability. Furthermore, both gemcitabine and docetaxel are FDA-approved systemic anticancer drugs and are not cost-prohibitive. Patients should be treated with 1300 mg oral sodium bicarbonate the evening before and morning of every treatment instillation to minimize the treatment irritation of gemcitabine. As with all intravesical therapies, patients should avoid diuretics or bladder irritants such as caffeine and restrict fluids the morning of treatment to minimize drug dilution.

A practical technique for administration of sequential intravesical chemotherapy is to insert an indwelling catheter and let the bladder drain

completely. First, instill 40 mg of docetaxel in 50 cc of saline and cap the catheter and retain the solution for 90–120 minutes if possible. Then, drain the bladder and instill 1 g of gemcitabine in 50 cc of sterile water and remove the catheter and instruct the patient to void 1 hour later.

Of paramount importance when implementing salvage intravesical chemotherapy is the need for vigilant disease surveillance in order to mitigate the risk of progression and subsequent metastasis. Acceptable oncologic outcomes are only achieved when recurrent or progressive disease is detected early and acted upon, usually with radical cystectomy. Because of the inaccuracies in detection of postinduction response with office based white light cystoscopy and cytology alone, it is our practice to perform a formal restaging TURBT with exam under anesthesia with blue light utilization if available to assess response. Prior studies have shown that as many as half of recurrences found in the operating room would have been missed on routine office surveillance [61]. In patients with a history of CIS, it is also important to perform random bladder biopsies and prostatic urethral biopsy in men.

The role of a high-quality TURBT on initial tumor restaging prior to salvage intravesical chemotherapy and in detection of recurrent tumors is likely underappreciated in the literature as this variable is difficult to quantify. For this reason, it is recommended that patients being considered for treatment of high-risk recurrent NMIBC with non-FDA-approved agents be treated in a center with experience in TURBT, vigilant surveillance, and if possible clinical trial options available. Those that do proceed with salvage intravesical therapy must ensure that the patient understands the more than 50% likelihood of cancer recurrence along with a significant risk of progression and cancer mortality while also ensuring that the patient will be compliant with rigorous surveillance.

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11 Device-Assisted Therapies for Nonmuscle-Invasive Bladder Cancer: A Practical Approach

J. Alfred Witjes

Abbreviations

BCG	Bacille Calmette Guèrin
CHT	Chemo HyperThermia
EMDA	Electro Motive Drug Administration
HIVEC	Hyperthermic IntraVEsical Chemotherapy
MMC	Mitomycin-C
NMIBC	NonMuscle Invasive Bladder Cancer
RF	RadioFrequency
TUR	TransUrethral Resection

Introduction

Current intravesical drug therapy for nonmuscle-invasive bladder cancer (NMIBC) has four limitations.

The first is that it is clear that even with optimal treatment, meaning a good and radical transurethral resection (TUR), in higher-risk cases, a re-TUR and adequate risk adapted standard instillation therapy recurrence rates of NMIBC remain high and progression to muscle invasive tumors can occur in up to 20% of high-risk cases [1]. This is lower as found in earlier studies and the EORTC risk calculator, probably due to better resection techniques, better resection equipment, and the increased use of (maintenance) Bacillus Calmette Guèrin (BCG). The second problem is that standard intravesical therapy has side effects, especially (maintenance) BCG therapy. We know that only a minority of patients will be able to finish a 3-year maintenance BCG schedule. Third, there is a problem with BCG availability due to stopping production of one of the most used BCG strains. Finally, a limitation of current therapies is that there is not a real salvage therapy for those high-risk patients failing BCG therapy. In these patients, radical surgery remains the treatment of choice.

In all, there is a clear need for other treatments than those mentioned in guidelines: intravesical chemotherapy with mitomycin-C (MMC) or epirubicin and BCG.

Device-assisted intravesical instillation therapy is used in order to improve the efficacy of intravesical chemotherapy by means of the combination with heat (chemo-hyperthermia or CHT) or an electrical current (electromotive drug administration or EMDA), designed to both promote drug uptake and increase therapeutic results.

CHT has been used for several decades and can be done in several ways.

Results with radiofrequency (RF)-induced CHT (the Synergo™ system) have been reported most. With this system, a chemotherapeutic drug

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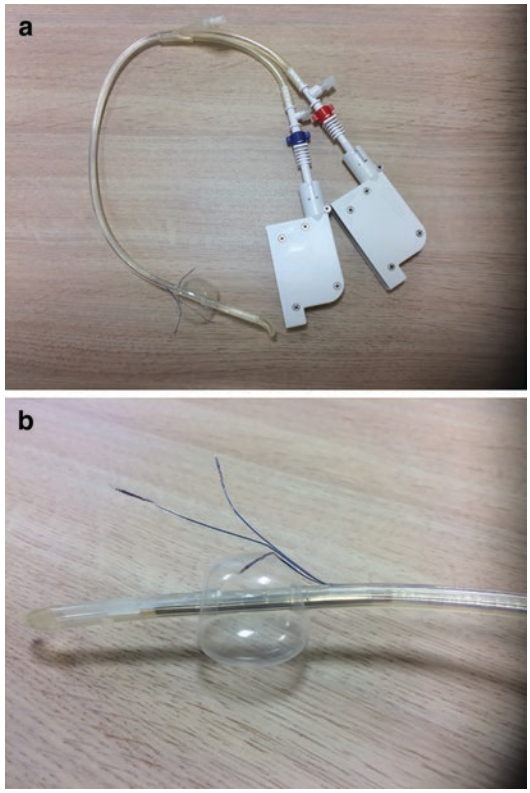

Fig. 11.1 (**a**) Synergo catheter. (**b**) Tip with thermocouples pushed out

(MMC or epirubicin) is administered in the bladder, while the bladder wall is heated to 41–42 °C using a 915-MHz microwave applicator that is incorporated in the tip of a three-way (20 French) transurethral catheter (Fig. 11.1). The instillation fluid is recirculated and cooled to prevent overheating of the urethra, and the bladder wall temperature is monitored using three thermocouples that are also incorporated in the catheter. Conductive intravesical CHT means recirculation of heated drug solutions in the bladder. Two systems are available: HIVEC (Hyperthermic IntraVEsical Chemotherapy) with the Combat™ system or the Unithermia™ system. Although this technique is somewhat easier to apply as compared to Synergo, reported results on its clinical efficacy are still very limited. Finally, external radiofrequency-induced CHT can be applied. Two systems have been used (the BSD 2000® system and the Alba Hyperthermia System®),

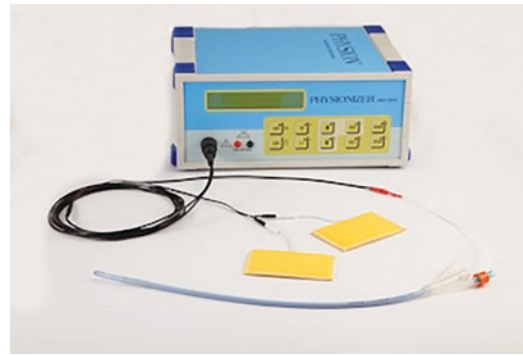

Fig. 11.2 EMDA device and catheter

but reports on results are even more sparse compared with the other two methods.

The latest systematic review on CHT looked at 15 publications [2]. The authors concluded that, although this method is promising, evidence is limited due to lack of high-quality randomized trials. Two randomized trials with BCG as the comparator, published after this review, showed different results. RF-CHT was compared with BCG in a randomized controlled trial with intermediate- and high-risk NMIBC patients [3]. RF-CHT was found to be safe and effective, with a significantly higher 24-mo recurrence-free survival as compared to BCG in the per-protocol analysis. A major limitation of this trial, however, was premature closure. Another trial did not find a difference in patients with recurrence following induction/maintenance BCG, although this trial also had major limitations such as patient selection, treatment regimens, and outcome measurement [4].

Intravesical EMDA is administered by a generator that delivers an electric current between two electrodes: the active intravesical electrode, integrated into a specifically designed catheter, and the ground electrodes, which are placed on lower abdominal skin (Fig. 11.2). Studies with EMDA are limited. The results of EMDA were recently reviewed in a Cochrane review, identifying 3 studies that could be used for analysis [5]. The authors concluded that there is no evidence that EMDA with MMC is better than MMC alone or BCG. EMDA with MMC, combined with BCG, may result in a delay in time to recurrence

in selected patients as compared to BCG alone. Also, one dose of MMC with EMDA before the TUR might be better than one dose of MMC after the TUR. Whether EMDA with MMC also results in more (severe) side effects remains uncertain. The authors, however, acknowledge that EMDA might play a role in situations where established drugs are not available.

Indications

I will focus on the three systems that are used regularly in clinical practice: the Synergo system, the Combat system (HIVEC), and the EMDA system. We personally have experience with the Synergo system since 2001 [6], and the Synergo system has the most publications, followed by EMDA. Literature on HIVEC is sparse.

Synergo

Important exclusion criteria for Synergo treatment are a bladder diverticulum >1 cm (presumably not heated sufficiently; bladder volume < 150 ml, or even better <200 ml, and a urethral stricture impeding insertion of the rather stiff 20F Synergo catheter. General contraindications for intravesical therapy are also applicable, such as persistent hematuria and active urinary tract infection.

Risk group: looking at the published literature and the inclusion criteria mentioned for several studies, Synergo is predominantly given in intermediate- and high-risk patients including CIS and in BCG unresponsive or refractory patients refusing or unfit for radical surgery. Our own experience, however, has also shown that patients with high recurrence rate of low-grade Ta tumors can do very well on a maintenance Synergo schedule. Although these patients are usually at a very low risk of tumor progression, avoiding yearly admissions and TUR procedures is obviously less of a burden than outpatients intravesical instillation therapy. In all, there are several risk groups that can be treated with Synergo, although, in practice, we never use it as primary treatment, but always after intravesical chemo of BCG.

Synergo has been used both in the ablative setting in patients with (residual) papillary tumors or CIS at initiation of treatment and in the prophylactic setting, meaning after a complete TUR.

HIVEC

Although in the UK, studies are ongoing, published data on HIVEC are minimal. Looking at the inclusion and exclusion criteria of the HIVEC 2 study protocol, again a limited bladder capacity (<200 ml) was considered an exclusion criterion.

Risk groups included in the HIVEC 2 protocol are more or less low and intermediate risk: patients with primary or recurrent Ta or T1, grade 1 or 2 tumors. Grade 3 tumors and CIS were an exclusion criterion, as were primary solitary low-grade small Ta tumors. The HIVEC study recruited between April 2014 and December 2017 191 patients, with a 24-month disease-free survival as end point. Results are awaited.

One of the 2 publications on this methodology also included some patients with T1 and/or CIS and/or grade 3 tumors [7]. In the same study, both results were described in the prophylactic setting after complete TUR (16 patients) as well as in the ablative or neoadjuvant setting for both papillary tumors and CIS (24 patients).

EMDA

Going through the inclusion and exclusion criteria for EMDA, as summarized by Jung et al. [5], only a bladder capacity of <200 ml is mentioned as exclusion, apart from the general contraindications for intravesical therapy. EMDA trials have been done in all categories of NMIBC patients, including Ta and T1 and CIS, although usually combined with BCG instillations. A TUR of papillary tumors was performed, meaning that treatment was with a prophylactic intent, obviously with the exception of CIS patients, where com-

plete response was the end point. One trial reported a preTUR EMDA/MMC application, as a neoadjuvante strategy, in patients with papillary tumors.

In summary, for these three device-assisted intravesical treatments, usual contraindications for intravesical therapy are applicable, such as bladder infections, hematuria, and urethral strictures. No system can treat urethral tumors. For Synergo, a bladder diverticulum is a relative contraindication since this might not be heated enough. A realistic problem for all three methods is a low bladder volume, less than 150–200 ml. These patients will not be able to tolerate device-assisted treatment, which obviously has a more severe effect on the bladder than "cold" MMC. In the trials where Synergo was randomized against BCG the side effect profile of BCG was more general (fever, malaise) compared to more local side effects for Synergo (cystitis like complaint, see below).

EMDA has been used as a preTUR treatment in one trial with better results compared to a single postoperative instillation of MMC. In the prophylactic setting, after complete TUR, all methods have been used, although the HIVEC 2 study did not include high-risk patients. In the ablative setting, only results with Synergo and HIVEC have been reported.

Both for efficacy and side effects, most data are reported on Synergo, some on EMDA, and limited data on HIVEC.

Patient Preparation

Patients should be informed about the pros and cons of device-assisted therapies. Certainly, in high-risk and BCG unresponsive patients, where radical surgery is considered, patients should be counseled realistically. There certainly is a fair chance for bladder preservation, but no therapy cures everybody. From available literature on Synergo, it seems oncologically safe. A recent retrospective study compared 3 groups of 50 CIS patients who (1) did not have BCG, (2) did have some form of BCG treatment, and (3) were defined BCG unresponsive [8]. Progression to muscle-invasive disease was seen in 13.3% of patients, which was 16.0% in BCG-unresponsive, 13.0% in other BCG-treated, and 10.6% in treatment-naïve CIS patients ($p = 0.74$). The overall cystectomy-free rate and OS at mean follow-up of 3 years were 78.5% and 78.0%, respectively. So, although the risk of disease worsening seems acceptable, the EAU guideline provides a strong recommendation that radical surgery should be performed in BCG unresponsive patients since other treatments, such as immunotherapy, intravesical chemotherapy, device-assisted therapy. or combinations, must be considered oncologically inferior [9]. An exception is when a patient is unfit or unwilling to undergo major surgery, but "unfit or unwilling" obviously is not black and white either.

As with standard intravesical treatment, bladder infections and visible hematuria have to be ruled out before any device-assisted treatment is started. Patients are asked not to drink several hours before therapy to prevent bladder overfilling. Certainly, in hyperthermia trials, patients will get a blood sample tested periodically, for example, for hematology and kidney function. Outside trials we do that as baseline and on indication. Since all methods use rather thick (approximately 20 French) catheters, urethral strictures can hamper treatment. Prosthesis (hip prosthesis and pace makers) is not a contraindication to use device-assisted techniques.

To facilitate treatment compliance, patients are clearly instructed which side effects to expect from the treatment. Even though most patients we treat have had previous conventional intravesical therapy, device-assisted treatment is different. Subsequently, based on the experience of the initial session, we use simple pain killers and/or anticholinergic drugs during subsequent treatment sessions, where these drugs are used for 2–3 days around every treatment. We do not use standard antibiotic prophylaxis. Finally, it is our practice to have a specialized nurse present during the whole treatment to check the temperature, anticipate on problems, and support the patient,

which has markedly increased treatment compliance.

Administration

After preparation of the patient, insertion of catheter treatment starts.

In the case of Synergo, the target temperature at the bladder wall level, checked by three thermocouples, which are integrated in the catheter (Fig. 11.1), is 41-42 °C.The 50 ml chemotherapy solution is circulated and cooled. This is controlled by 2 thermocouples, also integrated in the catheter, which measure the temperature of the prostatic urethra. The goal is to reach the target temperature during 20 minutes per treatment session, which means that including initial warming up one treatment session lasts approximately 25 minutes (Fig. 11.3). During this time, the drug concentration falls due to urine production and "sweating" of the bladder. To be able to treat for approximately 1 hour, every treatment consists of 2 sessions as described above, which means the instillation fluid is changed for an identical new solution after approximately 30 minutes. The use of pain killers or anticholinergic drugs is mentioned in the previous paragraph.

For prophylactic treatment, a treatment session is done with twice 20 mg of MMC in 50 ml. In the case of ablative treatment or CIS, the dose is doubled to twice 40 mg MMC in 50 ml. In the case of MMC allergy, epirubicin can be used: twice 30 mg in 50 ml as prophylaxis or twice 50 mg in 50 ml in the case of ablative treatment or CIS.

The initial treatment cycle is 6–8 weekly treatments, with maintenance therapy every 6 weeks during the first year. Although this is the official treatment advise, we have learned with time that treatment beyond 1 year, with longer treatment intervals, has been able to keep patients recur-

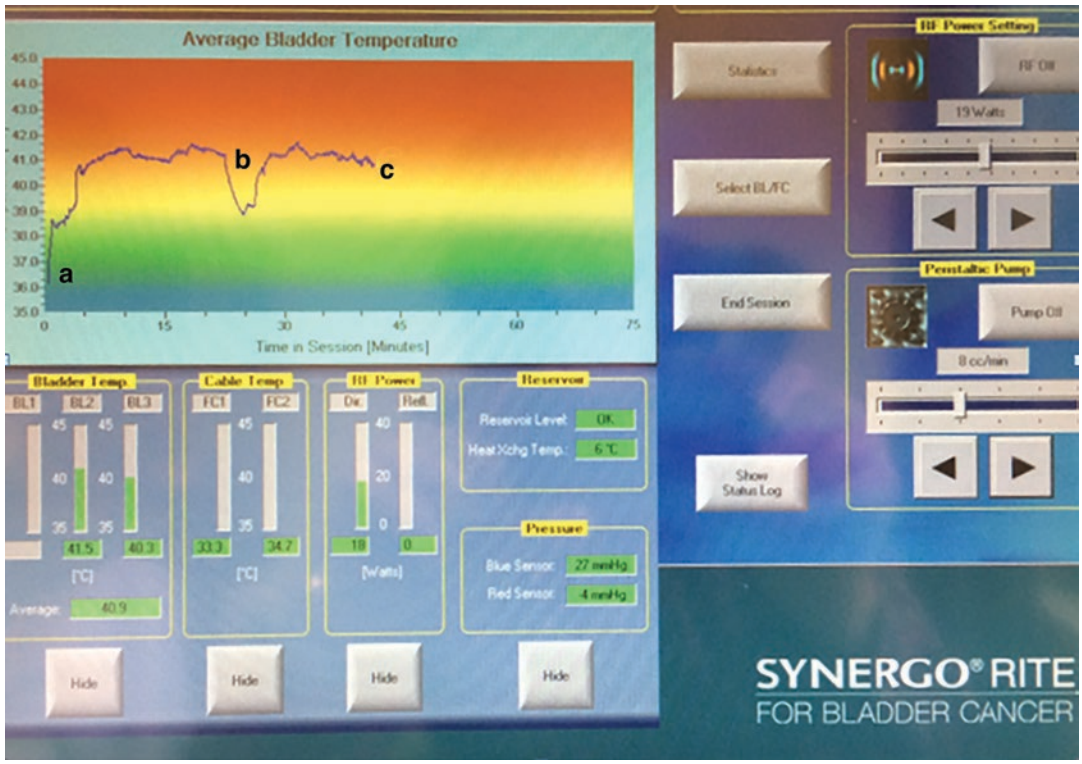

Fig. 11.3 Control panel with hyperthermia curve during 2 Synergo sessions: (*A*) initiation of treatment and heating; (*B*) changing of fluid and second heating; (*C*) temperature between 41 and 42 °C during second cycle

rence free for a long time. The longest patients we treated thus far had a recurrences of pTa tumors more than once per year and are tumor free with Synergo now since 2011, having had 7 years of therapy and currently receiving one treatment every 6 months. Obviously, there is no scientific base for this, but in the absence of side effects, patients like this approach are reluctant to stop treatment.

In the case of HIVEC, the drug solution will be maintained at 43 °C ± 1 °C for 1 hour (up to a maximum of 2 hours). Temperature is controlled externally (Fig. 11.4). Each instillation contains 40 mg MMC in 40 ml. Treatment again is 6–8 times weekly without maintenance thereafter.

EMDA treatment is also done with MMC, 40 mg in 100 ml during 60 minutes (initial study) or 30 minutes (later studies and current clinical practice). Treatment is done 6 times weekly with subsequent monthly maintenance sessions in year 1. EMDA treatment, however, is usually done alternating with BCG instillations, for example, EMDA/MMC at maintenance month 1 and 2, BCG at maintenance month 3, and so forth.

Fig. 11.4 HIVEC device and catheter

Management of Side Effects and Evaluating Recurrence

Side effects of hyperthermic device-assisted treatment are predominantly local and mild. Looking at the randomized study comparing Synergo versus BCG, the Synergo patients experienced more catheterization difficulties and urethral strictures and bladder spasms and pain [2]. Variable bladder dome necrosis is seen in most patients, although without complaints (Fig. 11.5). BCG, on the other hand, caused more day- and night-time urinary frequency and incontinence, hematuria, and general symptoms like fever, fatigue, and arthralgia. Evaluation for recurrence obviously is done with outpatient cystoscopy and a TUR and/or bladder biopsies in the case of abnormalities. The necrosis in the dome of the bladder could be mistaken for tumor. As mentioned, we use this technique since 2001, and initially, we have taken some biopsies of these necrotic areas, but never found tumor. So with sufficient experience, this should not be a source of doubt.

Although very limited data on HIVEC are published, side effects seem comparable with those seen after Synergo, except the bladder dome necrosis [7].

For EMDA, the recent Cochrane review was unable to analyze adverse events due to the way data were reported. Moreover, EMDA/MMC reported in these studies was combined with BCG. Looking at the randomized controlled trial comparing EMDA/MMC plus BCG versus BCG, reported side effects seem similar in both treatment arms, suggesting no significant additional toxicity due to EMDA/MMC with BCG [10]. Still, the Cochrane review was uncertain about the effect of postoperative EMDA/MMC on serious adverse events (RR 1.50, 95% CI 0.27–8.45), although evidence was very low [5]. Expected but mild side effects are, as with all catheterizations, some dysuria, urgency, and hematuria.

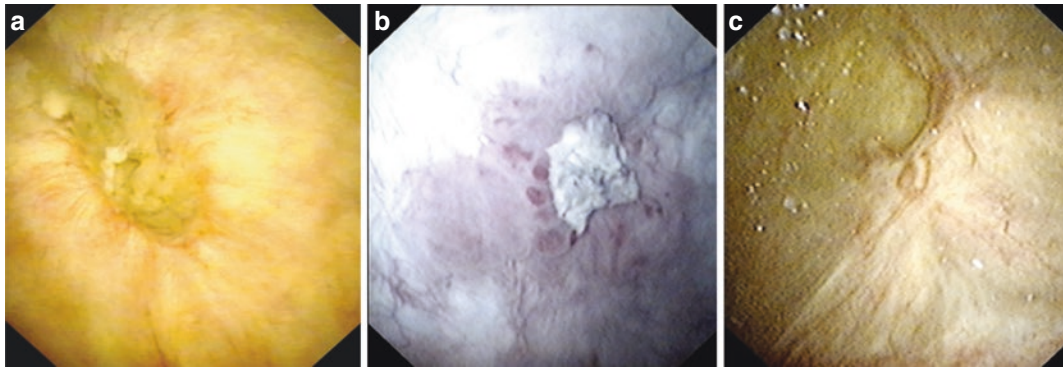

Fig. 11.5 cystoscopic image of bladder dome necrosis after (**a**) induction RITE treatment. (**b**) during maintenance therapy once per 6 weeks. (**c**) residual scar after stopping RITE treatment

In all, side effects seem frequent with hyperthermia (Synergo) but low grade and manageable. Data on EMDA are limited and difficult to interpret. As described above, for most side effects, symptomatic treatment is sufficient (pain killers and anticholinergic therapy). In the case of MMC allergy, Synergo has also been done and documented with epirubicin. Evaluation for recurrence is done as in all patients in follow-up for NMIBC. In patients treated with Synergo, it takes some experience to recognize necrosis in the dome of the bladder as such, which should not be mistaken for recurrent tumor.

Discussion

Current treatment of NMIBC has several limitations, such as efficacy, toxicity, drug availability, and the lack of second-line treatment in high-risk patients. Device-assisted therapy aims at improving the efficacy of intravesical chemotherapy and can be done with hyperthermia (intravesically or external) or an electrical current. Published literature on these device-assisted methods, however, is moderate to minimal, depending on the technique used, making clear recommendations difficult. Currently used methods used in clinical trials or clinical practice, discussed in this chapter, are based on hyperthermia or electromotive drug delivery and are intravesical methods of treatment.

Contraindications for intravesical device-assisted treatments are the usual ones for intravesical therapy (bladder infections, hematuria, and urethral structures). A contraindication for the three most used methods (Synergo, HIVEC and EMDA) is a bladder volume below 150–200 ml., and for Synergo, a bladder diverticulum is a relative contraindication. After complete TUR, all methods have been used, although the HIVEC 2 study did not include high-risk NMIBC patients. Ablative treatment has been done with Synergo and in a small cohort of patients with HIVEC. EMDA usually is combined with BCG, although it has been used as a preTUR treatment without BCG.

Before device-assisted treatment, patients should be informed well about alternatives (for example, cystectomy in the case of BCG unresponsive NMIBC) and what to expect for treatment efficacy and side effects, even though many patients will have had conventional instillation therapy before. In our experience, a good preparation and instruction before treatment and good support during treatment clearly improves compliance, so do short courses of pain killers and/or anticholinergic drugs around treatment sessions.

Treatment is done with MMC or epirubicin as alternative as has been done with Synergo in patients with an MMC allergy. MMC dose and concentration differ per indication and technique. Treatment sessions last for 30–120 minutes, also depending on the techniques used. The initial

schedule is 6–8 weekly instillation before the first check-up cystoscopy, with maintenance therapy thereafter in the case of Synergo or EMDA therapy.

Treatment-related side effects are the usual ones for intravesical therapy. Since all three methods use relatively thick catheters, urethral structures can impede the use of these techniques, as well as they can be caused by device-assisted instillations. Added side effects because of the device-assisted methods are usually local and mild, predominantly more bladder complaints (urgency, bladder spasms, and bladder pain), which seem least with EMDA. Treatment of side effects is symptomatic.

In all, these techniques could be an alternative for certain cohorts of patients (frequently recurring Ta tumors and BCG unresponsive patients) or in the case of limited availability BCG. Treatment seems safe, both with regard to side effects and with regard to the oncological outcome. Published literature is, however, moderate for Synergo, limited for EMDA, and almost lacking for HIVEC, so much more work has to be done before we can conclude that any of these treatments are standard of care for a certain indication.

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Intravesical Salvage Therapy After BCG/Regular Chemo

12

Michael A. O'Donnell and Nathan A. Brooks

Introduction

Since the initial description by Morales in 1976, intravesically administered BCG therapy has remained the gold standard therapy for patients with intermediate- and high-risk nonmuscle-invasive bladder cancer (NMIBC). Current major urologic associations recommend induction BCG with 1 year of maintenance therapy for intermediate-risk NMIBC and BCG induction with up to 3 years of maintenance therapy for high-risk NMIBC [1, 2]. Two large clinical trials supporting the use of maintenance BCG therapy for high-risk NMIBC demonstrated that five-year recurrence-free survival is only achieved in 60–64% of all patients. In a large pooled meta-analysis, the 5-year recurrence-free survival rate for those groups with the highest risk may be as poor as 22% [3–5]. Relapsing NMIBC thus presents a tangible clinical issue for the urologist. Current guidance suggests a risk-stratified approach to therapy including a second induction course of BCG for those with persistent or recurrent papillary disease or CIS, radical cystectomy with urinary diversion for patients fit for surgery with high-grade T1 disease, and clinical trial enrollment or intravesical chemotherapy for patients unwilling or unfit for radical cystectomy [2].

Data supporting the use of radical cystectomy in patients with NMIBC and BCG failure is hampered by its largely retrospective nature. Progression rates to muscle-invasive disease for those with high-grade T1 disease historically approach 43–70% of all cases for those undergoing radical cystectomy after BCG failure. However, additional evidence suggests that progression risk is increased when cystectomy is delayed by 2 years, suggesting a potential window to administer salvage intravesical therapy [6]. Because of the largely elderly and oftentimes frail nature of patients with NMIBC, many are not candidates for upfront cystectomy and additional evidence suggests that, even when indicated, radical cystectomy remains dramatically underutilized [7]. An understanding of progression and recurrence risk is needed to best stratify patients with high-grade disease after BCG failure [8]. Current evidence supports that the following risk categories stratify patients in descending order of likelihood of progression and recurrence. When risk stratification if optimized, salvage intravesical therapy and delayed cystectomy do not lead to worsening oncologic outcomes [9].

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1. BCG-Refractory: Persistent high-grade disease at 6 months despite BCG induction and a maintenance dose or stage or grade progression by 3 months after the first BCG cycle.
2. BCG-Unresponsive disease: Recurrence of high-grade disease (6 months for papillary disease, 12 months for CIS) after an induction course and at least one maintenance or reinduction course of BCG. Those patients with BCG-unresponsive disease often experience high-grade recurrences with increased likelihood of cystectomy [10, 11].
3. BCG-Relapsing: Recurrence of high-grade disease after disease-free status for at least 6 months after at least receiving BCG induction and 1 maintenance course. The prognosis for BCG-relapsing disease is generally better than for BCG-refractory disease [12].
4. BCG-Intolerant: NMIBC persistence because of the inability to tolerate BCG therapy.

Additional risk factors for intravesical therapy failure in patients with NMIBC include nonurothelial histology, urothelial histology with variant features, recurrent/high-volume/multifocal T1HG disease, T1HG with CIS, and T1HG with lymphovascular invasion [13]. These patients should be considered for upfront cystectomy.

Once risk stratification has been completed for patients with BCG failure and NMIBC who are either unfit or unwilling to undergo radical cystectomy, intravesical salvage therapy or clinical trial referral can be offered. The efficacy and effectiveness of intravesical salvage therapy are largely based on small, single-center retrospective data. This chapter will review patient preparation, instillation protocols, side effects of administration with management thereof and the efficacy of multiple salvage intravesical therapy options. Current options for therapy will be discussed as single-agent therapies, device-delivered therapies, multiagent therapy, current clinical trials and future therapy, as well as therapy follow-up protocols (Table 12.1).

Administration

Several strategies may be employed to address both the side effects of intravesical therapy and assist with an ideal duration of intravesical dwell time. For each of the chemotherapeutic treatments listed below, we recommend the following standard instructions:

Prior to Administration

- Restrict fluid intake the morning of therapy, especially limiting caffeine intake.
- Hold all diuretic medications at least 4 hours prior to instillation.
- For patients receiving gemcitabine, mitomycin C, or both, urinary alkalization with 1300-mg Sodium Bicarbonate taken the night before and the morning of treatment is recommended. Potassium citrate may be substituted for those who cannot take sodium bicarbonate.
- For all non-FDA approved agents, written consent from the patient should be obtained acknowledging that the use of these agents constitutes investigational, compassionate use therapy with uncertain benefit and toxicity.
- General Contraindications to therapy include:
  - Bladder perforation
  - Hypersensitivity to the agent or a component of the instillation
- Instillation should be delayed by 1 week for an active urinary tract infection (UTI), significant dysuria, or significant hematuria on the day of treatment or lasting more than 48 hours.
- Do not routinely use antibiotic prophylaxis for catheter placement unless indicated by current guidelines.
- When needed, administer anticholinergic and/or nonnarcotic pain medications prophylactically to assist in bladder spasm or pain management associated with therapy. For those with more severely reduced bladder capacity or bladder pain/irritability, consider a narcotic premedication, 10–15-minute bladder pretreatment with buffered 2% lidocaine (40 cc 2% lidocaine plus 4 cc 8.4% Sodium Bicarbonate solution), and/or

Table 12.1 Summation of intravesical therapy options after BCG failure

Agent	Complete response rate	1-year DFS	2-year DFS	Most common side effects	Cystectomy rate
BCG	65%	88%	40–50% (5-year DFS for BCG naive)	Bladder irritation/OAB/pain Hematuria Malaise Fever Systemic BCG infection	23%
BCG + IFN	NR	52%	45% (BCG failure × 1)	BCG-related effects ~2x greater risk of: Fever Constitutional symptoms	25%
Valrubicin (CIS only)	18%	10%	4% (BCG refractory)	Bladder irritation/OAB/pain Dysuria Hematuria UTI	30%
MMC	NR	58%	61% (3-year DFS for BCG naïve or fail × 1)	Bladder irritation/OAB/pain Suprapubic pain Dysuria Rash Bone marrow suppression	NR
Gemcitabine	39–50%	28–75%	10–21% (for BCG unresponsive)	Bladder irritation/OAB/pain Fatigue Nausea (especially common with gemcitabine)	32%
Docetaxol	55–77%	40–45%	22–32% (for BCG unresponsive)	Bladder irritation/OAB/pain Dysuria Facial flushing	31%
Gemcitabine + MMC	68%	48%	38% (for BCG failures)	Same as for single drug administration except that some patients do not tolerate the MMC component and have single-agent therapy	20%
Gemcitabine + docetaxol	66%	42–54%	27-34% (for BCG unresponsive)	Same for single-agent therapy	22%
BCG+ IFN + IL-2 + sargramostim	65%	55%	53% (for BCG failure × 1; and elderly >80)	Bladder irritation/OAB/pain Fever	27%

split dosing of meds (e.g., half the volume in half the time, repeated × 1). Leaving a Foley catheter in during treatment and hanging the drainage bag at ~40 cm can also be helpful by allowing involuntary bladder spasms to reflux up the tube and then drain back into the bladder to mitigate loss of medication.

- Instillation in men should be performed via 14–16 French coude catheter and for women using a 14 French straight catheter with ample lubrication.
- Crede pressure or gentle aspiration of the catheter is often used to ensure complete bladder emptying upon catheter placement to allow for maximal concentration of the chemotherapeutic solution.

After Administration

- Sit to urinate for 6 or more hours after administration to prevent splashing of the urine of skin. Wash hands and genitals afterward.
- Flush the toilet twice with the entire lid down after each void.
- Avoid using public toilets.
- Drink plenty of fluids (to thirst) after treatment dwell time.

Single-Agent Therapy

BCG +/– Interferon

A second induction course of BCG is currently recommended for most patients as first-line therapy after failure of an initial induction course of BCG. However, using the newer definitions of BCG failure, if the patient has received an additional maintenance course of BCG, this is considered the second BCG course. Additionally, a second course of BCG might not benefit patients with BCG-unresponsive disease. Previous works have suggested that disease-free survival (DFS) at 5 years may be near 40–50% after a second course of BCG [14, 15]. BCG should be administered using the same protocol as the initial induction course. Interferon (50 MU IFN-α2β, Intron A, Schering-Plough, Kenilworth, NJ, USA) can be added to the regimen. Addition of IFN to 1/3rd dose BCG therapy for those with prior BCG failure resulted in a 45% disease-free survival at 2 years in the largest, prospective study on the subject [15, 16]. In general, those who received IFN with BCG experience a greater incidence of fever and constitutional symptoms; however, this is rarely a limiting concern [17].

Valrubicin

Currently, Valrubicin is the only FDA approved therapy in the USA for patients who have BCG failure and CIS only. In the heavily pretreated population of the trials leading to FDA approval, the complete response to Valrubicin was only 18–30% at 6 months and only 4–8% of patients were disease-free at 2 years. Valrubicin can cause severe pain and bladder irritability immediately after instillation. This can be mitigated with 10–15-minute premedication with alkalinized 2% lidocaine. Otherwise, it is generally well-tolerated. Up to 12% of patients experience progression to muscle-invasive disease [18, 19].

Administration Patients receive 6 weekly intravesical instillations of 800 mg of valrubicin (Endo Pharmaceuticals, Malvern, PA) diluted in 55 cc of sterile saline (four vials of 200 mg/5 ml valrubicin for a total volume 75 cc).

Contraindications Allergic to polyoxyl castor oil or anthracyclines, bladder perforation.

Management of side effects
- Consider bladder pretreatment with alkalinized lidocaine for 10–15 min immediately prior to valrubicin instillation to avoid contact irritability.
- Patient urine may have a red color for the first day after treatment; this is related to the color of the solution.
- Overactive Bladder Symptoms (OAB) and Dysuria may consider pretreatment with antimuscarinic agents.
- Abdominal pain: Nonnarcotic pain regimen.
- Nausea: Pretreatment with ondansetron.
- Hematuria: Evaluation for UTI.

Mitomycin C, Electromotive Mitomycin C, and Heated Mitomycin C

Single-agent Mitomycin C (MMC) is often used as first-line intravesical therapy for patients with intermediate-risk NMIBC. Single-agent MMC (40 mg in 20 cc sterile water) has been related to chemical cystitis and skin rashes on the hands and genitalia. In patients who failed one or more courses of BCG without CIS, a randomized trial of MMC compared to Gemcitabine demonstrated a 36-month DFS of 61% [20]. Given this initial success, MMC has been further utilized in this setting using both hyperthermia (heated to 42 ° C by a catheter microwave system) and using an electromotive approach for drug delivery (Physionizer 30 generator with a pulsed electric current of 20 mA applied between the electrodes for 30 minutes). Retrospective studies indicate that RFS is improved for heated MMC compared to MMC alone but with significantly worse tolerability [6]. Neither of these devices is strictly approved in this setting in the USA. Ongoing clinical trials are being conducted to evaluate

MMC in conjunction with thermochemotherapy in the USA (RITE trial; completion 2025). Single-agent MMC therapy is not generally used for patients with high-risk, NMIBC after BCG failure.

Administration Patients receive 6 weekly intravesical instillations of 40 mg of mitomycin C diluted in 20 cc of sterile saline with a dwell time of 2 hours. For patients who respond to therapy, monthly maintenance administrations are generally given for 1–2 years or until recurrence.

Contraindications Allergy to MMC, bladder perforation.

Management of side effects
- Patient urine may have a blue/green color for the first day after treatment; this is related to the color of the solution.
- Overactive Bladder Symptoms (OAB) and Dysuria may consider pretreatment with antimuscarinic agents.
- Fatigue: Most patients take the treatment day off work.
- Systemic rash with pruritus: Management includes prednisone taper and topical steroid creams if minor.
- Skin irritation: Cleanse the skin after treatment and voiding for 24 hours.
- Nausea: Pretreatment with ondansetron.
- Hematuria: Evaluation for UTI.
- Pancytopenia or decrease in any single hematologic cell population: withhold MMC, hospital admission for significant, life-threatening decline.

Gemcitabine

Gemcitabine (gem) is a deoxycytidine nucleoside analog that blocks DNA replication. It is generally well-tolerated though can cause nausea necessitating antiemetic medication prior to instillation. Compared to MMC, single-agent gem is better tolerated with improved DFS [18]. The complete response rate ranges between 39–50%, and DFS survival at 1 and 2 years ranges from 28 to 75% and 10 to 21%, respectively [21–26].

Administration Patients receive 6 weekly intravesical instillations of 1–2 g of gemcitabine diluted in 50 cc of sterile normal saline.

Contraindications Allergic to solution components, bladder perforation

Management of side effects
- Overactive Bladder Symptoms (OAB) and Dysuria may consider pretreatment with antimuscarinic agents and oral bicarbonate to reduce acidic irritability.
- Fatigue: Most patients take the treatment day off work.
- Skin irritation: Cleanse the skin after treatment and after voiding.
- Nausea: Pretreatment with ondansetron 8 mg PO—this is especially common with gemcitabine.
- Hematuria: Evaluation for UTI.

Docetaxel

Docetaxel inhibits microtubule function and arrests cell division. Docetaxel is generally very well-tolerated in the bladder. Single-agent docetaxel administration leads to a complete response rate ranging from 55 to 77%. Disease-free survival at 1 and 2 years ranges from 40 to 45% and 22 to 32%, respectively [27–32].

Administration Patients receive 6 weekly intravesical instillations of 40 mg of docetaxel diluted with 50 cc of sterile saline (each vial of docetaxel is 20 mg in 2 cc). Final volume is 54 cc at a concentration of 37.5 mg/ml.

Contraindications Allergic to solution components, bladder perforation.

Management of side effects Side effects are generally minimal and may be managed as they arise as already discussed in other sections. Rare transient alopecia and skin rash have been reported.

Multiagent Therapy

As systemic chemotherapy has moved toward multiagent therapy, so has salvage intravesical therapy. Multiple effective single agents have been employed in combination therapy. Mounting evidence suggests that DFS for intravesical salvage therapy regimens is likely best achieved with a combination of therapy including Gemcitabine/MMC and Gemcitabine/Docetaxol (doce) therapy [33]. We favor gem/doce as it is better tolerated and may have superior DFS outcomes.

Gemcitabine/Mitomycin C

Two retrospective studies have evaluated the efficacy of sequentially administered gemcitabine (gem) and MMC for patients with largely high-risk NMIBC failing BCG and refusing cystectomy. In a study from the Mayo clinic, 37% of patients experienced DFS at a median of 22.1 months, while 3.7% of patients experience progression to muscle-invasive disease [34]. A second study from the University of Iowa demonstrated similar findings with a complete response rate of 68%, 2-year DFS of 38%, and cystectomy rate of 19% [35]. Instillations are generally well-tolerated; however, some patients do not tolerate the MMC component and receive single-agent gem only.

Administration Patients receive 6 weekly intravesical instillations of 1 g gemcitabine in 50 cc of normal saline followed by 40 mg of mitomycin C diluted in 20 cc of sterile saline with a dwell time of 1.5 hours for each agent. The gemcitabine is instilled first, then the bladder is drained without rinsing, and the MMC is instilled for 1.5 hours. For patients who respond to therapy, monthly maintenance administrations are generally given for 1–2 years or until recurrence.

Contraindications Allergy to MMC, Gemcitabine, or a component of either bladder perforation.

Management of side effects

- Patient urine may have a blue/green color for the first day after treatment; this is related to the color of the MMC solution.
- Overactive Bladder Symptoms (OAB) and Dysuria may consider pretreatment with antimuscarinic agents.
- Fatigue: Most patients take the treatment day off work.
- Systemic rash with pruritis: Management includes prednisone taper.
- Skin irritation: Cleanse the skin.
- Nausea: Pretreatment with ondansetron 8mg PO—this is especially common with gemcitabine.
- Hematuria: Evaluation for UTI.
- Pancytopenia or decrease in any single hematologic cell population: withhold MMC, hospital admission for significant, life-threatening decline.

Gemcitabine/Docetaxol

Gemcitabine/Docetaxol represents one of the most promising salvage intravesical therapy regimens. Two retrospective single-institution studies suggest that the complete response rate in a heavily pretreated population of patients is 66% with DFS of 42–54% at 1 year and 27–34% at 2 years [36]. Up to 11% of patients do not tolerate this regimen. In the study by Steinberg et al., of patients who underwent cystectomy, 10% had progression to muscle-invasive disease [37]. In addition to its chemotherapeutic properties, gemcitabine also acts as an exfoliant for urothelial cells allowing enhanced penetration of docetaxel, potentially improving efficacy and providing a rationale for the order of drug delivery [38].

Administration Patients receive 6 weekly intravesical instillations of 1 g gemcitabine in 50 cc of normal saline followed by 40 mg of docetaxel diluted in 50 cc of sterile saline (each vial of docetaxel is 20 mg in 2 cc). The gemcitabine is instilled first and left to dwell for 1.5 hours. Then, the bladder is drained without rinsing, and the docetaxel is instilled let dwell for 1.5–2 hours with or without the catheter plugged and in place. For patients who respond to therapy, monthly maintenance administrations are given for 1–2 years or until recurrence.

Contraindications Allergy to docetaxel, gemcitabine, or a component of either bladder perforation.

Management of side effects

- Overactive Bladder Symptoms (OAB) and Dysuria may consider pretreatment with antimuscarinic agents.
- Fatigue: Most patients take the treatment day off work.
- Skin irritation: Cleanse the skin.
- Nausea: Pretreatment with ondansetron.
- Hematuria: Evaluation for UTI.

Quadruple Immunotherapy

Quadruple (Quad) immunotherapy has been offered to octogenarians thought to have a poor immune response to BCG and those patients with delayed recurrence after initial BCG therapy (BCG-relapsing, not BCG-unresponsive patients). In a retrospective review of 52 patients with at least one prior BCG failure, the complete response rate was 65%, while 53% of patients experience DFS at 2 years. Twenty-seven percent of patients underwent cystectomy, and 11% of those experienced disease progression to muscle-invasive disease. Cancer-specific survival at 5 years was 82% [39].

Administration Patients receive 6 weekly intravesical instillations starting 4–6 weeks after endoscopic bladder tumor resection. Full-dose BCG is reconstituted in 50 ml of saline and combined with 1 ml (50 MU IFN), and 1.2 ml with 22 MU IL-2 (Proleukin, Prometheus Laboratories, Inc., San Diego, CA). A total volume of the three solutions of 52.2 ml is instilled into the bladder via catheter and retained for 2 hours. Prior to or at the same time, 250-mcg subcutaneous injection of sargramostim (Leukine, Sanofi-Aventis, Bridgewater, NJ) is injected subcutaneously into the abdominal wall. Sargramostim is injected with each therapy. For patients with a complete response to induction therapy, maintenance is performed with 3 weekly instillations at 3, 9, and 15 months from the completion of induction. BCG is dose reduced during these treatment cycles to 1/3rd dose BCG for the first instillation and then to 1/10th dose BCG for the second and third instillations in each maintenance cycle.

Contraindications Allergy to any component of therapy, bladder perforation.

Management of side effects

- Over 90% of patients will have a side effect while on this therapy, though rarely dose-limiting.
- Side effects are managed the same as BCG monotherapy-related side effects.
- The most common side effects of this regimen include dysuria, OAB, fatigue, fever, flu-like symptoms, and an injection site rash.

Current Clinical Trials and Future Therapy

Current clinic trials for salvage intravesical therapy for high NMIBC include those employing immunotherapies including the addition of PD-1/PD-1L inhibitors either as single-agent therapy or with BCG, BCG with immune priming via intradermal inoculation, or BCG in combination with the typhoid vaccine. Additional studies are focusing on prospectively evaluating single-agent and combination intravesical chemotherapy, photodynamic therapy, mTOR and FGFR inhibitors, and adjunctive delivery methods for multiple chemotherapeutic agents [40]. These

prospective studies and an increasing understanding of the genomic profiles of bladder cancer provide hope for the future for patients after BCG failure and will hopefully offer evidence-based, efficacious alternatives to radical cystectomy with results expected within the next decade [41].

Patient Follow-Up

Data regarding progression and recurrence for NMIBC have been hampered by largely small, heterogenous retrospective data. In these small studies, three-year bladder cancer-specific survival has been shown to range from no different to 30% lower for patients progressing to MIBC with initial NMIBC than for patients presenting initially with MIBC, likely related in part to initial understaging [42–44]. A large, systematic review of 3088 patients with up to 10 years of follow-up demonstrated that 21% of patients with high-risk NMIBC will progress to muscle-invasive disease along the course of treatment. Survival after progression to MIBC was found to be 35% with the risk of progression and death generally occurring within 48 months. Data are conflicting regarding the timing of cystectomy in this population, though significantly delaying cystectomy in the highest risk population is likely detrimental [45, 46]. Given that patients receiving salvage intravesical therapy are often in the highest risk category and generally unfit for or unwilling to undergo cystectomy, it is imperative to monitor for disease recurrence and progression to advise therapy with curative intent as soon as possible.

Most current guidelines recommend office-based, surveillance cystoscopy at predefined intervals for patients with high-risk NMIBC. Generally, cytologic evaluation, adjunctive urine molecular testing, and enhanced cystoscopy are recommended as adjunctive tests. Given the high-risk nature of patients with recurrent NMIBC after BCG failure, we prefer to utilize an advanced cystoscopic surveillance regimen performed under anesthesia ~6 weeks after completion of the final induction dose of therapy. The regimen includes the performance of bilateral upper tract washes for cytology, barbotaged bladder cytology, fluorescence in situ hybridization, bilateral retrograde ureteropyelograms, fluorescence cystoscopy with hexaminolevulinic acid, targeted bladder biopsies of any suspicious lesions, random bladder biopsies, and prostatic urethral biopsies. The rationale behind this surveillance regimen is to detect occult upper tract disease (present in up to 15% of high-grade NMIBC patients with a history of BCG failure) [47], small bladder lesions (florescence cystoscopy increases detection upward of 20% for all patients), and prostatic urethral recurrences (reported incidence as high as 12%) [48–50]. While prospective evaluation of such a strategy has not been performed, preliminary data from our patient cohort demonstrated a significant increase in recurrence detection (~40%) compared to standard white light office cystoscopy and voided cytology [51].

Summary

It is important to note that the data for salvage intravesical therapy are largely derived from small-scale, retrospective studies plagued by issues of patient and disease heterogeneity. Until randomized, controlled trial results are available for predefined patient and disease populations, salvage intravesical therapy after BCG failure should be offered to patients unfit for or unwilling to undergo cystectomy for high-risk, nonmuscle-invasive bladder cancer. This care should be delivered in the setting of a clinical trial where able. When administering the regimens discussed in this chapter, informed patient consent is strongly recommended. Multiagent therapy with an induction and maintenance course is preferred over single-agent therapy. Generally, the combination of gemcitabine/docetaxel is the most well-tolerated regimen. Close follow-up and surveillance are necessary as many patients will have disease recurrence or progression within 4 years of treatment. We prefer an enhanced surveillance regimen after the induction course to ensure that the patient is disease-free and to allow for early detection and

treatment of recurrences. The field of salvage intravesical therapy is becoming increasingly complex with several prospective trials set to impact this field and patient outcome over the next 10 years.

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13 Oncological Monitoring of NonMuscle Invasive Bladder Cancer (NMIBC)

Vishnukamal Golla and Karim Chamie

Background

An estimated 81,000 new cases of bladder cancer were diagnosed in the United States in 2018 [1]. A majority of those patients (75–85%) present with disease limited to the mucosa (stage Ta, T1, and CIS), which is collectively referred to as nonmuscle-invasive bladder cancer (NMIBC) [2]. Although the prognosis for NMIBC is generally favorable, it carries a high risk of recurrence (30–80%) and progression to muscle-invasive disease (1–45%) [3]. As a result, NMIBC requires lifelong surveillance to capture recurrence at an intervenable stage.

Algorithms for oncological surveillance of NMIBC vary significantly, even among national and international urological societies (i.e., EAU, NCCN, and AUA). Additionally, recent advancements in cystoscopic technology, urinary markers and imaging techniques have further complicated surveillance protocols for NMIBC.

This chapter aims to provide a practical blueprint for the oncological monitoring of NMIBC. It will be akin to a "pocket guide" rather than a "didactic treatise", utilizing an expert's practical insights that can be applied to a urologist's every day practice. Finally, we will include some of the latest advancements in the surveillance of NMIBC and clearly delineate their current role in management of NMIBC.

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Risk-Stratified Surveillance and Follow-up for NMIBC

Risk Stratification

Patients with NMIBC are stratified into low-, intermediate-, or high-risk categories. This grouping system is clinically important as it provides a framework for future treatment and surveillance decisions (Table 13.1). While previous chapters in this textbook discuss the merits of different published risk tables, here we will utilize the AUA/SUO risk stratification grouping. It is worth reiterating that the frequency and intensity of surveillance for NMIBC will hinge on the patient's risk group, which should be reassigned along with stage at the time of each recurrence [4].

Key Tips/Tricks Box 1

1. Assign each patient to a AUA/SUO risk category at the time of diagnosis of NMIBC.
2. Each recurrence/occurrence should have a stage and risk classification documented.

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Table 13.1 AUA NMIBC risk stratification

Low risk	Intermediate risk	High risk
PUNLMP	Recurrence < 1 year, LG Ta	All other HG lesions, CIS, BCG failures in HG patients
Single LG Ta lesion ≤ 3 cm	Single LG Ta >3 cm	All variant histology/ LVI/ HG prostatic urethral involvement
	LG T1 or LG Ta (multiple lesions)	
	HG Ta ≤ 3 cm	

Adapted from AUA/SUO Guidelines [4]
PUNLMP papillary urothelial neoplasm of low malignant potential, LVI lymphovascular invasion

Surveillance Algorithm

Oncological monitoring of NMIBC will involve some combination of surveillance tools such as cystoscopy, urine cytology/urine markers, and imaging. This section will lay the groundwork for a general follow-up algorithm with subsequent sections detailing specifics about these surveillance tools. Maintaining a rigorous surveillance protocol for NMIBC is critical as to capture progression to more advanced disease. The surveillance protocols outlined below are in the absence of disease recurrence and following appropriate treatment for intermediate- and high-risk groups.

First Surveillance Cystoscopy

Surveillance cystoscopy should be performed in a 3-month window from the index evaluation and treatment of NMIBC (i.e., date of initial TURBT), and is an important predictor for future recurrence and progression [5–7]. Therefore, in practice it is important for the urologist and office staff to ensure these patients do not delay this first surveillance cystoscopy.

Low-Risk Patient Follow-Up

Surveillance cystoscopies should be performed 6–9 months later and then annually thereafter for a minimum of 5 years. After 5 years of recurrence-free survival, the decision to continue with further surveillance should be based on shared-decision making [4]. For asymptomatic low-risk patients, there is no need to routinely surveil the upper tract with imaging.

It is important to note that if a < 1 cm papillary tumor recurrence is seen in a patient with low-grade (LG) Ta disease, the urologist has the option to perform an in-office fulguration rather than a TURBT in the operating room. If a TUR is performed for small lesions in a patient with a history of LG Ta, a deep resection is unnecessary [8].

Intermediate-Risk Patient Follow-Up

Cystoscopy with cytology every 3–6 months up to 2 years, every 6–12 months for the next 2 years, then annually in the absence of recurrence [4]. Upper tract surveillance imaging should be performed every 1–2 years.

High-Risk Patient Follow-Up

Cystoscopy with cytology for every 3–4 months up to 2 years, every 6 months surveillance for the next 2 years, then annually, again in the absence of recurrence. High-risk patients have an increased risk of upper tract recurrence and therefore upper tract surveillance imaging should be performed every 1–2 years [9].

Discontinuation of Follow-Up

For low-risk patients with 5 years of negative surveillance, the risk of recurrence is low and cystoscopy can be discontinued. However, late recurrence is common among intermediate- or high-risk patients, and lifelong surveillance is recommended [6, 10, 11].

Key Tips/Tricks Box 2

1. It is critical to perform the first surveillance cystoscopy after the diagnosis of NMIBC at the 3-month mark. This cystoscopy is an important predictor of recurrence and progression.
2. Upper tract imaging surveillance is unnecessary for low-risk NMIBC patients.
3. In-office fulguration can be performed for LG Ta recurrence (<1 cm).
4. Deep TUR is not required for small, LG lesions in patients with a history of LG Ta.
5. Discontinue follow-up for low-risk disease after 5 years. Continue with lifelong surveillance for intermediate- and high-risk disease.

Cystoscopy and Recent Advances

As inferred from the above surveillance schedules, cystoscopy is critical for the oncological monitoring of NMIBC. A renewed emphasis on improving the quality of cystoscopy has translated to the implementation of new technologies and techniques, which will be outlined in this section.

White Light Cystoscopy

White light cystoscopy (WLC) is currently the gold standard in NMIBC surveillance. This technique allows urologists to effectively map and subsequently resect bladder lesions. Although the cystoscope is practically a urologist's third arm, the following are very practical tips that can aid even the most seasoned clinicians.

Cystoscopy is typically performed with a flexible cystoscope in the office setting, thus making considerations surrounding patient comfort particularly important [8]. The instillation of topical intraurethral anesthetic lubricant (2% lidocaine Urojet jelly) and a well-timed squeeze of the saline bag while passing the cystoscope from the external urethral sphincter to the bladder neck are both evidenced-based techniques to accomplish this goal [12, 13]. There is some controversy as to the minimal amount of dwell time needed for the lidocaine jelly to be effective. In most clinical scenarios, anecdotal evidence shows that 5–10 minutes is adequate. However, in patients with severe pain during flexible cystoscopy, a longer dwell time of 25 minute along with the utilization of chilled lidocaine jelly can be used [14, 15].

The entire urothelium should be thoroughly inspected and the clinic note should describe tumor location, size, number, and general appearance (papillary or sessile) and comments on mucosal abnormalities. One easy tip to is to aspirate all the urine out of the bladder and have fresh saline irrigant flow in which can significantly improve visualization. Also, for WLC, it can help to not over distend the bladder (instill 50–100 cc unless patient has a large capacity floppy bladder) so you do not flatten out small lesions that are then missed. Clinic notes should also contain a bladder diagram to notate the location of tumors.

Despite being the gold standard, WLC is limited by its failure to identify all cancerous areas, particularly carcinoma in situ (CIS) and small papillary satellite lesions [16]. It is estimated that as high as 20% of tumors are missed with standard WLC [17]. This gap in surveillance efficacy has spurred several novel endoscopic imaging techniques to improve the detection of bladder cancer. Most relevant to this practical guide is the use of blue light cystoscopy (BLC) and narrow-band imaging (NBI), which will be detailed in the subsequent sections.

Blue Light Cystoscopy (Fluorescent Cystoscopy)

Outcomes

Blue light cystoscopy (BLC), also known as fluorescent cystoscopy (FC) or photodynamic diagnosis (PDD), can improve the endoscopic detection of CIS and small papillary lesions when

compared with WLC [18–20]. In prospective studies, the detection rate of Ta (95% vs. 83%), T1 (95% vs. 86%), and CIS (92% vs. 68%) lesions in all cases was improved for BLC when compared with white light cystoscopy. Even recurrence-free survival rates improved at 8 years at 73% vs. 45% for FC and WLC, respectively. Data on improving progression-free survival were not statistically significant when comparing the two modalities [21].

This procedure first involves the intravesical instillation of a photosensitizing drug prior to cystoscopy [22], which preferentially accumulates in neoplastic cells with rapid cell turnover such as in bladder tumors [23]. Upon exposure with blue light (360–450 nm), the cancerous tissue illuminates with a red hue, rendering it distinguishable from the blue-green normal tissue [24]. There are currently only two photosensitizing agents that have been studied for use in blue light cystoscopy, 5-aminolevulinic acid (5-ALA), and hexaminolevulinate (HAL). However, HAL (marketed as Hexvix/Cyview by Photocure, Norway) is the only agent approved in both the United States (FDA approved in 2010) and Europe (2005), so we will center our discussion on this formulation.

Drug Administration, Technique, and Safety Profile

HAL is typically dispensed as 100 mg powder reconstituted in 50 mL of dilutent and should be utilized within 2 hours of reconstitution. HAL is instilled into an empty bladder and retained for 1–3 hours to ensure adequate fluorescence, then emptied [25]. It is important to note that cystoscopy must be performed within 60 minutes of emptying the bladder of the photosensitizing agent. Given the time needed for instillation and retention of HAL, streamlined processes should be in place to coordinate drug delivery from the pharmacy with early patient arrival to the clinic, along with education of relevant nursing staff [22].

There is an initial learning curve for BLC with a suggested minimum of 5 cases to learn the technique and approximately 30 required to achieve proficiency [26]. When BLC was first introduced, it required the utilization of a specialized rigid cystoscope (D-Light C Photodynamic Diagnostic system (KARL STORZ Endoscopy-America, USA) under general or spinal anesthesia. With rigid cystoscopy, the first step involves inspection and mapping of the bladder under WLC followed by BLC using 30°and 70° lenses. It is important when performing BLC to minimize tangential viewing which can result in fluorescent artifacts. Practical tips to minimize these artifacts include adequate distention of the bladder to flatten mucosal folds [17], and orienting the cystoscope perpendicular to the bladder wall. Larger angle optics (30° or 70° lens) can cause tangential illumination, and equivocal lesions should be further investigated with a 0° or 12° lens [17].

Bladder tumors typically appear red and fairly bright with clearly demarcated edges while CIS will occasionally appear as a reddish halo [17]. This is in contrast to nonmalignant inflammation that will appear pink with poorly demarcated margins. Once a lesion has been identified under BLC, it is important to switch to white light cystoscopy for biopsy or TUR as there is poor depth perception under BLC. Blood can significantly diminish the effectiveness of BLC so any biopsied or resected area should be meticulously coagulated before proceeding further. Due to the natural decay of the fluorescence, any suspicious area should be biopsied or resected without delay. As one nears the end of the resection, a final check for completeness should be performed under BLC [20].

Proper care of the equipment being utilized for BLC should be maintained. Any defect in the quality of light source energy or damage to the light cables will reduce power from the tip of the endoscope and thereby negatively affect the accuracy of BLC assessment [17]. Periodic checks of the equipment by the clinic managers or company representatives can play a critical role in the accuracy of this tool.

BLC/HAL has a relatively benign safety profile adding to the list of advantages of this endoscopic modality. The adverse events reported with the use of HAL were mild and mostly related to the procedure (TUR) rather than the photosensitizing agent itself. Common serious adverse

events included hematuria (2.6%) and urinary retention (1%). Neither anaphylactic nor toxic reactions have been reported, even in patients with multiple instillations of HAL [27].

Key Clinical Uses

BLC carries the greatest advantage over WLC in the following clinical scenarios:

1. *If there is suspicion of NMIBC at time of initial TURBT or first re-resection.* There is strong evidence that BLC increases detection of bladder tumors (especially Ta and CIS) compared with WLC [28]. It has been shown to reduce residual tumor rates by approximately 40% compared with WLC because it allows for better demarcation of cancerous areas [23].
2. *In patients with + urine cytology but negative findings on WLC.* This clinical scenario is likely due to a missed CIS that is better detected with BLC [28].
3. *If a patient has intermediate-risk NMIBC due to a high-grade Ta tumor, multiple low-grade tumors, or multifocal CIS.* BLC has been to shown to improve lesion detection and decrease recurrent rates in the setting of tumor multiplicity [29, 30].
4. *NMIBC surveillance for tumor recurrence.* BLC has been shown to be superior to WLC alone in detecting a recurrent lesion with approximately 30% of patients with recurrent tumors having at least one Ta or T1 lesion that was detected by BLC but missed on WLC [28].
5. *Six weeks after completion of Bacillus Calmette-Guerin (BCG) induction.* Previously, there were concerns about a high false-positive rate when using BLC within 90 days of BCG administration. Newest data show that even within 60 days of BCG administration, BLC has superior tumor detection compared with WLC, with no significant difference in the false-positive rate [20]. Additionally, it can aid in assessing response to treatment at this critical time point.
6. *As a teaching tool for residents and trainees.* The clear visualization of tumors and margins allows for improved education for TURBT technique.

Advantages and Disadvantages

Previous studies noted high false-positive rates (upwards of 30%) when utilizing BLC/HAL, especially in the setting of prior BCG treatment and in the hands of less experienced practitioners. However, these false-positive rates have declined tremendously as equipment and technique have improved [26, 31].

Initially, BLC required rigid cystoscopy under spinal or general anesthesia. However, in Europe, a flexible blue light cystoscope (D-Light C PDD Flexible PDD Videoscope system, KARL Storz Endoscopy-America) has been in use for the past 3 years with remarkable results. Recently in the US, the first phase III study evaluating flexible BLC published comparable results to rigid BLC [32], prompting its FDA approval for use in the outpatient setting. This study showed that flexible BLC with HAL-detected bladder recurrence in 21.5% of patients undergoing surveillance cystoscopy that would have been missed with WLC alone. Additionally, 35% of patients with CIS were only diagnosed when using flexible BLC but missed with WLC. The false-positive rates for both WLC and BLC were similar at 9% and there was no increase in adverse events with multiple instillations of HAL.

This procedure carries additional costs given the need for specialized cystoscopic equipment/light source, photosensitizing drugs, and training of the office staff. The Karl Storz® PDD system (cystoscope and light cord) costs approximately $40,000 US dollars and each HAL dose an additional $600. Despite these up-front costs, evidence suggests BLC nets $5000 in savings per patient during a 5-year follow-up period [33, 34]. Given the additional resources and skillset required for BLC, the Centers for Medicare & Medicaid Services (CMS) have approved a complexity adjustment for the APC 5373 (Level 3 Urology and Related Services) for this procedure.

Summary

There are significant advantages to HAL-BLC when compared with WLC for the oncological monitoring of NMIBC. While associated with an initial learning curve and high up-front costs, the clinical scenarios discussed in this section are important opportunities for urologists to improve clinical outcomes with BLC.

Key Tips/Tricks Box 3

1. Cystoscopy is the gold standard for oncological monitoring of NMIBC.
2. BLC has improved tumor detection and recurrence-free survival when compared with WLC.
3. BLC should be utilized in the six clinical scenarios outlined in the section above.
4. Minimizing tangential illumination, achieving adequate hemostasis, and optimizing viewing angles can help mitigate false positives when using BLC.
5. While upfront costs for BLC/HAL can be considerable, this technique may be cost-effective when considering improved patient outcomes.

Narrow-Band Imaging (NBI)

Narrow-band imaging (NBI) is a novel endoscopic method that has also been shown to improve the detection of NMIBC [35]. It allows users to enhance the tissue contrast between bladder lesions and benign urothelium without the use of exogenous contrast instillation (i.e, HAL in blue light cystoscopy).

The optical technique filters white light into 2 discrete bands, green (540 nm) and blue (415 nm). This facilitates intense absorption by hemoglobin, but only of superficial penetration of tissue. Visually, this translates into capillaries and vessels appearing dark brown or green against white/pink background of normal urothelium. This enhanced contrast allows for better identification of malignant tumors, which are usually more vascularized [36].

There has been considerable evidence showing that NBI improves detection of CIS, small Ta lesions, and recurrent NMIBC. When performed with TURBT, it reduces the recurrence risk by at least 10% at 1 year [37–39]. Clinical scenarios in which NBI would be most useful include: *(1) Evaluation of tumor margins after TUR of a large lesion; (2) initial diagnostic cystoscopy where there is suspicion for NMIBC; and (3) cystoscopic surveillance for NMIBC.*

When compared with BLC, NBI carries a cost-savings advantage as well as a flatter learning curve [38]. As with WLC and BLC, NBI is associated with an increased false-positive rate due to inflammation following intravesical BCG therapy. Currently, no clinical trials have compared NBI cystoscopy with WLC or BLC—presenting an opportunity for valuable and clinically relevant research.

Key Tips/Tricks Box 4

1. Narrow-band imaging (NBI) improves detection of CIS, small Ta lesions, recurrent NMIBC, and when performed with TURBT reduces the risk of recurrence.
2. NBI does <u>not</u> require drug instillation prior and has a minimal learning curve.
3. NBI is cheaper than blue light cystoscopy.

Urine Cytology and Novel Urine Markers

While cystoscopy and urine cytology represent the current standard of care for the follow-up of patients with NMIBC, there has been an impetus to develop reliable urinary markers to replace and/or complement the two. It is important to understand that a urologist *should not consider urinary biomarkers a replacement for cystoscopy* by current standards, but should recognize cer-

tain scenarios where urinary markers can help guide clinical management. There are currently *four markers* approved by the FDA and/or commercially available in the U.S. (NMP22, BTA stat, FISH UroVysion, ImmunoCyt). While these markers have gained approval by the FDA, they have not been uniformly included in current guidelines. The following sections will elaborate on these markers and define a strategy for their use in the surveillance of NMIBC.

Interpreting the Statistics for Urinary Markers

New biomarkers are constantly being investigated and thus clinicians require a basic understanding of how to interpret their statistical descriptors. This section can serve as quick reference guide to interpreting the statistical terminology often presented in the scientific literature. Key definitions to understand include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). We will provide a brief overview of this terminology prior to proceeding with a discussion on urinary markers.

Sensitivity and Negative Predictive Value (NPV)

Here, sensitivity is defined as the probability of patients *with bladder cancer who are identified with a positive test.* Therefore, the lower a urine marker's sensitivity the greater the risk of a missed diagnosis and subsequent bladder cancer progression [40]. Negative predictive value is the *probability that patients with a negative urine test truly do not have bladder cancer.*

Urinary markers with *high sensitivity and high NPV* should be used to monitor for *bladder tumor recurrence*, because this minimizes missed tumors [40].

Specificity and Positive Predictive Value (PPV)

Specificity is defined as the probability of patients *without bladder cancer who have a negative urine test.* Conversely, PPV is the *probability that subjects with a positive urine test truly have bladder cancer.*

Clinically, markers with *high specificity and high PPV* are best suited for *bladder cancer screening* as they limit the number of false-positive cases. Tests with high specificity and high positive predictive value can also guide the need for additional biopsies when no disease is seen [40].

Urine Cytology

Urine cytology has been widely used in the monitoring of NMIBC since it was first reported by Papanicollaou and Marshall in 1945 [41]. A urine sample is centrifuged and the sediment is stained and evaluated under a light microscope. A cytopathologist classifies the sample normal, atypical, indeterminate, suspicious, or malignant [42, 43].

Urine cytology boasts a high sensitivity (>80%) for high-grade tumors and CIS (28–100%), which have weaker intracellular attachments that allow malignant cells to slough into the urine [44, 45].

For all grades of bladder cancer, cytology sensitivities are quoted in the range of 25–65% [45, 46]. It is limited by lower sensitivity for low-grade tumors and variable interpretation depending on the skill of the cytopathologist [47–49]. Thus, while a positive voided urinary cytology should prompt strong suspicion for bladder cancer, a negative result alone does not reliably exclude malignancy.

To maximize urine cytology's yield, a minimum of 10 mL of fresh urine should be collected and adequately fixed [8]. Working with an experienced cytopathologist can help increase specificity to >90% [40]. While still commonly practiced, there is little evidence to show improved results with urine barbotage [50]. In fact, some experts prefer voided cytology because it may capture a urethral malignancy. Finally, in low-risk bladder cancer patients with unremarkable cystoscopy, the routine use of urine cytology or other urinary biomarkers during surveillance should be avoided.

The limitations of traditional urine cytology invite a potential role for alternative adjunctive markers, as described below.

Nuclear Matrix Protein 22 (NMP22®)

Nuclear matrix proteins (NMPs) are part of the scaffolding of the cell nucleus. They function to regulate gene expression and DNA replication by distributing chromatids to daughter cells. They serve as useful urine markers because urinary NMP22 is present in a 25-fold greater concentration in patients with bladder cancer [51, 52]. However, cystitis, urolithiasis, and hematuria can falsely elevate urinary NMP-22 levels [53].

The sensitivity and specificity of NMP22 in NMIBC disease range from 54% to 63% and 55% to 90%, respectively [40]. NPM22 is noted to have a lower sensitivity in detecting recurrent tumors as these are often smaller than primaries (recurrent tumor, 45% vs. primary tumor, 65%) [54]. This along with a relatively high false-positive rate (33–50%) has limited its widespread adoption for screening or surveillance [40].

Fortunately, NMP anecdotally *has not been* susceptible to BCG-induced false positives, has a NPV >90%, and has higher sensitivity and comparable specificity to urine cytology [55, 56]. A point of care assay (NMP22®BladderChek) can provide immediate results at a reduced cost of $10–$30, compared with $57 for urine cytology [57, 58].

Bladder Tumor Antigen (BTA®)

The bladder tumor antigen (BTA) test is an assay that detects complement factor H-related protein in the urine that is selectively released by bladder tumors [43]. There are currently two FDA-approved formats for the test which include the qualitative BTA stat and quantitative BTA TRAK (Polymedco Inc. New York, NY). The BTA stat is a rapid (<30 minutes) point of care test approved for surveillance but not initial diagnosis. It has a sensitivity for NMIBC ranging from 45% to 75% and an overall specificity ranging from 64% to 89% [40].

Unfortunately, BTA suffers from the same limitations as NMP22 including a high false-positive rate in the presence of benign inflammatory conditions (i.e., UTI, ureteral stents, calculi or instrumentation) [56, 59]. Similar to urine cytology, it is not sensitive for low-grade and low-stage disease. Unlike NMP22, however, BTA stat demonstrates an increased false-positive rate in the setting of BCG use [60].

Clinically, BTA could serve as a cost-saving ($10/test) replacement for urine cytology in surveillance of select NMIBC patients—those that are BCG-naïve and free of inflammatory urological conditions that could promote a false positive [40].

UroVysion®FISH

UroVysion uses fluorescence in-situ hybridization (FISH) to detect aneuploidy in chromosomes 3, 7,17 and deletions at chromosome 9p21 [61]. For the surveillance of recurrent tumors, UroVysion has a median sensitivity and specificity of 79% and 70%, respectively. And while it does perform well for the detection of CIS and high-grade disease, it is comparable to urinary cytology for its poor detection of low-grade and low-stage recurrent tumors.

UroVysion excels in its detection of bladder cancer recurrence after intravesical BCG administration. A common scenario for urologists is an indeterminate result from both cystoscopy and cytology following BCG therapy secondary to treatment-induced inflammation [43]. Patients with a positive UroVysion result following BCG have a four-fold increased risk of recurrence, a ten-fold increased risk of muscle-invasive disease, and higher likelihood of nonresponse to BCG [62]. This test can also be used to adjudicate “atypical” urine cytology results or unclear cystoscopy with a NPV of 100% [63]. This could prove invaluable, as evi-

dence demonstrates that approximately 90% of patients with a negative bladder biopsy and atypical urine cytology but a positive UroVysion developed biopsy proved bladder cancer in <12 months [64].

UroVysion is limited by cost, running approximately $475–$700 per assay [58]. It also lacks a standardized definition of a positive result. Nonetheless, this biomarker has a practical role in the assessing response to intravesical BCG and adjudicating equivocal cytology results.

ImmunoCytTM

ImmunoCyt is an FDA-approved assay using three fluorescent-labeled antibodies against two bladder cancer mucins and carcinoembryonic antigen (CEA) [43, 56].

Its sensitivity for NMIBC is 60% with an overall specificity of 78% [65]. Fortunately, when combined with urine cytology, the sensitivity for low-grade tumor increases from 23% to 79% and to 99% for high-grade tumors [66]. This combination improved the sensitivity of cytology in CIS up to 100%. It also has the added advantage of a high sensitivity and specificity for recurrent disease (67% and 75%, respectively) and detects 71% of tumor <1 cm in size with a NPV of 95% [56, 59].

When compared with NMP22 and BTA, ImmunoCyt detects recurrent and/or low-grade and low-stage tumors with fewer false positives in the setting of benign urological conditions [56]. Recent evidence has shown that patients with low-grade Ta disease have undergone successful surveillance with biannual ImmunoCyt and annual cystoscopy. However, this strategy has not been validated in studies for routine clinical practice. Guidelines support use of ImmunoCyt to clarify results of indeterminate urine cytology.

While limited by the cost ($130–$385 per test) and manpower needed for the microscopic examination of slides and quality control [58], Immunocyt looks to be one of the most promising biomarkers for bladder cancer to date.

Key Tips/Tricks Box 5

1. *Four* FDA approved biomarkers used in bladder cancer surveillance.
2. Urinary biomarkers at this current time should not be used to replace cystoscopy for surveillance.
3. Each biomarker must be understood for their distinct advantages and disadvantages so that they can properly be used in a clinic setting.

Summary

While cystoscopy is currently the mainstay in bladder cancer surveillance with its high sensitivity and specificity, alternative noninvasive diagnostic methods are being investigated. Urinary markers have some obvious benefits as they allow a clinician to avoid invasive procedures and potentially decrease the cost of monitoring. Currently, there are only *four* FDA approved urinary markers: BTA, NMP22, UroVysion, and ImmunoCyt. While these biomarkers can aid clinicians in potentially improving the efficacy of surveillance with NMIBC, there are certainly limitations to be considered. With time and further advancements in novel urine markers, we might be able to achieve a more "perfect" surrogate for cystoscopy. But for the time being, these urinary markers should serve as adjuncts to cystoscopy and cytology in monitoring NMIBC.

Cross-Sectional Imaging

Computed Tomography Urography

Cross-sectional imaging plays an important role in the upper tract surveillance of intermediate- and high-risk bladder cancer. Multidetector row computed tomography urography (CTU) is the preferred imaging modality to assess the upper urinary tract, potential extravesical tumor extension, and even metastases [67, 68]. CTU is funda-

mentally a CT examination of the urinary tract with a combination of noncontrast- and contrast-enhanced images including the important excretory phase.

CTU has a higher diagnostic accuracy for detecting upper tract urothelial cancers compared with intravenous urography (IVU) which has largely been replaced [69]. With current advancement in CTU technology, filling defects as small at 0.25 cm are able to be detected by excretory urography [70]. In addition to diagnosing upper tract urothelial tumors, CTU can be used to diagnose bladder tumors with a sensitivity of 93% and specificity of 99%.

While CTU protocols vary between institutions, there are a few rules of thumb that can help the urologist increase their diagnostic performance. The quality of a study is primarily dependent on the optimal distension and opacification of the collecting system, ureters, and bladder. One technique is the use of IV hydration and/or Lasix (10–20 mg), which can increase excretion into the collecting system and allow adequate distention of the ureters [71–73]. It is important to discuss the institution-specific CTU protocols with radiologists to optimize urothelial cancer surveillance imaging.

It is worth mentioning the common clinical scenario of nonopacified ureteral segments on CTU. Evidence shows that these segments are unlikely to harbor undiagnosed urothelial carcinoma in the absence of secondary findings. Therefore, it is not prudent to attempt complete opacification of every segment of the upper tract with additional imaging or procedures as this will lead to increased radiation exposure with no clear clinical benefit [74].

Magnetic Resonance Urography

Magnetic resonance imaging urography is another potential imaging modality when CTU is contraindicated. The most common clinic scenario is when a patient has kidney disease but maintains a GFR is >30 mL/min/1.73m^2 but <45 mL/min/1.73m^2, which for many institutional protocols makes them ineligible for CTU but still qualify for a MRU [75].

MRU is similar to CTU in that contrast is injected and then parenchymal enhancement and excretory phases are imaged [73]. While it has the advantage of minimizing radiation exposure and potentially characterizing tumor characteristics with diffusion-weighted imaging (DWI), it has several limitations. These include poor resolution to detect nonobstructing stones, decreased sensitivity for tumor detection (69%), increased expenses, and protracted time and effort to perform the study [73, 76]. To date, CTU remains the dominant modality with MRU limited to specific clinical scenarios including: patients with renal impairment (GFR <45 mL/min/1.73m^2), severe iodinated contrast allergy, and in the pediatric and pregnant population [73].

Key Tips/Tricks Box 6

1. CTU is dominant modality for surveilling upper tract in intermediate- and high-risk NMIBC.
2. CTU has a GFR cutoff of 45 mL/min/1.73m^2. MRU has a GFR cut-off of 30 mL/min/1.73m^2.
3. MRU has an inferior sensitivity in detecting upper tract tumors but may need to be used in certain clinical scenarios.

Bladder Biopsies

It is no longer recommended that random biopsies of normal appearing urothelial mucosa are required in order to detect CIS [25, 77, 78]. Studies have determined that these random biopsies do not aid in tumor detection and have the theoretical risk of tumor implantation where normal urothelial mucosa barrier has been violated. This poses a theoretical risk of increased tumor recurrence.

There is strong evidence that shows that in patients with intermediate- or high-risk disease

with persistent or recurrent disease, there is increased risk of urethral recurrence and possibly even metachronous upper tract urothelial tumors. As such, it is important for the clinician to consider performing a prostatic urethral biopsy and upper tract evaluation before continuing with additional intravesical therapy [79].

Options for prostatic urethral biopsy can include TUR or cold-cup biopsy of the prostatic urethral at the 5 and 7 o'clock positions, while upper tract evaluation can utilize CTU or MRU at the time of cystoscopy.

Variant Histology

While the exact incidence is unknown, the presence of variant histology in nonmuscle-invasive bladder cancer is well documented in the literature. Put simply, these variants *should no*t be surveilled by the normal NMIBC bladder cancer guidelines discussed prior. In patients with high-risk NMIBC with variant histology including pure squamous cell carcinoma (SCC), adenocarcinoma, sarcomatoid, plasmacytoid, and micropapillary bladder cancer, *upfront cystectomy should be offered* [80]. In the case of small cell variant NMIBC, this should be treated with *upfront chemotherapy* followed by patient-specific local therapy. Finally, the remaining NMIBC variants can be managed similar to the guidelines for high-risk NMIBC.

It is worth noting that at many times these variant histology bladder tumors may masquerade as NMIBC, but truly are at a more advanced stage. Therefore, it is critical that you have an experienced GU pathologist re-review these slides to avoid the mistake of potentially understaging the tumor.

Key Tips/Tricks Box 7

1. Variant NMIBC bladder cancer is rarely monitored and many times requires upfront cystectomy or chemotherapy.
2. An experienced GU pathologist should re-review all cases of variant histology in NMIBC to ensure accurate staging.

Lifestyle Modifications

While the link between bladder cancer and smoking has been well established, less commonly known is the association between smoking and bladder cancer recurrence [81]. As a result, as low as 7% of urologists and ~ 30% of primary care physicians actually discussed smoking cessation with smokers who had an active diagnosis of bladder cancer [82]. Research has shown that a failure to quit smoking once a diagnosis of noninvasive cancer has been made, portends a worse prognosis (i.e., stage progression) [83]. Fortunately, the most recent data suggest that smoking cessation can improve 3-year recurrence-free survival [84].

An active smoker with a diagnosis of NMIBC should have a frank discussion with their urologist about smoking cessation and should be offered resources to aid efforts to quit smoking. Some hospitals host smoking cessation clinics to which a patient can be referred.

Conclusion

Nonmuscle-invasive bladder cancer remains a prevalent disease with a significant morbidity and mortality. This disease often requires surveillance in perpetuity as a result of the high recurrence rates and risk of progression to muscle-invasive disease. As a result, patients are subjected to multiple invasive procedures that both impact their quality of life and contribute to the burden of cost currently plaguing our health system.

As a result, efficient and effective oncological monitoring of NMIBC is an essential tool that all practicing urologists must have. While there is considerable evidence detailing a variety of strategies for monitoring NMIBC, we believe that this is the first practical blueprint that urologists can utilize in their everyday practice. By incorporating tips and tricks by experts in the field we hope that we have given you a resource that will allow you to provide even better care for the patients.

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Radical Cystectomy

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Enhanced Recovery After Surgery Protocols

Saum Ghodoussipour and Siamak Daneshmand

Indications for Cystectomy and Morbidity of Surgery

With over 500,000 new diagnoses each year and 200,000 deaths, bladder cancer (BC) is one of the most common and lethal malignancies worldwide [1]. A quarter of all cases are muscle invasive with significant risk of mortality. While less lethal, nonmuscle-invasive disease has a risk for recurrence and progression [2, 3]. These risks are greatest in patients with T1 disease, high-grade disease after failure of intravesical therapy, and certain variant histologies [4]. The management of BC is therefore aggressive with radical cystectomy (RC), pelvic lymphadenectomy, and urinary diversion considered standard of care for muscle-invasive disease, certain high-risk

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nonmuscle-invasive diseases, and after failure of intravesical or trimodal therapy [4–6].

While RC leads to improved long-term survival, the operation is one of the most complex urological operations with risk of perioperative morbidity. Postoperative length of stay (LOS) has been reported up to 17 days in European studies and up to 9 days in US registry studies [7, 8]. Complications occur in up to 60% of patients and readmissions in 30% [9]. The adoption by urologists of enhanced recovery after surgery (ERAS) protocols has dramatically improved the perioperative care of patients undergoing RC. ERAS protocols, originally shown to be of benefit in colorectal surgery, are evidence-based multimodal pathways that optimize all elements of perioperative care. This includes preoperative, intraoperative, and postoperative modifications to enhance recovery and reduce stress following surgery. In this chapter, we describe the history and use of ERAS after RC, the evidence for the various components of the protocol and modern efforts to improve outcomes.

ERAS History and Use in Urology

While the use of ERAS after RC is a recent innovation, perioperative care pathways to improve outcomes were first developed to reduce the significant variation in outcomes seen across different centers in Europe in the 1990s [10]. The first protocols were mostly used in colorectal surgery and originally referred to as "Fast-Track" programs. Eventually, the focus shifted toward improving recovery, and an ERAS society was formally established in 2001 [11]. There are now several specialty-specific guidelines published, including a guideline for care after radical cystectomy that was published in 2013 [12]. However, acceptance of protocols has not been universal. Barriers to implementation include persistent surgical dogma, uncertainty over the benefits of each protocol intervention and apprehension in implementation due to perceived difficulty or lack of institutional resources. With improving evidence, acceptance is increasing.

Pruthi et al. were the first to show the benefit of a perioperative care pathway after radical cystectomy. Published in 2003, their pathway included limited bowel preparation, preoperative education, smaller incisions with initial preperitoneal dissection, use of stapling devices, prokinetic agents, early nasogastric tube removal, nonnarcotic analgesia, and early oral diet. In their cohort of 40 consecutive patients, they found a median hospital stay of 5 days. Only one patient developed postoperative ileus (POI), and hospital stay was 7 days in this patient [13]. In 2008, Arumaainayagam published their results with an enhanced recovery protocol after RC in the UK. They compared 56 consecutive patients before implementation of the protocol to 56 after implementation of the protocol. The protocol focused on reduced bowel preparation as well as standardized feeding and analgesia. They found a statistically significant reduction in LOS from 17 days to 13 days ($p < 0.001$) without change in readmission, morbidity, or mortality [8]. Pruthi et al. then updated their series in 2010 to include 362 consecutive patients. In an analysis of the 100 most recent patients in the pathway, they found a median time to bowel movement of 2.9 days, a median time to discharge of 5 days, complication rate of 39%, and readmission rate of 12% [14]. In 2014, we reported on our experience at the University of Southern California with 126 patients undergoing a pathway that included no bowel preparation, early feeding (regular diet on postoperative day one), nonnarcotic pain management, and mu opioid antagonist use (Table 14.1). Median hospital stay was decreased from 8 days in a pre-ERAS cohort to 4 days with no change in 30-day complication (68% overall, 14% major) or readmission rates (21%) [15]. We have since updated this cohort to show a decreased use of narcotics [16] and cost [17] compared to the pre-ERAS cohort. A recent update by Bazargani et al. included 377 consecutive patients treated with ERAS who were matched to a cohort of 144 patients treated pre-ERAS. Median hospital stay with the ERAS protocol was stable at 4 days, but there was a significant reduction in gastrointestinal complications compared to the pre-ERAS cohort (13% vs 27%, $p = 0.003$) with POI being the most common, but again significantly lower in the ERAS cohort (7% vs 23%,

$p < 0.001$) [18]. The use of ERAS after radical cystectomy has now been reported by several centers with a meta-analysis by Tyson et al. showing lower complication rates, shorter length of stay, faster return of bowel function but no significant difference in overall readmissions rates with ERAS [19].

Components of ERAS

While ERAS protocols for RC vary from institution to institution, key evidence-based interventions exist. Though the focus is on outcomes *after* surgery, these protocols address the patient's entire surgical journey, starting from the time of initial consultation through intraoperative management, in hospital care and after return home.

Preoperative Measures

Initial Assessment—Role of Prehabilitation and Nutrition

The initial assessment of patients undergoing radical cystectomy with ERAS is critical as certain nonmodifiable patient factors affect outcomes and may require individualized tailoring of the protocol [20]. One such risk factor associated with worse outcomes after RC is frailty [21]. Though definitions of frailty vary, it is commonly described as a physiologic state of increased vulnerability to stressors that results from decreased physiologic reserve or dysregulation of multiple physiologic systems [22–24]. In other surgical fields, frailty has been associated with postoperative complications such as delirium and surgical site infections [25–28]. After RC specifically, frailty has been shown to be an independent predictor of high-grade complications. Sathianathen et al. found an OR of 3.22 (95% CI 2.01–5.17), and Burg et al. found an OR of 4.87 (95% CI 1.39–22.87) for 30-day high-grade complications in patients with higher frailty scores [29, 30]. Given the association of age and frailty, an understanding of a patients' frailty is important to consider in preoperative discussion and education of the typically elder cystectomy population [31]. Though frailty is often considered an irreversible condition, a preoperative exercise program or "prehabilitation" has been shown to improve functional capacity for better toleration of surgery and to facilitate recovery [32]. Several trials examining the impact of prehabilitation on post cystectomy recovery are currently underway (NCT01840137, NCT01836978, NCT03347045). Early results are not powered to detect differences in clinical outcomes, but Jensen et al. have shown good adherence to preoperative exercise regimens with improved postoperative mobility [33] and Banerjee et al. have shown improvements in cardiopulmonary exercise measures including peak oxygen pulse, minute ventilation, and power output after participation in a prehabilitation program [34].

Often coexisting with frailty, malnutrition in the cystectomy population is an increasingly understood problem that is targeted with modern ERAS protocols. Malnutrition has classically been defined using laboratory-based values such as hypoalbuminemia. This has been linked to postoperative respiratory failure after major surgery and increased mortality and length of stay after cystectomy [35–37]. While malnutrition is

Table 14.1 Protocol interventions at the University of Southern California

Protocol interventions
Preoperative
Assessment of frailty and nutrition
Cystectomy education
No bowel preparation
Venous thromboembolism prophylaxis
Mu opioid antagonist
Intraoperative
Goal directed fluid therapy
Minimization of narcotic pain management
Postoperative
No nasogastric tube
Venous thromboembolism prophylaxis
Incentive spirometry
Early ambulation
Minimization of narcotic pain management
Mu opioid antagonist
Bowel regimen including neostigmine
Antiemetics around the clock
Regular diet on postoperative day one
Oral antibiotic prophylaxis on postoperative day one
Arranging home intravenous fluids (1 L QOD for 1–2 weeks)

present in over 70% of surgical patients using such laboratory-based definitions, recent guidelines have transitioned toward clinical definitions given the role of albumin as a nonspecific marker of the inflammatory response [38–40]. These guidelines define malnutrition in the setting of malignancy as a multifactorial problem marked by loss of skeletal muscle mass (sarcopenia) and a negative protein and energy balance [39, 40]. By definition, cancer cachexia cannot be fully reversed by conventional nutritional support, but growing evidence shows improved outcomes after surgery with early nutritional supplementation. Specifically complications, readmissions, and LOS have been shown to decrease with preoperative supplementation, and mortality has been shown to decrease in malnourished patients [41, 42]. The American Society for Enhanced Recovery and Perioperative Quality Initiative recently published a consensus statement on nutritional screening and therapy within ERAS. They recommended preoperative nutritional screening to include an evaluation of lean body mass, emphasis on overall protein intake greater than 1.2 g/kg/day, the use of oral nutritional supplements, abandonment of preoperative fasting rather allowing solid foods 8 hours before and clear liquids up to 2 hours before surgery, and a preoperative drink containing at least 45 g of carbohydrates [43]. More recent innovations in preoperative nutrition include immune-modulating nutrition or "immunonutrition." Several systematic reviews and meta-analyses in the colorectal literature have shown decreased LOS, wound complications, infections, and inflammatory cytokine levels in patients receiving preoperative immunonutrition with arginine and omega-3 fatty acids [44–46]. Data after radical cystectomy are limited, but pilot data are encouraging. Bertrand et al. randomized 30 patients to 7 days of preoperative immunonutrition and matched them to 30 patients without immunonutrition before RC. They found fewer postoperative complications (40% vs 76.7%, $p = 0.008$), POI (6.6% vs 33.3%, $p = 0.2$), and infections (23.3% vs 60%, $p = 0.008$) as well as a 3-day shorter LOS in the immunonutrition vs no immunonutrition group [47]. Hamilton-Reeves et al. performed a randomized trial of 29 patients who received specialized immunonutrition before and after RC (n = 14) or a calorie-matched oral nutrition supplement before and after RC (n = 15). Though not powered to detect clinical differences, they found a 33% reduction in postoperative complications (95% CI 1–64) and a 39% reduction in infections (95% CI 8–70) at 90 days. The expansion of myeloid-derived suppressor cells was lower in the immunonutrition group, and this was hypothesized to contribute to the lower rate of infections [48]. These preliminary results are currently being validated in a multicenter trial in the Southwest Oncology Group (SWOG S1600).

Education

While no specific evidence exists regarding preoperative counseling and education before RC, it should not be overlooked as an important component of ERAS. The medical interventions in ERAS protocols can reduce physical stress after surgery, but all care providers play a role in reducing the emotional stresses of surgery. Fears of surgery and unknown expectations provoke anxiety, which has known associations with poor pain control, wound healing, LOS, and even mortality after surgery [49–51]. Preoperative counseling may help to alleviate anxiety and improve patients' toleration of surgery [12, 52]. Patients also often have wishes and goals regarding their recovery, and these need to be addressed before surgery [31]. Our protocol includes a dedicated preoperative education course where patients meet in a group setting with an ERAS nurse practitioner, stoma/pouch specialist, and a pelvic floor therapist. In these sessions, we discuss what to expect during the hospital stay as well as what to expect after discharge, including time to recovery and potential lifestyle changes. Though always discussed in consultation with the surgeon, urinary diversion-related concerns such as catheterization and continence are discussed as are sexual health-related outcomes unique to men and women after RC. We also describe our ERAS protocol including the evidence behind the measures of the protocol and reasoning for their implementation.

No Bowel Preparation

One of the earliest interventions in ERAS protocols for RC was the omission of mechanical bowel preparation (MBP). The use of MBP is one example of surgical dogma, which was historically used to decrease infections and complications prior to any surgery that involved manipulation of the bowel [53]. Risks of infection in colorectal surgery were attributed to the high density of bacterial colonies in the colon and influenced urology, where the majority of urinary diversions use ileum, which has increased bacterial densities, though not to the same level as in the colon [54]. The benefit of MBP in colorectal surgery has been disproven in several contemporary studies including well-designed systematic reviews showing no differences in anastomotic leaks, wound infections, or overall complications [55, 56]. Shaffi et al. performed a retrospective review of patients undergoing RC and ileal conduit urinary diversion in Ireland from 1991 to 1991. They identified 64 patients who had surgery without bowel preparation and 62 with. There was no difference in rates of infection, anastomotic dehiscence, sepsis, or mortality. Bowel preparation had negative effects on POI, which occurred in 12 patients with bowel preparation vs 1 without, time to toleration of oral fluids (5.8 days with and 3.4 days without bowel preparation), and length of stay (31.6 days with vs 22.8 days without bowel preparation) [57]. More contemporary studies and reviews have shown no difference in overall complications including bowel leaks, obstruction, mortality, and recovery of bowel function or LOS after radical cystectomy [55, 58, 59]. More recent data have emerged suggesting that the addition of oral antibiotics with MBP may reduce surgical site infections and anastomotic leaks in colorectal surgery [60]. However, the data are heterogeneous and do not show a clear benefit when guideline-directed systemic antibiotic therapy is used. The elimination of an oral mechanical bowel preparation received a strong recommendation in the ERAS Society guidelines for perioperative care after colorectal surgery as well as RC and is no longer routinely used at our institution [12, 61].

Venous Thromboembolism Prophylaxis

The development of venous thromboembolism (VTE) is a rare but potentially fatal complication after radical cystectomy. VTE has been suggested to occur in 22% of patients undergoing pelvic surgery without prophylaxis and still in 5.5% of patients undergoing RC in the modern era [62, 63]. We therefore provide preoperative VTE prophylaxis with either heparin or low-molecular-weight heparin (LMWH) for all patients undergoing RC per AUA recommendations [64]. There is little data on when prophylaxis should be initiated, but we provide a single dose in the preoperative area. More data exist on the controversy of how long to continue VTE prophylaxis after RC. The use of extended prophylaxis requires consideration of the risks of DVT occurring after discharge vs risks of bleeding complications. A meta-analysis of randomized controlled trials comparing the standard use of LMWH to extended duration (3–4 weeks postoperative) after major abdominal surgery found a decreased risk of VTE (RR 0.44, 95%CI 0.28–0.71) without increased risk of bleeding (RR 1.2, 95%CI 0.61–2.06) [65]. A more recent Cochrane review identified 7 randomized controlled trials comparing prolonged prophylaxis (>14 days) to prophylaxis during hospital admission only, and they also found a significant decrease in the risk of VTE development (OR 0.38, 95% CI 0.26–0.54) [66]. We continue prophylaxis with LMWH for all patients undergoing RC with ERAS for a total of 4 weeks after surgery.

Mu Opioid Antagonists

Perhaps, the greatest evidence for any individual component of ERAS exists for Alvimopan. Alvimopan is a peripherally acting mu opioid antagonist that was first approved by the United States Food and Drug Administration in 2008 to accelerate GI recovery following partial large or small bowel resection with primary anastomosis [67]. The indications for the use of alvimopan were expanded to cystectomy after a multicenter randomized placebo-controlled trial led by Lee et al. in 2014. In this study, 277 patients were assigned to 12 mg of alvimopan or matching placebo administered preoperatively and then con-

tinued twice daily until discharge or a maximum of 15 in-hospital doses. Patients who received Alvimopan had accelerated GI recovery (defined as first toleration of solid food or first bowel movement) at 5.5 days vs 6.8 days with placebo (HR 1.8, $p < 0.001$), shorter LOS (7.4 vs 10.1 days, $p = 0.0051$), and fewer episodes of POI (8.4% vs 29.1%, $p < 0.001$) [68]. A later analysis of the study found that alvimopan decreased hospitalization costs by $2640 per patient by reducing POI associated healthcare expenditures and by decreasing LOS [69]. The evidence for the use of alvimopan was bolstered by a systematic review and meta-analysis that identified 5 studies with 613 patients undergoing radical cystectomy, almost half (294) received alvimopan. The use of alvimopan decreased the time to toleration of clear liquids (HR 1.34, 95%CI 1.19–1.51), solid food (HR 1.22, 95%CI1.12–1.43), first bowel movement (HR 1.27, 95%CI 1.12–1.43), and LOS (HR 1.17, 95%CI 1.10–1.25) [70]. A Cochrane review in 2018 summarized the findings by Lee et al. to conclude that alvimopan administered before and after radical cystectomy decreased the time to toleration of solid foods or bowel movement by 1.3 days, the time to discharge by 0.9 days and decreased the risk of major adverse events within 30 days by 355 fewer cases per 1000. There was no increased risk of readmission (RR 0.89, 95% CI 0.59–1.33) or cardiovascular events (RR 0.54, 95% CI 0.27–1.05) [71]. While alvimopan is not universally available, it has been a standard component of our institutional ERAS protocol where it is administered preoperatively and continued until the first bowel movement [15].

Intraoperative Measures

Fluid Management

A standardized approach to intraoperative fluid management is an important component of ERAS protocols, yet an ideal fluid regimen does not exist. A restrictive strategy has been employed to avoid fluid overload and its associated risks of mortality and morbidity [72, 73]. Some have even used vasopressors rather than extra fluids to maintain tissue perfusion. In a randomized, double-blind trial by Wuethrich et al., 166 patients were assigned to either a restrictive arm of 1 ml/kg/hr of lactated ringers during cystectomy and then 3 ml/kg/hr until the end of surgery combined with preemptive norepinephrine or a liberal arm where they received 6 ml/kg/hr of fluid throughout surgery. The authors found a lower rate of complications in the restrictive group (52% vs 73%, RR 0.7, 95%CI 0.55–0.88), a two-day shorter hospital stay (median 15 days vs 17 days, $p = 0.02$) and a nonsignificant decrease in 90-day mortality (0% vs 4.8%, $p = 0.12$) [74]. Our institutional protocol formerly included restriction of intravenous fluids after clamping of the ureters during cystectomy and lymph node dissection. However, a review of outcomes did not reveal any association between total fluids received and complications at 30 days (OR 1.07 for each 1 L, 95% CI 0.88–1.31, $p = 0.52$) or 90 days (OR = 1.16 for each 1 L, 95% CI 0.92–1.49, $p = 0.23$) [75]. Moreover, the harms of fluid restriction were shown in a multicenter, international randomized trial of restrictive vs liberal fluid administration during major abdominal surgery, almost 15% of which were urologic. The study included 1490 patients who had a restrictive fluid regimen with a goal net-zero fluid balance and 1493 with a liberal regimen. The patients in the restrictive arm received a median of 3.7 liters compared to 6.1 liters in the liberal arm ($p < 0.001$). There was no significant difference in patient-reported disability at 1 year following surgery (HR 1.05, 95% CI 0.88–1.24, $p = 0.61$). However, the rate of surgical site infection was higher in the restrictive group (16.5% vs 13.6%, $p = 0.02$), and importantly, the rate of acute kidney injury was 8.6% in the restrictive group compared to 5% in the liberal fluid ($p < 0.001$). It is possible that the harms of fluid restriction are real or that the benefits of fluid restriction are attenuated by the other interventions in ERAS protocols. This has led many, including at our own institution, to pursue a more individualized approach to fluid management.

Goal-directed fluid therapy (GDFT) has a goal of optimizing cardiac preload by administering fluids in response to metrics such as

stroke volume variation, often measured with esophageal Doppler monitoring [76]. The ability of GDFT to avoid gut hypoperfusion was shown in a meta-analysis of patients undergoing major abdominal surgery that found a significantly decreased risk of major GI complications with GDFT (OR 0.42, 95% CI 0.27–0.65) [77]. A randomized trial by Pillai et al. of 66 patients assessed the effect of GDFT with esophageal Doppler monitoring during radical cystectomy. They found that despite higher volumes in the GDFT group compared to the control group, there were lower rates of ileus (7 vs 18, $p < 0.01$), a shorter time to flatus (3.55 days vs 5.36 days, $p < 0.01$), and less infections (1 vs 8, $p < 0.010$) [78]. It is important to note, however, that these patients did not undergo surgery with an ERAS protocol. A meta-analysis of 1399 patients undergoing major abdominal surgery found similar results with shortened time to tolerate oral intake, first bowel movement, and reduced nausea and vomiting with GDFT. However, the benefits of GDFT were lost when analyzing a subset of patients undergoing surgery with ERAS [79]. Future studies are needed to investigate the appropriate fluid regimen in patients undergoing RC, specifically within an ERAS protocol. For now, we do favor an individualized approach with standardized care coordination between the surgical and anesthesia teams.

Minimization of Narcotic Pain Medications

A heavy emphasis on limiting narcotics is key to any modern ERAS program. This is important in every stage of a patient's surgical journey, including during preoperative and postoperative education, but hinges strongly on intraoperative management. In-hospital narcotics use is known to predict poor outcomes including POI and prolonged LOS [80–82]. The goal of ERAS analgesic regimens should therefore be to minimize narcotics while adequately controlling pain. This requires a multimodal approach with drugs targeting different mechanisms in the pain pathway [83]. Nonsteroidal anti-inflammatories (NSAIDS), cyclooxygenase-2 inhibitors, acetaminophen, and even gabapentin have been shown to reduce pain scores and opioid consumption after surgery [84–87]. A meta-analysis of randomized controlled trials including 4893 adult patients after surgery showed that multimodal analgesia can decrease morphine consumption by 15–55% [88]. A multimodal approach has been used in many of the published ERAS series in radical cystectomy and is utilized at our institution [19, 89–91]. Our protocol includes the intraoperative administration of ketorolac and intravenous (IV) acetaminophen, which has been shown to improve analgesia and reduce morphine consumption as compared to oral acetaminophen in several randomized trials [92–94]. A recent study by Audenet et al. showed the feasibility of a completely opiate free pain regimen during cystectomy. Their study included 52 consecutive patients undergoing robotic-assisted radical cystectomy (RARC) with a pain regimen that included acetaminophen 1000-mg, gabapentin 600 mg, and celecoxib 600 mg per os before surgery. Intraoperative anesthesia included the use of ketamine and propofol, but not fentanyl. IV acetaminophen was given every 6 hours during surgery, and a 30 mg ketorolac infusion was given at the end of the case. Postoperative care continued with IV hydromorphone only given as needed. When compared to 41 patients not treated with the opiate free protocol, those treated without opiates had shorter time to regular diet (4 vs 5 days, $p = 0.002$), LOS (5 vs 7 days, $p < 0.001$) and an 8.6% reduction in costs at 30 days ($p = 0.032$) [95].

In the study by Audenet, a regional block with bupivacaine was given in the operating room before surgery [95]. Regional pain control with local anesthetics through transversus abdominis plane blockade has been used with success in cystectomy and other major urologic surgeries [90, 96, 97], while others have had success with liposomal bupivacaine [98]. While direct comparisons of blockade strategies are limited, the 2013 ERAS guidelines for cystectomy recommended the use of thoracic epidural analgesia to be continued for 72 hours after cystectomy [12]. This recommendation was largely based off of success with epidural use after open colorectal surgery [99]. We have avoided epidurals after

open cystectomy in our protocol, favoring the intraoperative placement of subfascial catheters with continuous infusion of ropivacaine due to improved postoperative mobility and an earlier discharge window [15]. Overall, the measures in our study have lead to a decreased use of opioids compared to our pre-ERAS cohort [16].

Minimally Invasive surgery

Other guideline statements on ERAS in pelvic surgery recommend minimally invasive surgery (MIS) to be included as a protocol intervention due to a decreased inflammatory response, more rapid recovery, and lower complication rates compared to open surgery [61]. RARC is a growing treatment option for patients with bladder cancer, but the literature to date does not suggest an advantage to the open approach. Early studies suggested shorter LOS and fewer complications with RARC, but these studies were composed of retrospective series that used open surgeries performed in the pre-ERAS era as the comparator group [100, 101]. There have been two randomized controlled trials comparing RARC to open RC and neither found a benefit in terms of complications or LOS. RARC was associated with lower estimated blood loss in both studies, but also longer operating room time and higher costs [102, 103]. A recent study by Tan et al. compared 45 patients who had open RC before ERAS, 50 with RARC without ERAS, and 50 with RARC with ERAS. They found that RARC decreased LOS from 17 days in the open cohort to 11 days and 7 days with RARC without and with ERAS, respectively ($p < 0.001$). Complications similarly decreased at both 30 days (74.4%, 64%, and 38%, $p = 0.001$) and 90 days (86%, 78%, and 42%, $p < 0.001$) for open RC, RARC without ERAS, and RARC with ERAS, respectively. On multivariate analysis, ERAS was associated with a LOS less than or equal to 10 days (OR 0.2, 95% CI 0.07–0.57) and lower 90-day complication rates (OR 0.17, 95% CI 0.06–0.4), but the robotic approach was not independently associated with outcomes [104]. A recent report from our institution found a median LOS of 4 days after open RC and 6 days after RARC but no significant difference in major complications (20% vs 23.8%, $p = 0.51$) or readmissions (32.2 vs 36.4%, $p = 0.4$) at 90 days. Surgical approach was not predictive of readmissions or major complications on multivariable analysis [105]. RARC is certainly feasible, and it is performed at the discretion of the operating surgeon at our institution, but ERAS remains an important part of patient's care regardless of the surgical approach.

Postoperative Measures

Many of the postoperative measures included in ERAS protocols are a continuation of earlier implemented ones. This includes interventions such as a continued focus on mobilization, nutrition, VTE prophylaxis, use of alvimopan, and nonnarcotic pain management. Several of the more essential measures are highlighted here.

No Nasogastric Tube

The routine use of postoperative nasogastric tube (NGT) was prevalent in the pre-ERAS era. NGT placement was done for patients undergoing major abdominal surgeries including cystectomy in order to hasten the return of bowel function and prevent bowel anastomotic leaks as well as pulmonary complications from aspiration events. This practice has fallen out of favor as several studies have shown no benefit and sometimes even harm from NGT placement. A Cochrane review of 33 studies including 5240 patients who were randomized to standard NGT placement vs selective placement found that patients without NGTs actually had an earlier return of bowel function and decrease in pulmonary complications without difference in anastomotic leak rates [106]. In 2005, Park et al. found no difference in rates of POI when patients had their NGT removed within 24 hours of cystectomy vs at first flatus [107]. Adamkis et al. performed a randomized trial in 43 patients undergoing cystectomy. They compared NGT removal within 12 hours of surgery vs maintenance until flatus. There was no difference in POI, time to regular diet, or any other complications [108]. Moreover, Inman et al. showed that NGT placement after cystectomy may prolong GI recovery. In their review of 430 patients who had NGT after cystectomy vs those who did, NGT use was associ-

ated with longer time to first bowel sounds, first flatus and a longer LOS without difference in POI, bowel obstruction, anastomotic leaks, or aspiration pneumonia [109]. We avoid the routine use of NGTs at our institution. Some patients may ultimately need one placed for ileus with nausea and vomiting, but other measures of our protocol mitigate these risks. Among others, these include the use of regular antiemetics and the continuation of alvimopan, which has been shown to decrease risk of NGT placement [110].

Early Feeding

Along with prolonged use of NGTs, delayed feeding until full return of bowel function was a dogmatic practice common in the pre-ERAS era. Early oral feeding is now an emphasis of most ERAS protocols given evidence that using the gut is the best way to maintain intestinal integrity, modulate the immune response, and stimulate motility [111]. Another formerly common practice in the cystectomy population was the use of parenteral nutrition until patients could tolerate solid food by mouth. Several prospective studies and trials have shown that parenteral nutrition compared to early oral feeding not only increases LOS and complications, mostly infectious, but also increases costs [112, 113]. A 2006 Cochrane review looking at randomized controlled trials of early feeding (within 24 hours) in colorectal surgery identified 13 studies with 1173 patients and found no advantage to delayed feeding [114]. ERAS society guidelines for both colorectal surgery and cystectomy now recommend oral nutritional supplementation to be started on the day of surgery [12, 61]. It has been our practice to start clear liquids on the day of surgery and transition to a regular "cystectomy diet" that is composed of low-fiber, low-residue, smaller-volume meals given more frequently for easier digestion [15]. Rarely, patients are unable to tolerate an early diet due to a period of gastroparesis. Few predictors for this situation exist, but we have successfully managed patients with known gastroparetic symptoms before surgery with gastrojejunal or nasojejunal feeds. This practice is supported by a study from the Netherlands, where patients who received nasojejunal feeding as standard practice in an ERAS protocol for RC had similar complications and LOS but lower rates of POI (11.9% vs 34.3%, $p = 0.009$) compared to a group with early oral feeding [115].

Early Ambulation

Just as prehabilitation aims to maintain or improve functional capacity before surgery, an early emphasis on ambulation ensures that patients continue on the path to recovery. Many of the studies that assess early mobilization after surgery are of poor quality and without standardized outcomes [116]. While there are no studies directly assessing the role of early ambulation after RC, it has been a component of ERAS since the earliest guideline in 2013 [12]. Though bed rest was often accepted as patients recovered from surgery in the pre-ERAS era, the association between bed rest, VTE, and in-hospital complications, such as pneumonia, has been known [117, 118]. We encourage patient mobilization on the day of surgery and ensure patients are ambulating on postoperative day 1. This requires coordinated care with nursing teams and often with the assistance of our physical therapy colleagues.

Modern Efforts in ERAS

As the literature regarding ERAS for RC continues to grow, an increasing emphasis must be placed on improving protocols and obtaining a better understanding of outcomes. The primary outcome reported by many of the early studies in ERAS was LOS. However, LOS is driven by many factors, including nonmodifiable ones like patient age, race, and comorbidities but also by financial and cultural pressures [20, 119]. For example, there is a greater pressure on earlier discharge in the USA as compared to European centers. It is therefore important to consider other measures more indicative of patient recovery. Modern efforts include an analysis of outcomes beyond the index admission that may affect readmission, the patient experience, and costs.

Despite the improvements in perioperative care seen with ERAS, readmission rates remain

rather high at 21–31% [120–123]. Most readmissions occur within 2 weeks of discharge and are due to infectious causes or a failure to thrive/dehydration [124, 125]. Opponents of ERAS argue that an earlier discharge simply results in patients later being readmitted. Our series have not shown any difference in readmission rates before and after implimentation of ERAS [15, 125], and others have similarly found no correlation with decreased LOS and increased readmission [126]. The criteria for discharge from the hospital have not changed in pre-ERAS and ERAS eras, but patients do seem to be ready for discharge earlier. Still, our protocol has measures that aim to decrease readmissions. These include a strict follow-up schedule and the administration of IV fluids at home. The benefits of such measures are unclear, but efforts to improve late outcomes will continue.

The ability of ERAS to improve the patient experience needs to be further characterized moving forward. Many of the measures in ERAS can improve the patient's surgical experience including preoperative education to decrease anxiety, omission of NGTs, and multimodal analgesic management to decrease pain. There is emerging evidence highlighting these benefits. Karl et al. found an improved quality of life with ERAS [127], Baack-Kukreja et al. found improved patient-reported outcomes including pain, drowsiness, dry mouth, and interference with functioning [128], and Frees et al. found less pain and bowel symptoms in patients undergoing RC with ERAS [91]. As future measures are investigated, similar measures of subjective recovery need to be considered.

As excitement for ERAS grows, it will be prudent to ensure the cost-effectiveness of protocols and any added measures. This first requires ensuring that the evidence of benefit for interventions is strong and that protocols do not become overly complicated, difficult to follow, and poorly implemented. As it stands now, ERAS protocols have shown significant cost savings that may be attributed to standardized utilization of healthcare services and streamlined inpatient care [17, 129, 130].

Conclusion

ERAS for RC has modernized the perioperative care of patients undergoing RC. This has led to proven benefits in LOS, patient experience, and costs. With growing evidence, acceptance of ERAS protocols is sure to increase. In order to continue improvement, a need for more evidence-based measures is needed to improve outcomes including late complications, readmissions, the patient experience, and associated costs.

Open Radical Cystectomy Male/Female

Fiona C. Burkhard, Bernhard Kiss, and George N. Thalmann

Radical Cystectomy

Management of muscle-invasive bladder cancer and recurrent nonmuscle-invasive bladder cancer has become a multimodal approach including neoadjuvant chemotherapy treatment, surgery, and radiation therapy in select patients depending on tumor stage, nodal status, age, and comorbidities [131, 132]. Outcome has not changed much in the last 30 years indicating the often aggressive biology, late diagnosis, and the need for better differentiation of tumor biology (markers) and more personalized treatment [133].

Open radical cystectomy with bilateral extended lymph node dissection is the mainstay of therapy for all stages of muscle-invasive bladder cancer offering cure to a substantial number of patients [134–136]. The surgical principles of this intervention were first described by Leadbetter in 1950 [137] and Marshall in 1956 [138]. In those days, radical cystectomy had a high perioperative mortality of 5–10%. This has significantly decreased in centers of excellence where 90-day mortality is around 1–2% in an increasingly older and more morbid population at risk [139]. Recent advances in robotic surgery

have made this an alternative approach in select patients in centers of excellence [140–142].

Male Cystectomy

The patient is placed in the Trendelenburg position with an overextended pelvis to allow adequate access to the small pelvis (Fig. 14.1). Access to the peritoneal cavity is gained through an infraumbilical incision. The urachal remnants/ligaments are identified at the umbilicus and dissected toward the bladder, forming a triangular peritoneal flap. Care is taken to not resect too much peritoneum in order to be able to cover the blood vessels when closing the abdomen. Readaptation of the peritoneum enhances recovery of intestinal function and decreases pain postoperatively [143, 144] The space of Retzius is then opened between the bladder and the pubic bone. In the case of extensive anterior tumors, this may require sharp dissection along the pubic bone. After opening the Retzius space, both vas deferens are identified cranio-laterally and ligated close to the internal inguinal ring. Cecum and sigmoid colon are detached from the lateral abdominal wall and the intestine placed in the upper abdomen allowing for an increased working space. The dorsal peritoneum is incised on both sides along the external iliac vessels up to the crossing of the ureters. Depending on extent and localization of the tumor, the peritoneum is spared to allow readaptation at the end of surgery (Fig. 14.2). Once the iliac vessels are identified, an extended meticulous pelvic lymph node dissection should be performed. This not only improves staging and potentially has a survival benefit, but alleviates cystectomy as the vascular dorsolateral pedicles are visualized. The skeletonized dorsolateral bladder pedicles (superior/inferior vesical vessels and prostatic branches) are divided and ligated in a descending manner (Fig. 14.3). At the level of the urinary bladder, the ureters are dissected to where they enter the bladder muscle, divided, and ligated. Preservation of the ureteral blood supply is of utmost importance to avoid ureteral strictures. The peritoneum in the rectovesical cavity (Douglas' space) is incised dorsal to the seminal vesicles. The seminal vesicles are an important landmark for an antegrade nerve-sparing dissection. The space between bladder/seminal vesicles/prostate and rectum is accessed mainly by blunt and when necessary by sharp dissection. This exposes the dorsomedial bladder pedicles that are then divided in a stepwise fashion to the vesico-prostatic junction. On the nontumor bearing side, the dissection is lateral to the seminal vesicles (Fig. 14.4a). On the tumor-bearing side, the dissection plane is more dorsolateral (Fig. 14.4b). Dissection usually stops at the junction of bladder and prostate.

The procedure continues ventrally by removing the fat off the endopelvic fascia and then opening the endopelvic fascia on either side of the prostate. After opening the second thin layer of the endopelvic fascia, the levator muscle fibers are peeled off and the prostatic capsule prepared. With the help of an angled Babcock clamp gliding along the prostatic surface, Santorini's plexus is bunched, ligated, and transected. The prostate is dissected by sharp preparation along its ventral aspect toward the apex. Lateral dissection offers a better exposure of the usually "Donut-like" shape of the prostate

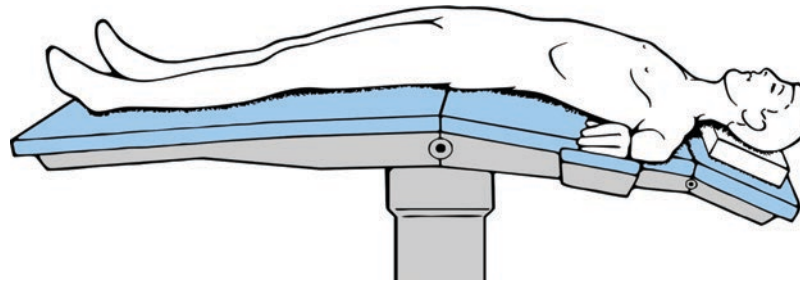

Fig. 14.1 Positioning with a tilt in Trendelenburg position. (Urs E. Studer, Keys to Successful Orthotopic Bladder Substitution, Springer)

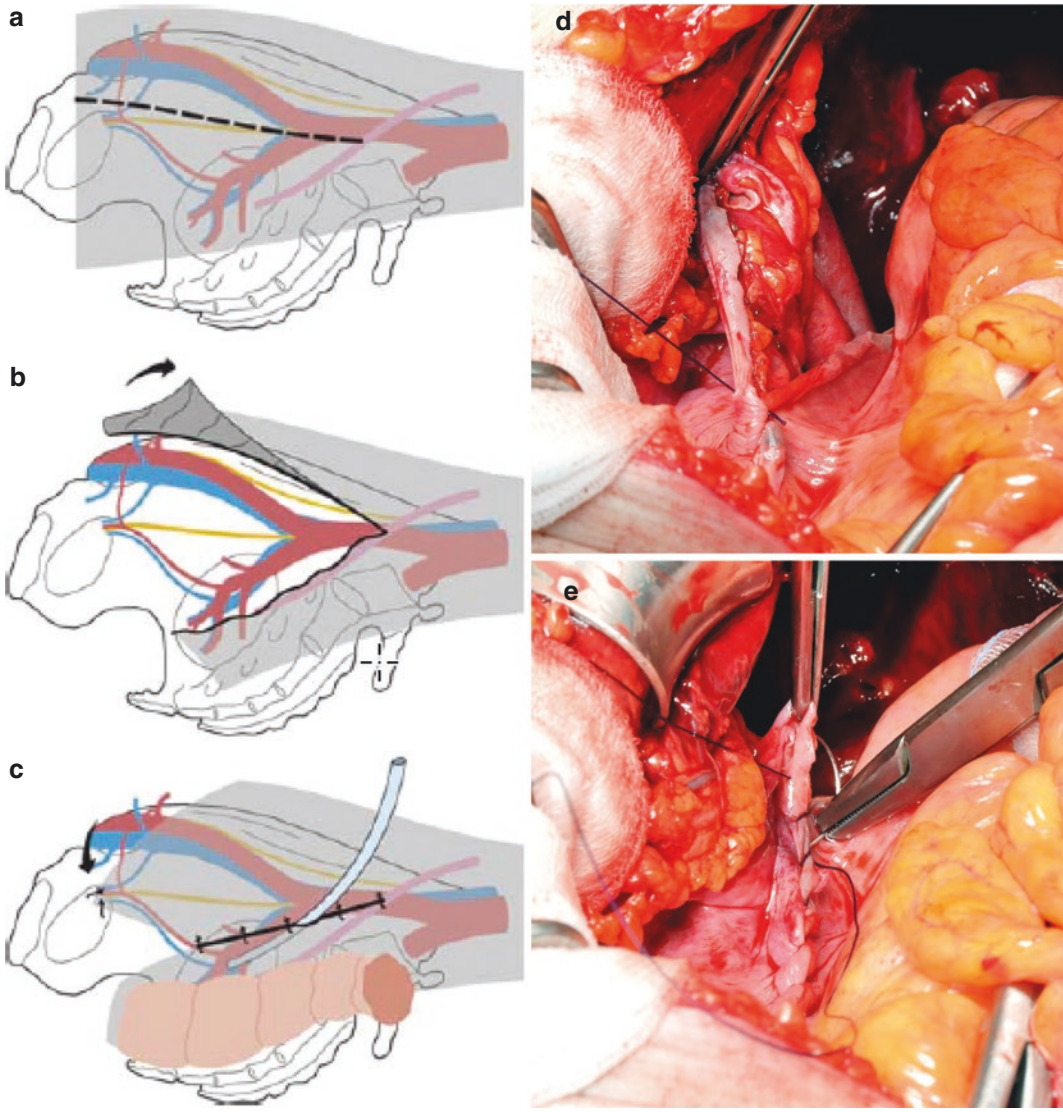

Fig. 14.2 Incision of the peritoneum over the blood vessels for pelvic lymph node dissection (**a**). Lymph node dissection according to the extended template (**b**). Closure of the peritoneum (**c**). The peritoneum is closed with a running suture (**d**–**e**). (Roth et al. [144])

around the urethra. Once the ventral urethral wall is transected, the Foley catheter is retracted, followed by the transection of the posterior urethral wall distal to the verumontanum. The fused layers of Denonvilliers fascia are sharply dissected, and thus, the entire space between the rectum and the prostate from the former peritoneal reflection is opened. The remaining dorsolateral prostatic pedicles are divided and ligated in a retrograde manner and the specimen sent for pathologic analysis. Hemostasis is achieved with an additional suture ligation at Santorini's plexus parallel to the urethra above and below the plexus. Bleeding in the region of the remaining neurovascular structures is taken care of with 4–0 sutures.

Male Nerve-Sparing

This requires a modification at two stages, if the extent of cancer allows such an approach. First, transection of the dorsomedial pedicles has to be performed close to the posterior bladder wall and immediately on and lateral to the seminal vesicles. Using an Overholt clamp (bent) for this step facilitates direct dissection toward the bladder neck, along and not across the course of the pelvic plexus. Electrocautery, and other energy sources should be avoided at this stage. Second, following bilateral opening of the endopelvic fascia, the periprostatic fascia is incised. This allows gentle dissection of the neurovascular bundles off the entire lateral aspect of the prostate. Importantly, too much exposure of the urethral stump, especially the lateral aspect, has to be avoided.

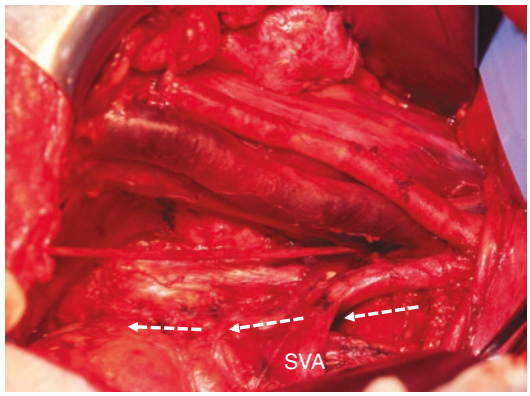

Fig. 14.3 After pelvic lymph node dissection, the lateral vascular pedicle is dissected over ligatures (Dotted lines: resection line). SVA superior vesicle artery

Seminal Vesicle-Sparing Surgery

Functional outcome in men undergoing radical cystectomy and urinary diversion for bladder cancer depends on preservation of the neurovascular bundles. Recent anatomical studies [145] have shown that the innervation of the pelvis is more complex than initially assumed. In men with anterior tumors, it is therefore possible to preserve more nerve tissue by sparing the seminal vesicles on one or both sides. For seminal vesicle preservation after dissection of the superior and inferior vesicle blood vessels, the peritoneum is incised with the vas deferens as a reference and the seminal vesicles bluntly dissected off the bladder until the base of the prostate is reached (Fig. 14.5). Care is taken to keep the dissection ventrolateral to the seminal vesicle(s) and, thus, away from the pelvic plexus, which is located lateral and dorsal to the seminal vesicle. Dissection then proceeds caudally toward

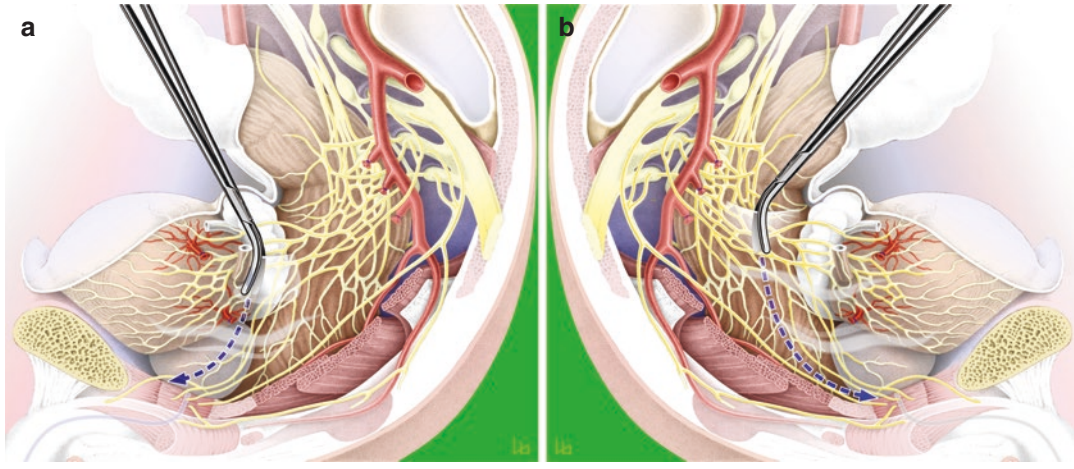

Fig. 14.4 (**a**) Resection line in men for nerve-sparing on the nontumor bearing side along the seminal vesicles lateral to the ureter. (**b**) Resection line in men on the tumor-bearing side. Note the wider excision line

the angle of the vesico-prostatic junction [146] (Fig. 14.6). A lateral incision of the prostatic capsule ventral to the neurovascular bundle is made next running from the base to the apex, and the prostatic parenchyma is then dissected off the posterior prostatic capsule. The prostatic apex is approached directly along the lateral aspect of the prostatic capsule toward the membranous urethra, which is developed out of the donut-shaped prostatic apex (Fig. 14.7). The urethra is transected sharply at the level of the distal verumontanum, and the bladder is removed en bloc together with the prostatic parenchyma. Then, the dorsal prostatic capsule between the neurovascular bundles and any visible remnant of prostatic tissue, attached to the prostatic capsule covering the neurovascular bundles, can be removed until only the capsule of the prostate adjacent to the neurovascular bundles remains left in situ (Fig. 14.8). Whenever feasible, preservation of both seminal vesicles with the adjacent neurovascular tissue is attempted; however, in patients with strictly unilateral tumors, the seminal vesicle on the contralateral side may be preserved (Fig. 14.9).

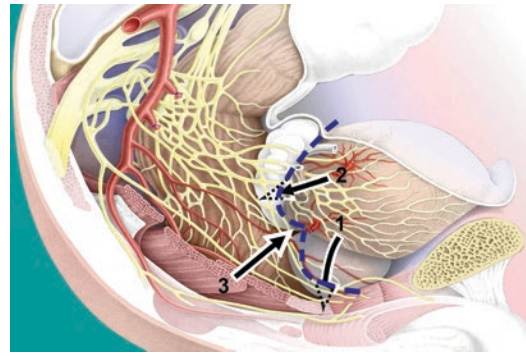

Fig. 14.5 Resection line in men for seminal vesicle sparing on the nontumor bearing line

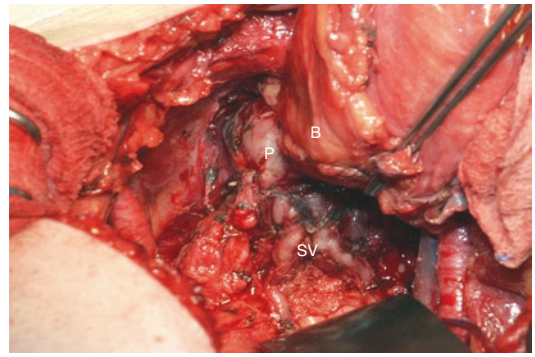

Fig. 14.6 Intraoperative view from cranially. The bladder (B) is lifted up to expose the seminal vesicles (SV) which are dissected to the base of the prostate (P)

Female Cystectomy

The approach and pelvic exposure in females are performed in a similar fashion to males as described above. Anterior pelvic exenteration, including the bladder, uterus, ovaries, fallopian tubes, urethra, and anterior vaginal wall, is still considered the standard procedure. In carefully selected (e.g., younger) patients who are sexually active and still wish to have children a genital organ-sparing approach can be taken [147]. Extended pelvic lymph node dissection, division, and transection of the dorsolateral blood supply as well as dissection of both ureters are performed as described above.

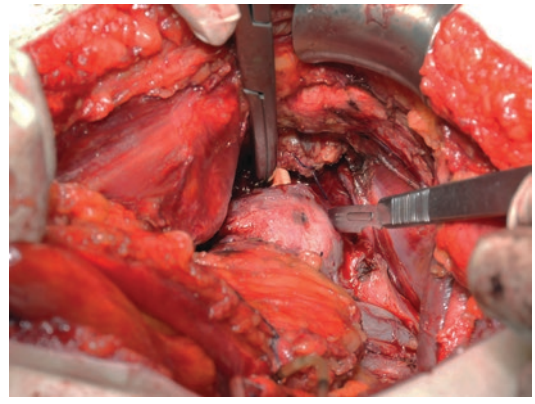

Fig. 14.7 The urethra is transected, and the prostate capsule is incised laterally ventrally to the neurovascular bundle

Cysto-Hysterectomy

The location of the tumor is decisive for the surgical approach. If the tumor is in the region of the trigone or dorsal bladder wall, then the uterus and a section of the anterior vaginal wall should be removed with the bladder (cysto-hysterectomy). Gentle traction using a uterine clamp exposes the

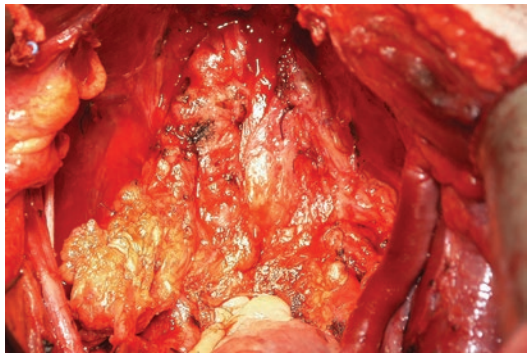

Fig. 14.8 Seminal vesicles remain in situ so that more nerve tissue may be preserved. The dorsal capsule of the prostate between the neurovascular bundles has been resected

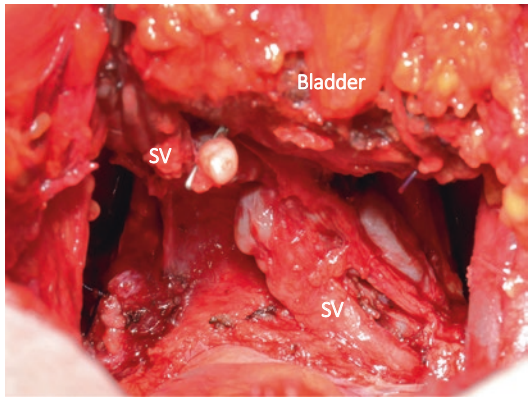

Fig. 14.9 Unilateral preservation of the seminal vesicles (SV): On the right side, the SV is preserved, whereas on the left side, the seminal vesicle remains on with the bladder specimen. Incision of the prostate capsule medial to the left vas deferens

peritoneal reflection between the posterior wall of the uterus/vagina and the anterior rectal surface. A clamp in the vagina allows helps identify the vaginal vault for placement of the peritoneal incision dorsal to the uterus and identify the whitish vaginal wall in the midline. It is important to dissect the dorsomedial bladder pedicles on both sides with a safe distance from the bladder wall. Distally, the pelvic floor is incised. The anterior vaginal wall is then incised full thickness at the vaginal dome posterior to the cervix with the uterus anteverted. The Foley catheter is pulled back into the open vagina to help identify the external urethral orifice, which then can be circumferentially excised. Bleeding from the clitoral plexus needs to be anticipated and sutured as done for Santorini's plexus. It is recommended to check for vaginal bleeding at the end of the procedure. The vagina is closed with an inverted running suture after mobilization of the cranial portion of dorsal vaginal, which is folded down and sutured to the remaining anterior vaginal wall. In females undergoing continent urinary diversion, the vaginal wall is dissected 1 cm above the dissection level of the urethra just below the bladder neck. If deemed necessary, the suture line can be covered to help prevent fistula formation. However, in our hands, this is rarely done and fistula is not occurred with the exception of patients who have had prior radiotherapy.

Nerve-Sparing Female Cystectomy

In women, the neurovascular bundle runs along the dorsolateral aspect of the vaginal wall. To achieve nerve-sparing, the dorsomedial pedicle should be transected laterally at the 11 or 1 o'clock position on the nontumor bearing side (Fig. 14.10).

If a genital organ-sparing approach is oncologically feasible, nerve-sparing is alleviated and the dissection is performed at the level of the anterior vaginal wall. For uterus and vaginal sparing surgery, the peritoneum is incised at the vesico-uterine This junction and the whitish anterior vaginal wall are identified. Dissection is performed in the midline along the avascular plane of the ventral uterine and vaginal. Ideally, dissection is performed using cold scissors, ligatures, and sutures in order to prevent potential thermal damage to the neurovascular structures. Transection of the urethra takes place immediately distal to the bladder neck. Further distal urethral mobilization and exposure must be avoided in order to avoid damage to the nerves innervating the urethra and the urethra itself.

Individualized cystectomy

Since the introduction of radical cystectomy and thanks to anatomical studies, pelvic tumor surgery has evolved. Radical surgery has two goals to achieve: First, complete removal of the tumor,

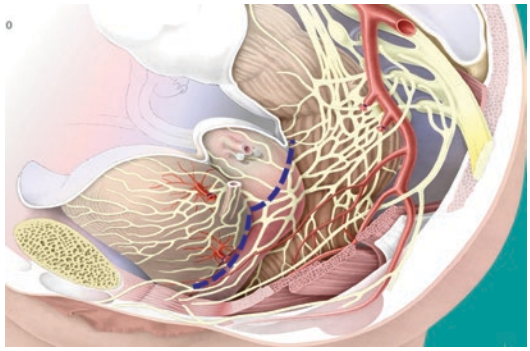

Fig. 14.10 Resection line in women on the nontumor bearing side. Opening of the vagina at the top of the vaginal vault dorsal to the uterus. The whitish vaginal wall is identified. Distally, the pelvic floor is incised. The anterior vaginal wall is then incised full thickness at the vaginal dome posterior to the cervix with the uterus anteverted. On the nontumor bearing side, the resection line is at the 2 or 10 o'clock level, for anterior tumors at both

in this case the urinary bladder, with negative surgical margins including the resection of all potential primary lymphatic landing sites; second, to preserve as much pelvic functionality as possible in order to maintain postoperative quality of life and body image. This can be summarized as individualized cystectomy. Compromise has no place between these two goals. Oncological safety is most important when planning these kinds of interventions. Bladder cancer is a deadly disease, and all "shortcuts" will put the patient at danger of progression. Positive margins are a death sentence. Nevertheless, quality of life is essential and, therefore, whenever feasible from an oncological standpoint, organ preservation and nerve-sparing should be offered where adequate and advantageous for functional outcome [148].

Robot-Assisted Radical Cystectomy

Naif A. Aldhaam, Ahmed S. Elsayed, Ahmed A. Hussein and Khurshid A. Guru

Preoperative Workup and Care

There are no key differences in preoperative preparation between RARC and ORC. Enhanced Recovery After Surgery (ERAS) protocols are multidisciplinary and multimodal perioperative care pathways designed to achieve early recovery after surgical procedures by maintaining preoperative organ function and reducing the stress response following surgery [149]. ERAS pathways also include preoperative counseling and education with verbal and written information regarding surgery and urinary diversion. Intraoperative recommendations include maintaining a fluid balance and avoiding epidurals [150]. At our institution, all patients with bladder cancer who plan for RARC are presented to the weekly NEEW (Nutrition, Education, Exercise, and Well-being) cystectomy pathway meeting where they are evaluated by a surgeon, anesthetist, physiotherapist, occupational therapist, nutritionist, social worker, stoma nurse, and oncology specialist nurse [151]. Patients are advised to consume a low-residue diet for 2 days prior to surgery, but can continue eating up to 6 hours prior to surgery and drink liquids up to 2 hours before surgery. No bowel preparation is given. Patients are given one dose of ertapenem at induction for perioperative prophylaxis.

Patient Positioning and Port Placement

Under general anesthesia, the patient is positioned in 30° lithotomy Trendelenburg position with arms adducted and tucked to the sides. All pressure points must be padded, and the patient is secured to the table. For patients with a high risk of cardiopulmonary complications such as obese patients, the robot can be docked at the side of the patient, while the patient is in a supine position if using the Xi Da Vinci®. After sterilization of the surgical field (abdomen, perineum, and groin), an 18 French Foley catheter and nasogastric tube are inserted. The abdomen is insufflated using the Veress needle or, alternatively, using an open Hasson technique. A standard six-port transperitoneal approach is used (Fig. 14.11). The 8-mm camera port is first placed an inch above and to the left of the umbilicus. The abdominal cavity is then inspected. All other ports are introduced under vision. Three 8-mm robotic trocars are

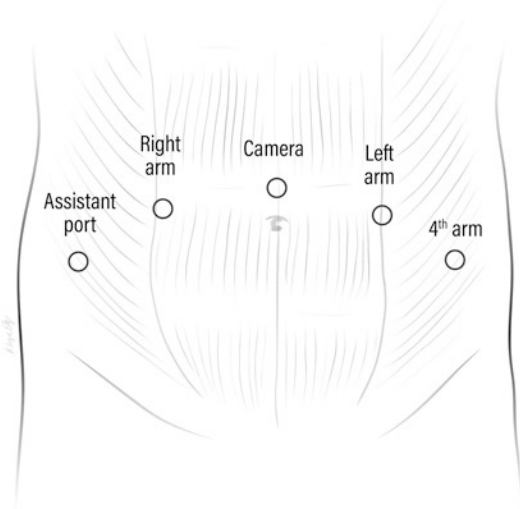

Fig. 14.11 Port configuration

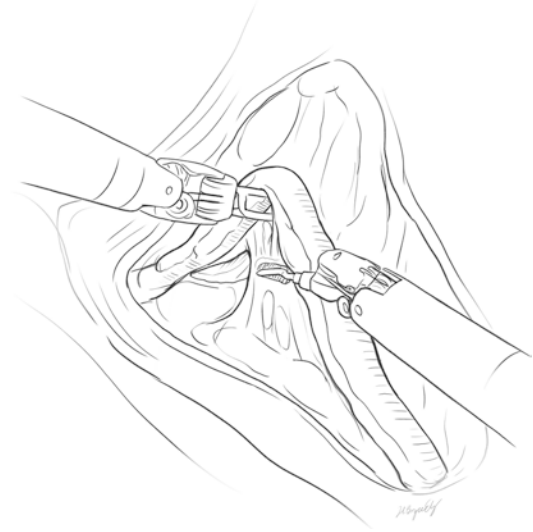

Fig. 14.12 Periureteral space

introduced in addition to the 15-mm assistant port, and a 5-mm suction port. An additional 15-mm short suprapubic port is placed to facilitate bowel anastomosis at the end of the procedure.

Robot-Assisted Radical Cystectomy in Males

The "Technique of Spaces" has been previously described [152]. This technique deconstructs the procedure into discrete steps facilitating teaching and reproducibility. Nerve-sparing RARC may be considered as an option in patients with low disease stage and who are potent preoperatively. Prostate cancer should be excluded first, and nerve-sparing should only be provided to highly motivated patients [153].

(Instruments used are ProGrasp forceps, Monopolar hook, Maryland bipolar forceps, Cobra Forceps, and Needle drivers).

Periureteral Space

The ascending colon on the right and sigmoid colon on the left are retracted using the fourth arm to expose the retroperitoneum. This is followed by incising the posterior peritoneum longitudinally at the level of the bifurcation of the common iliac arteries. The ureters are then identified and dissected with adequate periureteral tissue until the ureterovesical junction (Fig. 14.12).

Lateral Pelvic Space

This is identified by incising the peritoneum just lateral to the medial umbilical ligament in a hockey-stick fashion. The vas deferens is encountered, dissected, and divided. Blunt, sweeping, and lateral to medial movement are performed. Dissection is continued until the endopelvic fascia is reached (Fig. 14.13). The endopelvic fascia is kept intact if nerve-sparing RARC is planned. This step is completed by connecting the periureteric space with the lateral pelvic space. The distal ends of the ureters are clipped by 2 sequential Hem-O-locks, and the ureter is divided in between the clips. An initial distal ureteric specimen is taken for histopathology analysis.

Anterior Rectal Space

The zero-degree lens is preferred for this step. This space consists of the rectum posteriorly, and the bladder, prostate, and the seminal vesicles anteriorly. The lateral boundaries are the vascular and neurovascular pedicles. The peritoneum between both ureters is incised transversely. This space is dissected bluntly, typically between the anterior and the posterior borders of Denonvilliers fascia, and distally until the apex of the prostate (Fig. 14.14).

Fig. 14.13 Lateral pelvic Space

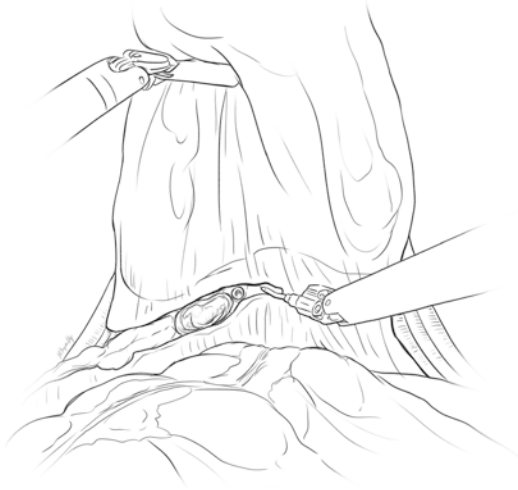

Fig. 14.14 Anterior rectal space

Control of Lateral Vascular Pedicle

Applying medial traction on the bladder using the fourth arm with a ProGrasp helps to expose the lateral vascular pedicles of the bladder. If nonnerve-sparing RARC is planned, the lateral pedicles are divided using a vascular stapler Endo-GIA™ (Medtronic, Fridley, Minnesota in the USA) (Fig. 14.15). However, if a nerve-sparing RARC is planned, athermal dissection of the neurovascular pedicle is performed, and hemostasis is achieved using Hem-o-lock clips and judicious bipolar cautery (Fig. 14.16).

Fig. 14.15 Nonnerve-sparing control of the neurovascular bundle

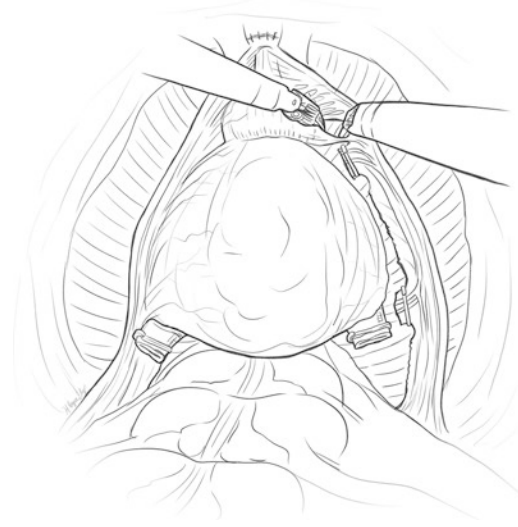

Fig. 14.16 Nerve-sparing control of the neurovascular bundle

Anterior Vesical Space and Apical Dissection (DVC Control and Urethral Transection)

Incision of the median umbilical ligament (urachus) to release the bladder from the anterior abdominal wall is carried out once the posterior dissection is complete. This is also known as the

"bladder drop." Dissection of the retropubic fat is performed, and the superficial dorsal vein is cauterized. The dorsal venous complex (DVC) is divided using electrocautery or an Endo-GIA stapler if an ileal conduit urinary diversion is planned. Athermal division of the DVC with cold scissors is done for continent urinary diversion candidates (Fig. 14.17). A Hem-o-lock clip is applied on the urethra just distal to the prostatic apex to prevent urine spillage, and the urethra is then cut freeing the specimen. For nerve sparing RARC, the DVC is bluntly dissected and controlled. Using a 2–0 barbed V-loc ™ absorbable suture (Medtronic, Fridley, Minnesota in the USA) on a ½ circle needle, a horizontal continuous suture is used to secure the DVC complex. After incision of the urethra, the bladder is placed in an Endo Catch bag (Covidien, Dublin, Ireland). The pelvic cavity is irrigated and examined for any bleeding.

Robot-Assisted Anterior Pelvic Exenteration in Females

Male and female cystectomies share common steps. The key differences will be highlighted below.

Cystectomy with preservation of the internal genital organs (organ-sparing cystectomy) is feasible in females with low-risk and confined bladder cancer, and this technique has shown satisfactory functional and oncologic outcomes with proper case selection [154–156].

Control of the Ovarian Pedicles

Vertical incisions are performed a few centimeters above the common iliac vessels bilaterally. It is crucial to identify all anatomical landmarks prior to dividing any of them. After dissection of the ureters is completed, the uterus is retracted using the cobra grasper on the fourth robotic arm. The infundibulopelvic suspensory ligaments and the ovarian pedicles are identified, dissected, and divided close to the uterus using either the Hem-o-lok® clip (Teleflex Medical, Research Triangle Park, North Carolina) or the Endo-GIA 45-mm vascular stapler (Medtronic, Fridley, Minnesota in the USA). The posterior peritoneum is further incised along the broad ligament lateral to the fallopian tube toward the bladder on each side. When the round ligaments are encountered, they are incised. The uterine artery is dissected and divided on each side (Fig. 14.18).

The periureteral and lateral pelvic spaces are similar to male cystectomy steps.

Anterior Rectal Space

Using the fourth arm, the uterus is lifted anteriorly toward the abdominal wall. The posterior peritoneum between the lateral pelvic spaces and posterior to the uterus is incised. Using apple or a sponge stick manually manipulated by the right-

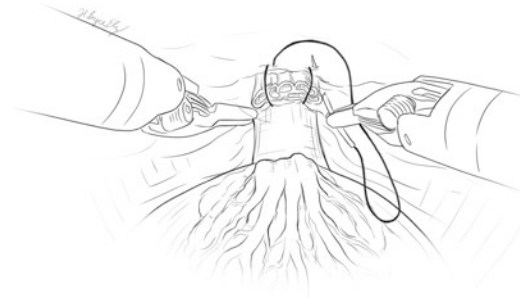

Fig. 14.17 Dorsal venous complex

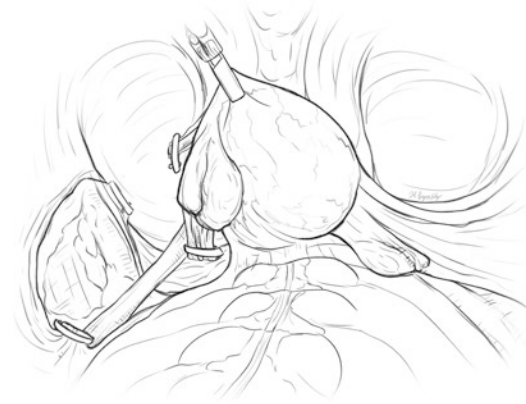

Fig. 14.18 Control of the ovarian pedicles

side assistant, the correct plane at the uterovaginal junction can be identified. This plane is opened using monopolar cautery (Fig. 14.19).

The vascular pedicle and anterior vesical space steps are similar to male cystectomy.

Apical Dissection (DVC Control and Urethral Transection)

With proximal traction and manual manipulation of the Foley catheter, dissection of the urethra is carried out intracorporeally to complete the urethrectomy (Fig. 14.20). If the planned urinary diversion is a neobladder, maximal preservation of urethral length with cold scissor dissection should be attempted. The whole specimen is placed in a retrieval bag and then removed transvaginally.

Closure of the Vagina

The forth arm is used to flip the posterior vaginal wall anteriorly. Two 2/0 Vicryl V-loc sutures are used to close the vagina (Fig. 14.21). The vagina is not closed until the pelvic lymphadenectomy is complete to enable retrieval of all specimens.

Robot-Assisted Extended Pelvic Lymph Node Dissection

The author prefers to perform an extended pelvic lymph node dissection (PLND). The boundaries are the lymph node of Cloquet and circumflex iliac vessels distally, the obturator nerve and vessels medially, the genitofemoral nerve laterally, and the common iliac artery proximally.

Extended PLND includes obturator, presacral, and iliac lymph nodes. The retroperitoneum is incised at the level of the ureter crossing the common iliac vessels. Dissection is continued, exposing the psoas muscle and genitofemoral nerve. Internal iliac lymph nodes are harvested first, exposing the obturator nerve and vessels. Dissection is then continued caudally until reaching the lymph node of Cloquet. The lymph nodes within the triangle of Marseille are then dissected by opening the fascia between the external iliac artery and vein. The

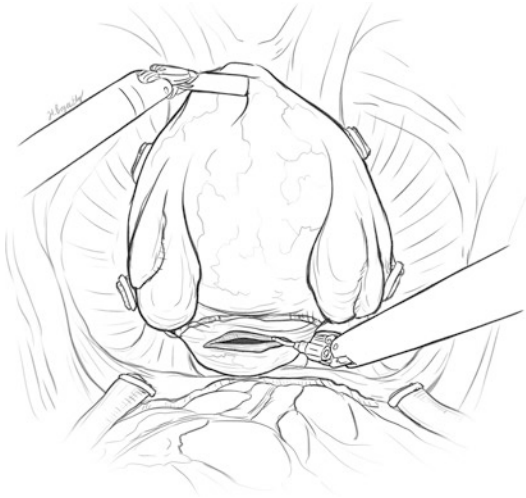

Fig. 14.19 Anterior rectal space

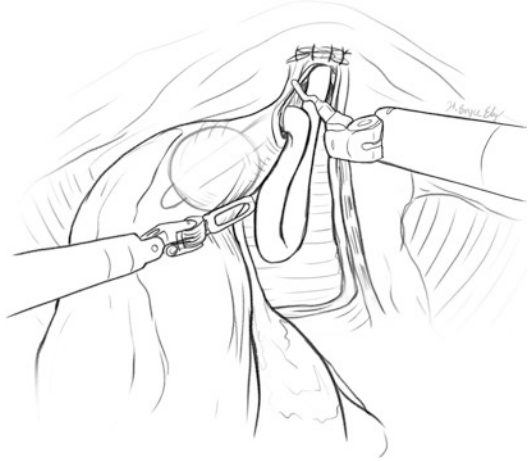

Fig. 14.20 Urethrectomy

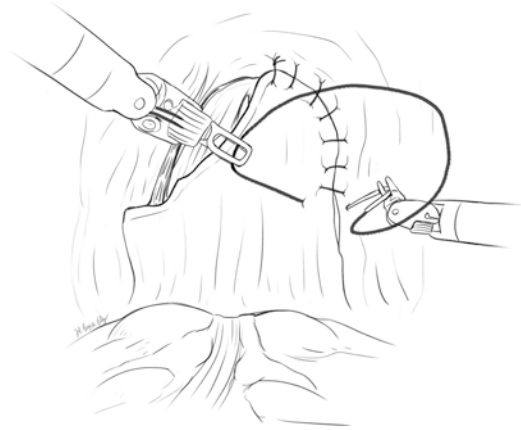

Fig. 14.21 Closure of the vagina

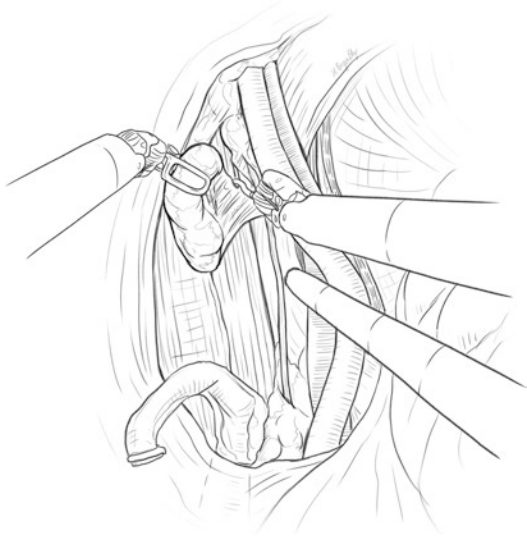

Fig. 14.22 Pelvic Lymph node dissection

external iliac vein is retracted medially and lymph nodes adherent to the psoas muscle are freed until visualizing the obturator nerve (Fig. 14.22).

Conclusion

Robot-assisted radical cystectomy has gained widespread acceptance and has increased in popularity. Though robot-assisted surgery shares the same basic principles with open surgery, it allows for better visualization and reach. Dividing radical cystectomy into discrete steps helps with reproducibility and teaching.

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Organ-Sparing Approaches for Radical Cystectomy (Partial Cystectomy, Radical Cystectomy in Women with Reproductive Organ Preservation, Prostate-Sparing Radical Cystectomy)

Marco Moschini, Mohamed Saad, Xavier Cathelineau and Rafael Sanchez-Salas

Introduction

The rationale of an organ-sparing approach in an aggressive disease such as bladder cancer (BCa) has been debated for years. In patients treated with radical cystectomy (RC) and bilateral pelvic lymph node dissection, the overall estimated 5-year recurrence and cancer-specific mortality (CSM) rates range from 30 to 52% and from 28 to 35% [134, 157–159], respectively. Therefore, several eminent urologic surgeons in the past considered insufficient from an oncological point of view, an approach associated with an higher risk of not removing clinical significant prostate and urothelial cancers [160, 161].

On the other hand, when RC is proposed, high rates of perioperative complications [162] and impaired functional outcomes with a consistently decrease of quality of life parameters and incontinence and sexual dysfunction are reported [163]. An increasingly attention to quality of life for oncologic patients but also new technologies have recently changed the scenario of the organ-sparing surgeries. The advent of new technologies might help to improve the selection of patients avoiding those at major risk of having recurrences after surgery. For example, a careful preoperative screening focused on to assess the presence of clinically significant prostate cancer or presence of prostatic urothelial cancer is fundamental before proposing a prostate-sparing approach. In this regard, the role of multiparametric magnetic resonance imaging (mpMRI) is well established in the diagnoses of prostate cancer and its increasing in the field of BCa, with a new description of VIRADS [164], a standardized reporting criteria for bladder MRI.

Cancer control should always prevail, and urological surgeon has to evaluate the risk of an organ-sparing procedure and to discuss it with the patients presenting it as a feasible alternative in case of positive preoperative selection, selecting those who might need a concomitant neoadjuvant chemotherapy or extended pelvic lymph node dissection.

Preoperative Evaluation

A complete preoperative evaluation is fundamental before proposing a partial cystectomy, a reproductive organ preservation or a prostate-sparing radical cystectomy. In addition to the standard preoperative evaluation represented by CT scan or MRI for the correct staging of the disease, a careful screening of the concomitant organs is needed to reduce the risk of local recurrence or untreated disease. Surgical technique and the risks related to it have to be carefully discussed with the patients, highlighting the additional risks that might be related to an organ-sparing surgery. No specific differences exist regarding type of anesthesia or instrumentation, and the details of each surgery will be discussed in each paragraph. A concomitant lymphadenectomy is a fundamental part of the treatment of urothelial cancer that should always be delivered also in patients treated with organ-sparing surgery.

Partial Cystectomy

Partial cystectomy is a complete ablation of abnormal bladder with a security margin with the objective of preserving adequate bladder function. It has no role in the standard treatment of bladder cancer. However, it might be proposed in patients with a solitary lesion in which radical cystectomy is contraindicated or in case of adenocarcinoma of the urachus, an embryologic remnant of the allantois. Moreover, partial cystectomy might be safely offered to patients affected by urothelial carcinoma in bladder diverticula [165], localized unifocal urothelial carcinoma in adequate locations (dome and lateral wall), or informed patients not willing to undergo cystectomy. Preservation of potency and continence are easily achieved with the technique. Other indication for partial cystectomy is nonurological cancer of the bladder, adjacent tumors bladder invasion, or benign diverticulum.

Surgical Technique

Partial cystectomy of urothelial bladder cancer involves a full template lymph node dissection with mobilization of the bladder. In our practice, once the patient is sleeping in the theater, we proceed with rigid cystoscopy to objectively define the location of the lesion. Bladder is washed and completely drained. With a bipolar loop we proceed to score the limits of dissection and ureteral catheters are placed to avoid urine spilling. We do not fill the bladder for the dissection, and the cystoscope can be left on-site to guide the abdominal approach.

A partial cystectomy can be performed by an extraperitoneal approach for lesions located at the anterior wall or at the vesical dome. In the case of lesion located in the posterior wall, an intraperitoneal laparoscopic or robotic approach is possible. One to two centimeters of visual margin with a confirmatory intraoperative frozen section to exclude presence of microscopic disease is recommended in the resection margin. In the case of orifices involvement, a ureteral reimplantation might be necessary. In our practice, we do not recommend partial cystectomy if ureteral reimplantation is mandatory. To avoid spillage of tumorous cells, we place a single J catheter at the beginning of the procedure. For the urachal tumor, a partial cystectomy should also include the removal of the urachus to the umbilicus. Similarly, for the normal partial cystectomy, a 2 cm free margin has to be taken from the tumor.

Outcomes of Partial cystectomy

Survival outcomes in bladder cancer patients treated with partial cystectomy are inferior to patients treated to radical cystectomy [166]. However, good survival outcomes can be achieved especially for patients without concomitant carcinoma in situ and with no lymph node metastases [166, 167]. Surgery can be performed open, laparoscopic, or robotically with similar perioperative and survival outcomes [168]. In the case of recurrence of urothelial carcinoma after partial cystectomy, a radical cystectomy seems feasible, although associated with worse survival outcomes than for patients treated with primary radical cystectomy [169]. Considering patients affected by urothelial carcinoma in bladder diverticulum, partial cystectomy seems associated

with similar survival outcomes than radical cystectomy and can be safely proposed [165, 170].

Radical Cystectomy in Women with Reproductive Organ Preservation

The classical form of radical cystectomy in women consists the removal of bladder, urethra, uterus, and a portion of the anterior vaginal wall. Reproductive organ-sparing radical cystectomy has been proposed to improved sexuality, psychology, and even potential fertility. These benefits have to be cautiously balanced against the potential risk to oncological outcomes. A careful preoperative staging must be performed, excluding involvement of the concomitant organs to assure the possibility to achieve negative surgical margin. This surgical technique should be applied for lesion located anteriorly within the bladder.

No prospective trial tested the effect of this surgery, but several retrospective single-center series explored perioperative, functional, and surgical outcomes. After an appropriate selection, women treated with this surgery were found with fewer short- and long-term complications compared to radical cystectomy. Moreover, similar survival outcomes have been reported [171, 172]. These findings were recently confirmed in a systematic review [173]; however, it has to be highlighted that still limited data support these findings that need to be validated in a prospective trial to guarantee the safety and the correct selection.

Prostate-Sparing Radical Cystectomy

Prostate-sparing radical cystectomy represents an attractive option for male patients affected by bladder cancer. However, an accurate preoperative screening is fundamental before proposing this procedure. Without a proper preoperative screening, prostatic urothelial carcinoma is found approximately in 20–30% of the patients treated with radical cystectomy for bladder cancer [174, 175] and almost half of them are diagnosed with an incidental prostate cancer. However, with a proper preoperative screening, these rates fall to 10% and 8%, respectively.

No definitive data exist regarding the definition of optimal preoperative screening. A preoperative or intraoperative analysis of the whole prostatic urethra is recommended to minimize the risk of having prostatic urothelial carcinoma. This might be obtained by performing a preoperative transurethral resection of the prostate or a simple prostatectomy to analyze the whole prostatic urethra. Kasouff et al. [176] reported 99% and 100% negative predictive value in diagnosing prostatic urothelial cancer for preoperative transurethral resection biopsy and for frozen section, respectively. Considering the evaluation of prostate cancer, digital rectal examination, PSA evaluation, and transrectal sonography are recommended. If there is a suspicion for prostate cancer, prostate biopsy may be necessary. In this regard, the role of mpMRI is increasing, with excellent specificity reported for patients found with a negative exam [177]. Blue-light cystoscopy can be deployed to rule out the presence of carcinoma in situ. However, no standardized criteria have been defined, and every center performing this type of surgery should carefully discuss with patients the risk associated with it. After this screening voted to the reduction of the risk of incurring in prostatic urothelial carcinoma and incidental prostate cancer, male patients' candidate to an orthotopic diversion is screened on the bases of continence and potency expectations. In this regard, only a minority of patients remain suitable for the approach, accounting for less than 10% [178, 179].

Surgical Approaches

Several different surgical approaches have been developed to treat male patients' candidates to radical cystectomy. These patients should receive an extended lymph node dissection. A nerve-sparing procedure might be offered, using the same technique used in radical retropubic prostatectomy, with the preservation of the neurovascular bundles of the prostate. Using this technique, Furrer et al. [180] reported 89% and 69% of urinary continence in daytime and nighttime,

respectively. Moreover, an increased recovery of erectile disfunction was reported in patients treated with nerve-sparing procedures compared to those treated with normal radical cystectomy. Prostate or capsule prostate-sparing procedures, for example, have the advantage of the avoidance of the neurovascular bundles laterally and the striated sphincter at the apex. In our experience, we initially performed preoperative TURP and then proceeded with the cystectomy part. This approach was later changed, and a prostatic adenomectomy is performed after the vesical pedicles are controlled and seminal vesicles dissected and preserved. During the adenomectomy, we pay special attention to avoid spilling. The whole preservation of the capsule allows for a simple anastomosis of the neobladder.

Outcomes of Prostate-Sparing Cystectomy

In the only existing prospective trial evaluating the effect of prostate-sparing cystectomy on functional and survival outcomes, 40 patients were randomized and compared to nerve-sparing radical cystectomy. Authors found no differences between the two study groups for both functional and survival outcomes; however, the study was underpowered, and no definitive conclusion can be made. Considering retrospective results, few reports analyzed the outcomes of this technique. Survival outcomes in carefully selected patients seem noninferior to patients treated with standard cystectomy [181–184]. Recently Voskuilen et al. [185] reported a two centers experience of patients treated with prostate-sparing cystectomy. Of the 185 patients included in the study, a median follow-up of 7.5 years was reported with a 5-year overall survival of 71%. Twenty patients (10.8%) experience a local recurrence, slightly higher than the normal population treated with radical cystectomy [186].

On a functional level, retrospective data shown that prostate-sparing cystectomy is superior to nerve-sparing radical cystectomy. Nerve-sparing cystectomy series reported 77% to 98% daytime continence, nocturnal continence rates of 54% to 95%, and potency rates of 33% to 63%, [187–189], while prostate-sparing surgery data indicate a daytime continence rates of 80% to 100%, nocturnal continence rates of 37% to 100%, and potency rates of 82% to 100% [181, 183, 190–192]. A recent systematic review [178] found that prostate-sparing cystectomy is associated with better sexual outcomes than standard cystectomy without comprising oncological outcomes in well-selected patients. However, differences exist considering definition of surgical techniques, definition of continence or potency, and a lack of general consensus in the current literature, highlighting the need of a randomized trial assessing for these limitations.

Cystectomy Surgical Technique – Pelvic Lymph Node Dissection

Utsav Bansal and Seth P. Lerner

Evidence for Pelvic Lymph Node Dissection

It is well established that a bilateral pelvic lymphadenectomy (LND) should be performed in those patients undergoing a partial or radical cystectomy for nonmetastatic muscle-invasive or high-risk nonmuscle-invasive bladder cancer [5]. Lymph node metastases are the most significant prognostic indicator of outcomes following a radical cystectomy, and so a thorough anatomic LND provides important pathologic stage information informing prognosis and contributes to locoregional control of the disease [193]. Studies have shown that on average, 25% of patients will have pathologic proven pelvic lymph node metastasis at the time of surgery [134]. As described by the American Urologic Association (AUA) guidelines, a "standard" node dissection includes the external and internal iliac and obturator, both superficial and deep, lymph nodes [194]. In 1982, Skinner reported local pelvic recurrence rates of 5–15% in patients who underwent meticulous bilateral pelvic LND with N0 and N+ disease, respectively [195].

Standard vs. Extended LND

Despite several large studies, both prospective and retrospective, the optimal proximal extent of the LND has been in question. In addition to the standard template, an extended lymph node dissection (eLND) includes bilateral common iliac, presciatic (fossa of Marcille), and presacral up to the aortic bifurcation, and a so-called "super-extended" includes distal caval and paracaval, interaortocaval, and paraaortal nodes up to the inferior mesenteric artery [196]. Some retrospective studies suggested that an extended LND (eLND) is associated with improved survival [196, 197]. In the only prospective randomized Phase III trial reported to date, Gschwend et al. found no statistically significant difference in five-year recurrence-free survival (65% extended vs. 59% limited, $p = 0.36$), cancer-specific survival (76% vs. 65%, $p = 0.10$), and overall survival (59% vs. 50%, $p = 0.12$), though their study was underpowered to detect a smaller benefit with an eLND [195, 198]. The Southwest Oncology Group (SWOG) completed recruitment of 659 patients for a similar Phase II trial in 2017 and estimated a 10–12% improvement in RFS at 3-years compared to a standard dissection (65 vs 55%) [198].

Leissner et al. performed a multicenter, prospective trial in which all patients underwent an eLND to the aortal bifurcation. Among the 290 patients, 81 (28%) had lymph node metastasis and 35% of all positive lymph nodes were identified proximal to the common iliac bifurcation [199]. Moreover, 20 (6.9%) of patients had so-called skip metastases with positive nodes at or above the level of the common iliac vessels with no evidence of disease distal to the common iliac bifurcation [199]. Although the most frequently locations for pathologically positive lymph nodes are the obturator (74%) and external iliac (65%) lymph nodes, 19% of patients who undergo cystectomy also have positive common iliac nodes [200, 201]. This provides evidence for extending the LND to include the extended template at least up to the level aortic bifurcation.

Lymphatic Drainage from Bladder

Our understanding of lymphatic drainage of the bladder dates back to historical anatomic texts from Rouviere to the contemporary seminal work of Leadbetter and Cooper who categorized drainage into six areas: (1) the visceral lymphatic plexus within the bladder wall that extends into the muscular layer; (2) the intercalated lymph nodes within the perivesical fat; (3) pelvic collecting trunks—the lymph nodes medial to the external iliac and hypogastric lymph nodes; (4) regional pelvic lymph nodes—the external iliac, hypogastric, and sacral lymph nodes; (5) lymphatic trunks from the regional pelvic lymph nodes; and lastly, (6) common iliac lymph nodes, which is thought to be the cutoff before the second tier of metastases between the pelvic lymph nodes and those surrounding the inferior mesenteric artery [137, 202].

The large collecting trunks are organized in three regions around the trigone, anterior, and posterior bladder walls. The collecting ducts around the trigone arise medial to the ureters, pass anteriorly to the ureters, and follow the uterine artery in females and vasal artery in males to terminate in the external iliac nodes. The posterior wall collecting ducts travel anterior to the ureter, cross the umbilical artery, and drain into the external iliac nodes. Lastly, the anterior bladder wall ducts follow the middle vesical and umbilical arteries. Some will then merge with the posterior collecting ducts to drain into the external iliac lymph nodes, while the rest will drain into the hypogastric and common iliac lymph nodes [200].

Smith and Whitmore performed one of the first studies of lymph node mappings in patients undergoing a radical cystectomy in 1981. They found that the primary sites of bladder lymphatic drainage were the obturator/hypogastric and external iliac lymph nodes with a metastases rate of 74% and 65%, respectively, and 19% positivity rate in the common iliac lymph nodes [201]. The risk of additional morbidity of extended lymph node dissection to the level of the inferior mesenteric artery was initially thought to outweigh the benefits. However, Leissner et al.

found that among the 57% of patients who had node-positive disease within the standard dissection, 31% of patients also had disease proximal to the common iliac vessels and aortic bifurcation [199]. This has led to surgical techniques that allow for safe and effective removal of suprailiac lymph nodes nodal packets [134, 199].

These mapping studies have confirmed the systematic progression of disease from pelvic to the common iliac and further to the lymph nodes distal to the inferior mesenteric artery. The secondary lymphatic drainage is the common iliac nodes, while the para-caval and para-aortic are considered tertiary lymphatic drainage [193]. However, multiple reports have also described infrequent skip metastases seen in <10% of patients [199, 203, 204]. For instance, the trigone and posterior bladder wall drain directly into the presacral nodes [193]. Roth et al. injected technetium nanocolloid into six different regions of the bladder and mapped the lymph node draining with SPECT/CT plus intraoperative gamma probe demonstrating frequent cross-over, thereby demonstrating the need for a bilateral LND in all patients [205, 206].

Lymphadenectomy Boundaries and Surgical Technique

The minimum dissection for a bilateral "standard" lymphadenectomy includes all lymphatics distal to the common iliac bifurcation and includes the external iliac, internal iliac, and the obturator lymph nodes. The anatomic limits of the dissection are Cooper's ligament and LN of Cloquet distally, laterally the genitofemoral nerve, and complete removal of the potential LN bearing tissue anterior and posterior to the obturator nerve form the pelvic sidewall to the bladder. The extended LND boundaries include the genitofemoral nerve laterally and all LN bearing tissue between the CI arteries and in the case of the super-extended template up to the origin of the IMA [202].

Our preference is to perform the LND first as this exposes the relevant anatomy for the cystectomy and simplifies the procedure in addition to identifying LN metastases outside the true pelvis which may affect intraoperative decision making. The peritoneal reflection is divided lateral to the cecum and ascending colon and inferomedial to the terminal ileum. The mesentery of the right colon and terminal ileum is then carefully mobilized and transposed cephalad toward the duodenum, in order to expose the retroperitoneum and distal vena cava proximally. Attention is then paid to the right ureter as it crosses the right common iliac vessels. The ureter is carefully dissected, maintaining its collateral blood supply from the spermatic cord, both proximally and distally into the true pelvis. We previously divided the ureter early but now keep it intact until the posterior dissection of the bladder where it is then divided between hemoclips in order to facilitate dilation for the subsequent anastomosis and the margin sent for frozen inspection [200]. On the left, the peritoneum is divided laterally to the sigmoid and ascending and the sigmoid mesentery is mobilized in order to fully expose the presacral, proximal common iliac, and para-aortic nodes and also facilitates transposition of the left ureter to the right lower quadrant for the urinary diversion [193]. The left ureter is handled similar to the right. The bowels are then packed cephalad in order to maintain the proximal exposure [200].

When performing an ePLND, the node dissection should begin at the proximal boundary, which may be between the aortic bifurcation and IMA according to surgeon preference and extend distally to the femoral canal with each region submitted separately in packets [193, 200]. Bochner and colleagues have shown convincingly that submission of nodes in packets versus en bloc results in increased number of nodes identified by the pathologist [207]. Detection of node metastasis increases with the number of nodes and thereby improves pathologic staging [208, 209]**.** The proximal and distal lymphatics should be ligated with hemoclips in order to prevent leakage [202]. The dissection is carried lateral to the genitofemoral nerve on each side by incising the medial fibroareolar tissue. The nodal tissue anterior to the common iliac arteries is dissected in both medial and lateral directions away

from the vessels and clipped at their origin. Great care is taken to clip and divide any small vessels on the anterior surface of the IVC and the proximal common iliac (CI) vein [200]. In addition, extra care with minimal manipulation of the CI and external iliac arteries is necessary in patients who have undergone pelvic irradiation or have significant atherosclerotic vessels in order to prevent plaque migration [202].

The lymphatic package anterior to the left common iliac vein caudal to the bifurcation is swept inferiorly off the sacral promontory. However, it is important to maintain the presacral fascia intact to avoid any unnecessary blood loss. Superficial veins located anteriorly to this fascia may be divided using electrocautery. The presacral dissection can be done before or prior to the cystectomy though this lymphatic tissue may be best visualized after the cystectomy is completed and the attachments to the sigmoid mesentery can be clipped and divided. The presacral nodes should be removed separately as metastases can occur in this region without positive nodes distal to the common iliac bifurcation. [200].

The pelvic peritoneum is then incised over the right external iliac vessels and the vas deferens or round ligament sealed and divided with the Ligasure™ or between hemoclips. For optimal visualization, the bladder and sigmoid colon are retracted and the lower abdominal wall elevated with the use of self-retaining retractor. The distal limit of the dissection is then carried to the level of Cooper's ligament and the lymph node of Cloquet located within the femoral canal bilaterally by identifying the circumflex iliac vein crossing over the external iliac artery.

Meticulous dissection of the external iliac vessels distally to the circumflex iliac vein is required to enhance lymph node retrieval and delineate important anatomical structures. The external iliac vessels are circumferentially mobilized using the split and roll technique. A sponge is passed laterally to the vessels and into the obturator fossa, sweeping the lymphatic tissue medially toward the bladder and dissecting the node bearing tissue off of the pelvic sidewall. There are small tributaries entering into the internal iliac vein that may be clipped or managed with bipolar cautery. It is important to identify the obturator nerve at this time. This allows for proper dissection of the obturator nodes inferomedially toward the bladder with sufficient hemoclips employed to prevent lymphoceles postoperatively. The dissection is then carried caudally to expose the lateral vascular pedicle of the bladder and distal limit of the template bilaterally. The pedicles may then be taken in standard fashion and cystectomy with urinary diversion completed based on shared decision making with the patient. A closed suction drain should be placed in the pelvis at the end of the case to prevent possible lymphocele and urinoma from developing [200].

Minimum Number of Lymph Nodes for Evaluation

Until recently, there has been minimal consensus on an adequate number of lymph nodes during retrieval. In 2006, Koppie et al. published a retrospective review on patients who underwent a radical cystectomy at Memorial Sloan Kettering Cancer Center from 1990 to 2004. Out of a total of 1121 patients, 87% underwent a lymph node dissection with a median number of nine lymph nodes removed [209]. They found that the probability of overall survival increased with increasing number of nodes removed, providing evidence for an extended dissection [209]. More recently, Capitanio et al. found that removal of 45 lymph nodes achieved a 90% probability of detecting metastases. The largest increase in identification of node metastases was seen with the removal of 15 to 30 lymph nodes with an increased probability of identifying node metastases from 10% to 80%, respectively [208]. The authors indicated that identification of 25 nodes was associated with a 75% sensitivity for detection of node metastasis [208]. However, in their prospective, multicenter trial, Gschwend found that an extended LN, with a median number of 31 lymph nodes versus 19 nodes in the standard dissection arm, did not confer significantly increased 5-year overall, cancer-specific, nor recurrence-free survival [195].

Complications of LND

The node dissection adds operative time and potential for surgical toxicities, namely lymphatic leaks/fistulae and lymphoceles and risk of vascular injuries. A lymphocele may present as pelvic or groin pain, lower extremity or scrotal swelling, or fevers secondary to bacterial colonization of a lymphocele. Pelvic ultrasound and/or CT scan can assist in diagnosis. Treatment options include observation, percutaneous drainage, sclerotherapy with tetracycline, and lastly surgical marsupialization of the cavity if a symptomatic lymphocele persists [200]. In their prospective trial, Gschwend et al. found an increased rate of lymphoceles requiring drainage in those who underwent an extended dissection at 90 days postoperatively (8.6% vs. 3.4%, $p = 0.04$) [195]. Thus, a thorough understanding of lymphatic anatomy and scrupulous use of hemoclips can help prevent this complication.

The benefits of a lymph node dissection far outweigh the cumulative risks. Among 102 octogenarians who underwent a radical cystectomy with and without a pelvic lymph node dissection, there was no significant difference in the number of perioperative (7% vs 5%; $p = 0.75$) or postoperative complications (58% vs 43%; $p = 0.19$), respectively [210]. Moreover, there was no significant additional risk in cardiac complications (9% vs. 4%, $p = 0.51$), thromboembolic events (5% vs 0%, $p = 0.31$), or Clavien grade 3–5 complications (27% vs 21%, $p = 0.56$) in this elderly population, though more complications were seen in the dissection group [210].

The question then stands whether the benefits of an extended dissection compared to a standard dissection outweigh the risks. One cohort with 46 matched patients in each arm found that although an extended dissection increased operative time by 63 minutes, there was no significant difference in perioperative mortality, early complications, need for blood transfusions, or postoperative morbidity (defined as within 30 days of surgery) [211]. Similarly, a Canadian group found no difference between the two modes of dissection in terms of length of hospital stay, and intraoperative, early (0–30 days), intermediate (30–90 days), and late (>90 days) postoperative complications. However, there was a significantly increased risk of blood loss and need for blood transfusions for those patients in the extended dissection cohort [212].

Prognostic Factor in Survival

Ultimately, the reported benefit in survival with minimal complication rate of an extended lymph node dissection has led to its widespread incorporation into surgical technique. In 2001, Leissner et al. reported that if ≥16 lymph nodes were removed, 5-year tumor-free survival increased in patients with bladder-confined tumor (85 vs 63%), pT3 tumors (55 vs 40%), and in those with at most five lymph node metastases (53 vs 25%) [213]. In a number of studies, no other factor has been such a significant indicator of prognosis [202, 213, 214]. Although Gschwend et al. did not find a statistical difference in recurrence-free, cancer-specific, nor overall survival between extended and limited dissections, they do conclude that a larger trial may detect a clinically relevant difference [195].

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Surgical Technique: Urethrectomy

15

Nathan Y. Hoy, Hadley M. Wood, and Kenneth W. Angermeier

Introduction

Urethral recurrence rates after radical cystectomy for bladder urothelial carcinoma range from 4% to 14%.[1, 2] Total urethrectomy is the treatment of choice for urethral recurrence, as well as a prophylactic measure in patients at high risk. Risk factors for urethral recurrence include those with multiple tumors, and tumor involvement of the bladder neck, prostatic urethra, and prostatic stroma.[3, 4]

The most common indications for urethrectomy are urethral involvement with tumor, pathology demonstrating prostatic stromal invasion, and high-grade prostatic urethral recurrence following Bacillus Calmette-Guerin therapy.[5–7] The American Urological Association nonmetastatic muscle-invasive bladder cancer guidelines state men with cancer at the urethral margin, whether on frozen section or permanent pathology, should have a urethrectomy.[8, 9]

Surgical Technique

Preoperative Preparation

Cross-sectional imaging in the form of a CT scan or MRI can serve several useful functions:

- To assess for any abdominal or pelvic metastatic disease
- To assess the location of bowel that may have adhered to the pelvic floor and encountered during the proximal dissection
- To assess for any residual prostatic tissue that may need to be concomitantly excised with the urethra
- To assess for local extension into the corpora cavernosa that may necessitate penectomy

Patients are given preoperative pharmacologic venous thromboembolism prophylaxis and have intermittent pneumatic compression devices placed on both legs. Prophylactic antibiotics in accordance with the latest AUA antimicrobial prophylaxis guidelines are given.[10]

Patient Positioning and Preparation

After completing the anesthetic, the patient is position in a high dorsal lithotomy position with the arms outstretched. A gel roll is placed under the buttocks to help elevate the perineum

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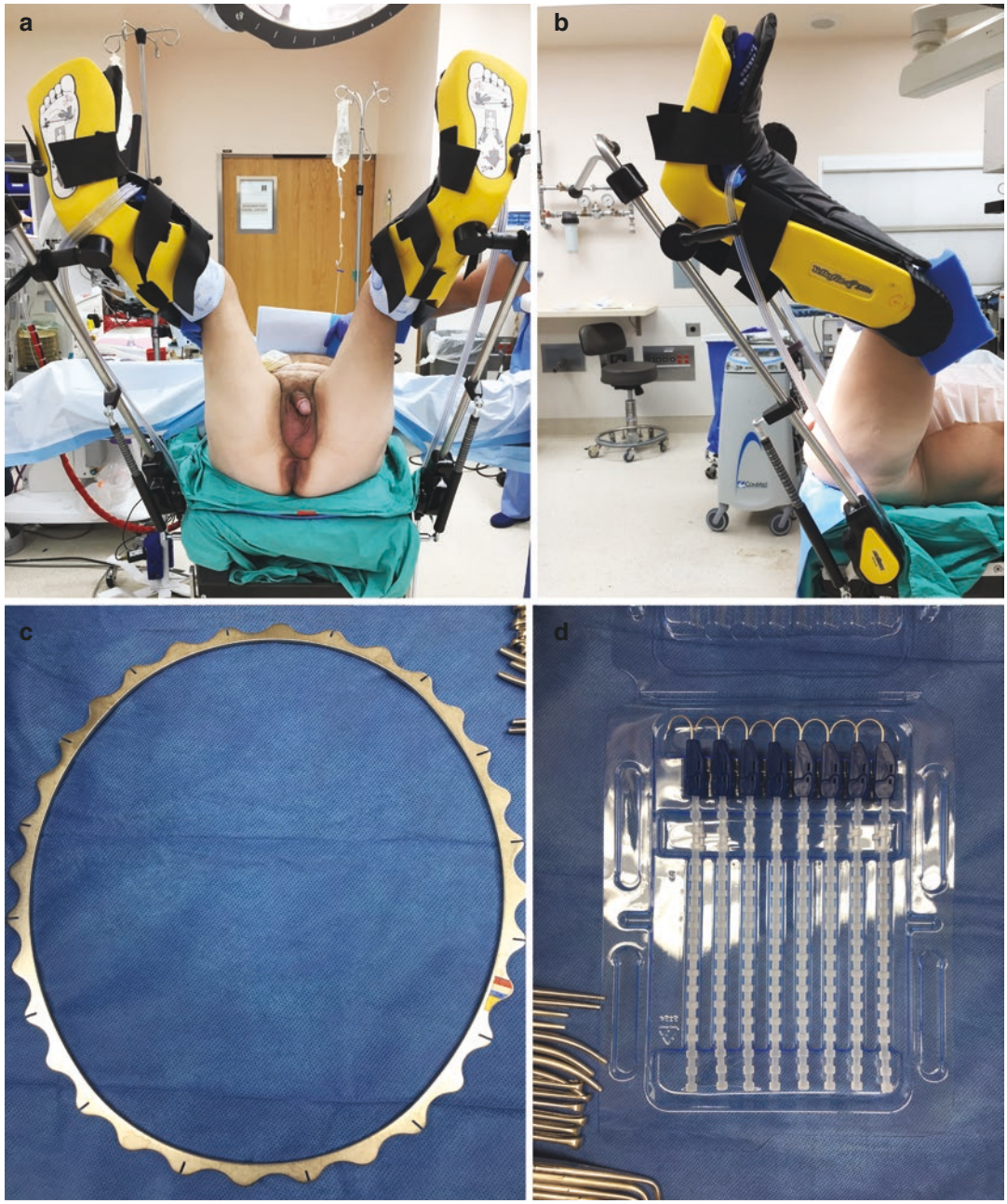

Fig. 15.1 (**a**, **b**) High dorsal lithotomy position with gentle flexion of the hip and knees in yellow-fin stirrups. A gel roll is placed under the buttocks to help elevate the perineum; (**c**, **d**) Modified Denis-Brown retractor and retracting hooks used to assist with exposure

(Fig. 15.1a, b). Care is taken to properly pad all pressure points, especially the lateral knee, in order to avoid a peroneal nerve injury. A perineal retractor should be readily available to assist with exposure. We utilize a modified Denis-Browne retractor with adjustable stay hooks (Fig. 15.1c, d).

Incision

After the patient is draped, we begin by marking out a perineal modified lambda incision (Fig. 15.2a). The lambda incision helps with accessing and exposing the most proximal portion of the urethral dissection. This is then deepened with electrocautery until the bulbospongiosus muscle is encountered and divided in the midline. At this point, the retractor is placed to assist with exposure of the spongiosum (Fig. 15.2b).

Dissection of the Distal Urethra

The urethra is then elevated off the corporal bodies dorsally using sharp dissection. A penrose drain can then be placed around the urethra to assist with retraction. Dissection is carried distally in the dorsal urethral plane to mobilize the urethra off of the corporal bodies completely to the level of the glans (Fig. 15.2c). This involves inverting the penis into the perineal incision (Fig. 15.2d). Once the urethra has been completely dissected to the glans, the penis is reverted. The next step is the dissection of the fossa navicularis, which is assisted with the placement of a glans traction suture. A tennis racquet-shaped circumscribing incision is marked around the meatus with the "handle" at 6 o'clock (Fig. 15.3a). This incision is made and carried down with tenotomy scissors to core out the fossa navicularis (Fig. 15.3b). The majority of this dissection can be completed from the normal penile anatomic location, but it is often

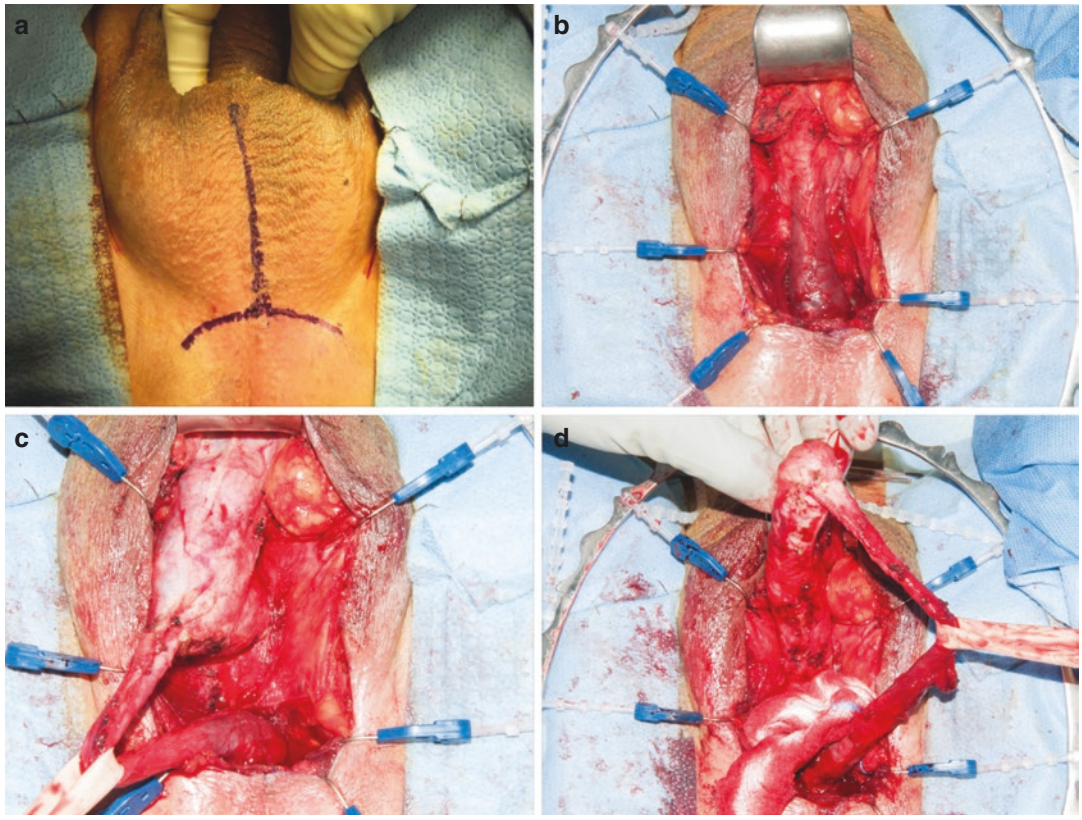

Fig. 15.2 (**a**) Modified lambda perineal incision; (**b**) Divided bulbospongiosus muscle revealing the corpus spongiosum; (**c**) Distal dissection in the dorsal urethral plane to mobilize the urethra off of the corporal bodies, penrose drain used to assist with retraction; (**d**) Dorsal urethral dissection carried out distally to the glans with complete inversion of the penis into the perineal wound

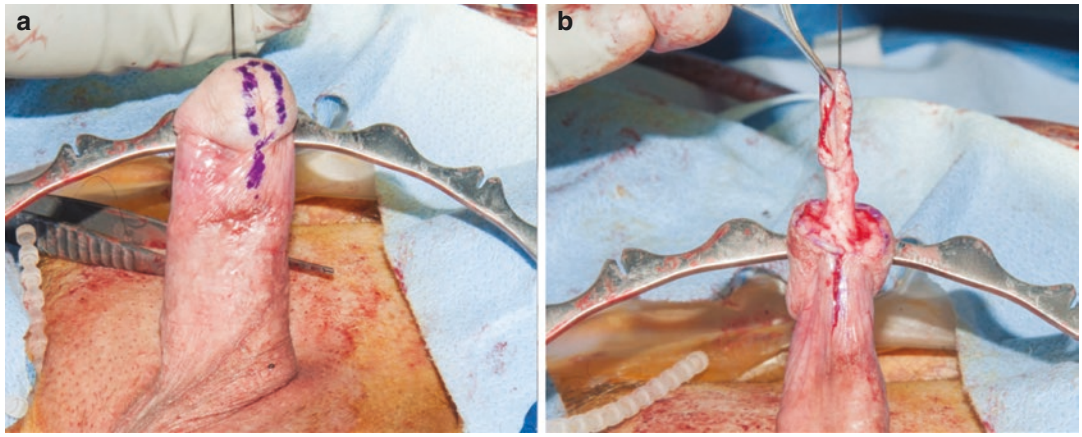

Fig. 15.3 (**a**) Incision around the meatus marked out in the shape of a tennis racquet with the handle at 6 o'clock to assist with the dissection; (**b**) The distal urethra is sharply dissected out from the overlying glans tissue

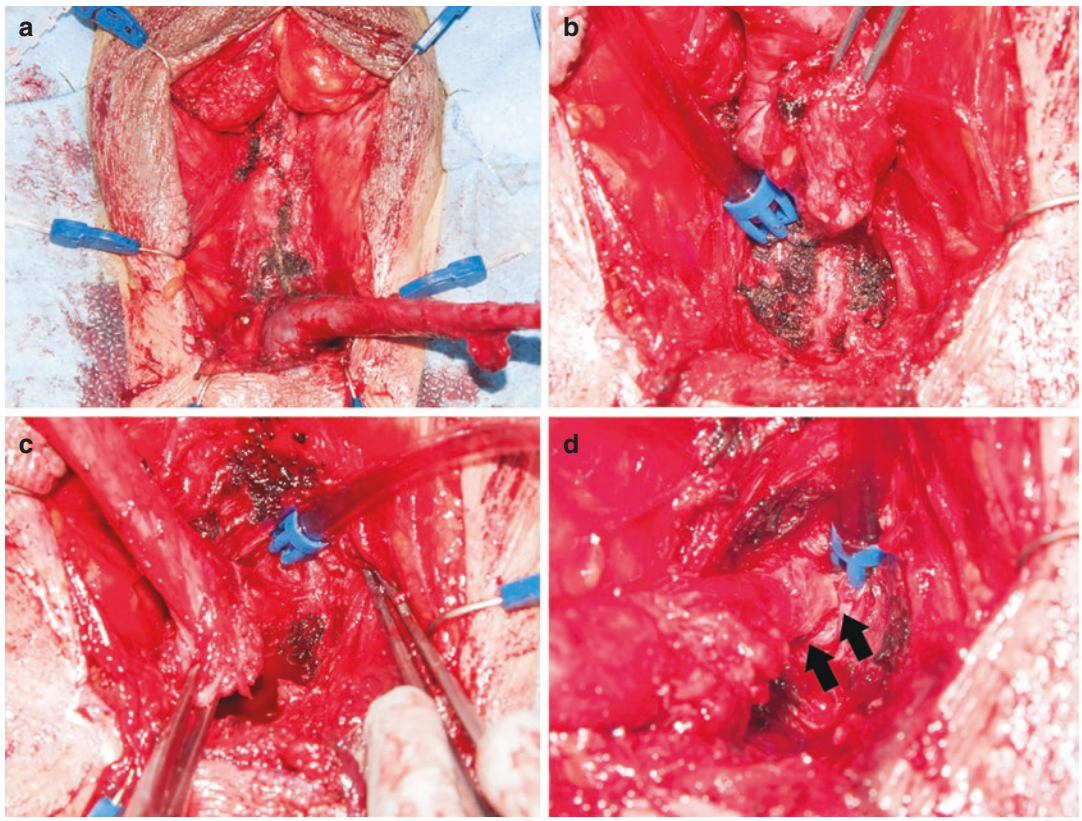

Fig. 15.4 (**a**) Transection of the completely dissected distal urethra, which is now free in the perineal incision; (**b**) Ventral dissection of the bulbar urethra with transection of the central tendon, forceps holding up bulbar urethra; (**c**) Exposure of the membranous urethra; (**d**) Circumferential dissection of the membranous urethra off the surrounding external urethral sphincter muscle (arrows indicate membranous urethra)

easier to invert the penis back into the perineal incision to take down the most proximal remaining attachments of the urethra within the glans. Before completely releasing the distal urethra and reverting the penis, hemostasis of the distal corporal bodies should be obtained (Fig. 15.4a).

A Raytec sponge is placed into the urethral bed to help with hemostasis while the proximal dissection occurs.

Dissection of the Proximal Urethra

Using the urethra as a handle, the proximal dissection is then started. It is important not to place too much traction on the urethra as it is possible to avulse the urethra, particularly at the location of the tumor. The dorsal dissection is carried proximally under the divergence of the corporal bodies until the membranous urethra is encountered. Ventrally, the central tendon is released, and the dissection follows the curve of the bulb of the corpus spongiosum (Fig. 15.4b). The bulbourethral arteries are identified bilaterally, as the dissection is carried around the bulb at the 4 and 8 o'clock positions and controlled with electrocautery or ligation. The membranous urethra is then encountered (Fig. 15.4c) and dissected off the surrounding external urethral sphincter musculature circumferentially (Fig. 15.4d). At this point, it is useful to insert a foley catheter into the urethra, advance it as far as possible, and clamp the distal urethra to prevent movement of the catheter. This allows the surgeon to use the catheter as a palpable guide to determine the proximal extent of the dissection. Care must be taken with the proximal dissection to avoid any bowel that may be adhered to the superior surface of the urogenital diaphragm following cystectomy. Once this proximal limit is reached, the urethra is transected sharply proximal to the lumen and sent to pathology (Fig. 15.5a).

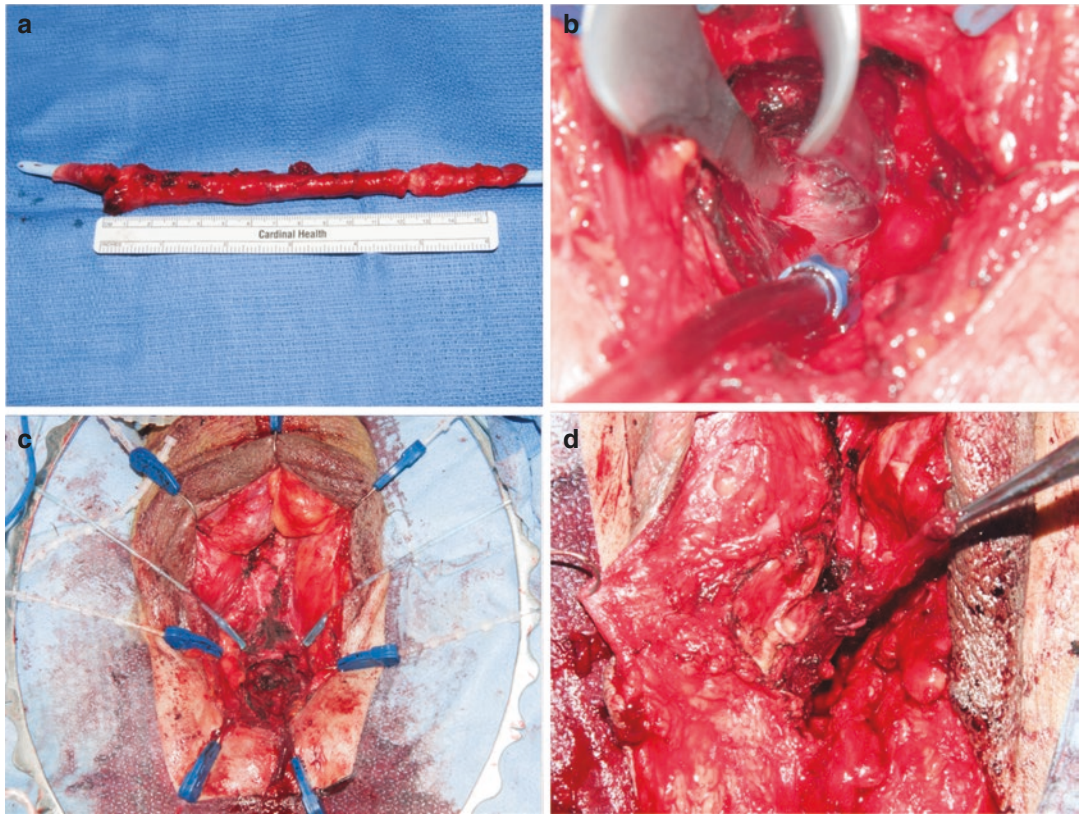

Fig. 15.5 (**a**) The complete urethrectomy specimen; (**b**) Use of a nasal speculum to aid in visualization of the proximal dissection and ensure there is no further urethral tissue to excise; (**c**) Perineal wound after the urethra has been completely removed; (**d**) Dissection of bulbospongiosus muscle flap that will be placed into the deep cavity to obliterate the dead space, forceps holding the distal tip of the bulbospongiosus flap

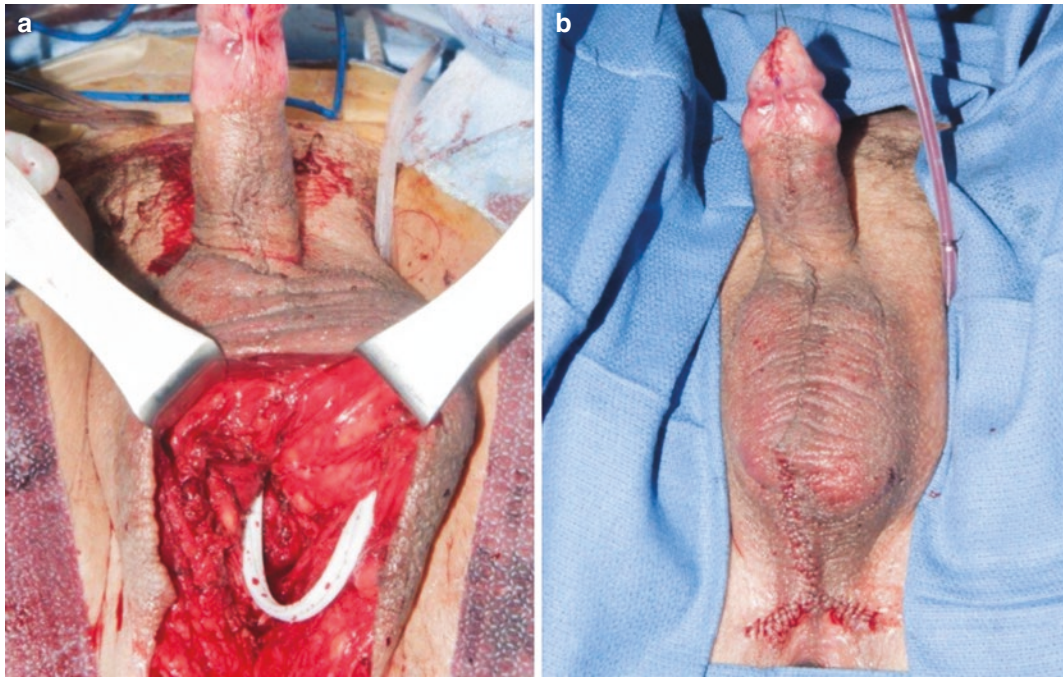

Fig. 15.6 (**a**) Placement of a channel drain along the perineal surgical bed and coursing up into the shaft of the penis; (**b**) Final appearance of closed glans incision and perineal incision

A nasal speculum may be a useful adjunct to visualize the most proximal resection bed to identify any residual urothelium for resection or cauterization, ensure a complete resection, and obtain hemostasis (Fig. 15.5b). Bleeding can be brisk at times and most often occurs between 11 and 1 o'clock where the dorsal venous complex lies. These are usually easily controlled with a suture on a UR-type needle.

Closure of the Surgical Site

The perineal wound is then irrigated with normal saline and packed. The sponge in the urethrectomy bed is removed, hemostasis along the bed of the urethra confirmed, and the glans closure completed. The deep glans tissue is closed with interrupted 4–0 polydioxanone sutures and then the superficial glans closed with 5–0 polyglactin 910 interrupted sutures.

For the perineal closure, it is important to obliterate the cavity that is created after the urethra is removed (Fig. 15.5c). Either one or both of the bulbospongiosus muscles can be mobilized to create a muscle flap to fill the cavity. The bulbospongiosus muscle is divided distally, and its lateral attachments are taken down, leaving the proximal muscle attached as this is the direction of the blood supply from the perineal artery (Fig. 15.5d). The flap is then sutured into the proximal cavity with 3–0 polyglactin 910 suture. A 7-mm channel drain is placed and brought out the patient's groin, lateral to the scrotum, and secured with a drain stitch (Fig. 15.6a). The drain can be placed along the length of the operative site all the way up into the penis. Remaining soft tissue in the perineum is then closed with interrupted 3–0 polyglactin 910 sutures in two layers. Colles' fascia is then closed with running 3–0 polyglactin 910 suture. The perineal incision is then closed superficially with a running baseball 4–0 polyglactin 910 suture (Fig. 15.6b). A tegaderm dressing is then applied to the perineal incision, followed by fluff gauze, and mesh underwear.

Postoperative Care

Patients may be admitted overnight for observation and analgesia. The channel drain is removed when output is minimal. Patients are advised to avoid heavy lifting, squatting, and high leg raising activities such as climbing a ladder, to avoid traction and pressure on the perineum for 4 weeks. Patients are routinely seen in clinic 4–6 weeks postoperatively for a wound check and review of the pathology.

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16 Management of Common Complications After Radical Cystectomy, Lymph Node Dissection, and Urinary Diversion

Samuel Haywood, Timothy F. Donahue, and Bernard H. Bochner

Introduction

As the standard therapy for muscle-invasive bladder cancer, radical cystectomy is commonly performed in an elderly population with significant comorbidities. A mean age of approximately 68 years has been reported previously [1], and extending the indication to patients of advanced age has shown increasing acceptability in the literature [2, 3]. Accordingly, complications occur frequently, as a review of the Memorial Sloan-Kettering cystectomy experience demonstrated an overall complication rate of 64% within 90 days of surgery [4]. As such, the urologist performing these procedures needs to be comfortable with the management of these complications. In this chapter, we seek to review the management of common complications after the radical cystectomy as well as the pelvic lymph node dissection and urinary diversions.

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Gastrointestinal Complications

The gastrointestinal system is most commonly associated with complications following radical cystectomy and urinary diversion. In the MSK review, GI complications accounted for 29% of total complications [4]. The most common GI complication is a postoperative ileus. The definition of postoperative ileus has varied significantly in the literature. As such, the reported incidences also show a wide range, but can be as high as 20–30% in some series [4–7]. Clinically, the patient will demonstrate delayed return of bowel function with nausea and/or vomiting, and on examination will demonstrate abdominal distention with absence of bowel sounds. Management of ileus initially involves bowel rest, intravenous fluid resuscitation/support, and monitoring for electrolyte abnormalities. Imaging can be used to rule out bowel obstruction or an underlying cause such as a pelvic fluid collection. If the patient is symptomatic or ileus continues, a nasogastric tube should be placed to decompress the system. This will relieve symptoms, lower the risk for

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aspiration and allow the bowel to return to a more normal caliber which may facilitate return of normal function. Finally, if the ileus persists longer than 7–10 days, initiating the patient on parenteral nutrition may be necessary.

While the majority of patients experiencing postoperative ileus will resolve with supportive measures, an ileus is associated with discomfort/anxiety to the patient, and, objectively, to increased length of hospital stay and overall costs [7]. As such, there has been significant effort devoted to preventing postoperative ileus. A number of evidence-based strategies have been combined into enhanced recovery after surgery (ERAS) protocols which have improved GI complication rates. These include avoidance of a bowel preparation [8], omitting a standard nasogastric tube after surgery [9, 10], use of non-narcotic pain medication with avoidance of narcotics, and the use of Ч-receptor antagonists prior to surgery [11, 12]. These combination of strategies have been effective in significantly decreasing rates of postoperative ileus [13, 14] as well as length of stay and hospital cost [15].

Several other potential interventions deserve further mention. The use of a preoperative epidural catheter placement to reduce systemic narcotic consumption is common among ERAS protocols, although data in the literature has been mixed [6, 16]. Further, optimizing nutrition by preoperative carbohydrate loading and early refeeding after surgery has been incorporated into ERAS protocols given data in the general surgery literature, but specific studies in the cystectomy population are lacking. Finally, analysis of stapler size used for the bowel anastomosis has been studied and does not appear to contribute to the time to bowel recovery [17].

At our institution, the routine pathway for our cystectomy patients does not include bowel prep unless there is concern for concurrent bowel resection or there is a planned use for the colon in the urinary diversion. An epidural catheter is placed in the preoperative holding area, and patients receive alvimopan, NSAIDs (unless contraindicated by history of gastric ulcers or chronic kidney disease), and gabapentin (age < 65). The patient leaves the operating room without nasogastric tube. Postoperatively, the patient is maintained on alvimopan twice daily until first bowel movement, and pain is controlled with a combination of regular acetaminophen, ketorolac, and the epidural catheter managed with the assistance of the pain management team. Diet is instituted with liquids on the first postoperative day, with advancement to solid food on postoperative day 2 unless clinical status dictates otherwise.

Bowel obstruction after cystectomy and diversion is significantly less common, with reported incidences below 10% [4, 7]. Clinically, bowel obstruction presents similarly to postoperative ileus in the early phase, as characterized by abdominal distention, nausea/vomiting, abdominal pain, and lack of bowel function. This abdominal pain may be intermittent, although progression to constant or localized abdominal pain should concern the team for possible bowel compromise. Imaging will be helpful in further evaluation, specifically to distinguish from an ileus and determine the location and degree of obstruction. Plain films of the abdomen in bowel obstruction may demonstrate air-fluid levels and lack of distal bowel gas, while an ileus typically shows gas throughout the entire GI tract. The best imaging study, however, is the computed tomography with oral contrast administration. This modality has reported diagnostic values of greater than 90% sensitivity and specificity for obstruction [18].

Management of bowel obstruction is differentiated based on degree of obstruction: partial versus complete; the extent of bowel dilation, and the presence or absence of symptoms concerning for bowel compromise. In a complete bowel obstruction, imaging does not identify passage of any bowel contents or gas beyond the area of obstruction. As with postoperative ileus, supportive management in the initial therapy of choice in partial bowel obstruction, including nasogastric tube placement, intravenous fluid and electrolytes, and bowel rest. Over 85% of postoperative bowel obstructions will resolve with this management [19, 20]. If extended periods of bowel rest do not resolve the obstruction (7–14 days), parenteral nutrition should be initiated and reoperation should be considered.

Other gastrointestinal complications management of note includes GI bleed, bowel anastomotic

leak, and enterocutaneous fistulae. However, these complications are quite rare.

Infectious Complications

Infectious complications are the second most common type seen after cystectomy. Incidence of infections after cystectomy can approach 25% of cases, and an analysis of NSQIP database found that almost half of readmissions occur related to an infectious etiology [4, 21, 22]. Of note, >50% of these complications will occur after discharge, most common around the end of the second week [23]. Postoperative infections include a broad category of issues, and include fevers, abscess, urinary tract infection, sepsis, and pyelonephritis.

Management of these infectious complications is relatively standard, and includes appropriate cultures, empiric antibiotic coverage, and subsequent narrowing of antibiotic coverage once cultures return. Consideration must also be given toward source control. If abscess is noted on cross-sectional imaging, then consultation with interventional radiology for aspiration and/or drainage should be obtained. Further, the physician must also consider maximizing urinary drainage if the infection appears urologic in origin. This can include placement of an indwelling catheter into the urinary diversion or placement of percutaneous nephrostomy tubes if there is concern for urinary obstruction.

One source of debate includes method of urinary sampling in patients with ileal conduits. A recent randomized trial comparing clean stoma catheterization and sample collection via urine dripping from the stoma found similar clinically relevant information via either method [24].

Much of the available literature focuses on preventing infectious complications. Use of preoperative antibiotic prophylaxis is standard, but the specific regimen is quite variable. A recent retrospective study of >8000 patients undergoing cystectomy across the United States found greater than 500 unique antibiotic regimens, with only 15% of regimens corresponding to available guidelines [25]. Current guidelines from the American Urologic Association are available and guide the clinician toward an appropriate antibiotic regimen [26]. However, specific local variations may be applicable based on the antibacteriogram at each particular hospital and consultation with the microbiology lab may help identify region-specific antibiotics.

A number of groups have proposed strategies to reduce infectious complications. Among these strategies include fungal coverage with perioperative antibiotics [27], continuous prophylactic antibiotics for the first 30 days after cystectomy [28], and smoking cessation [21]. While these all have initial evidence suggesting a benefit, further study is required before becoming standard of care.

One limitation of extending antibiotic coverage is achieving a balance between adequate prophylaxis and treatment with the risk of *Clostridium Difficile* infection. Rates of symptomatic infection after cystectomy vary between studies, with values ranging from 2% up to 11.7% [29–31]. Treatment for diarrhea secondary to *Clostridium Difficile* is possible with several different antibiotics, although most frequently with oral vancomycin or metronidazole [32]. Further, a preoperative screening protocol may provide prevention. One Indiana University study utilized preoperative *Clostridium Difficile* testing with subsequent isolation and metronidazole treatment if positive, and rates of symptomatic infection postoperative declined by approximately half [33]. Emphasizing meticulous hand hygiene principles amongst all caregivers is of utmost importance in preventing spread of this infection.

Wound Complications

Wound-related complications provide another frequent source of complications. This grouping spans a wide range of acuity, including wound seroma, superficial wound infection, superficial wound dehiscence, and fascial dehiscence. Altogether, wound complications occur in about 15% of all cystectomies, with superficial wound infection compromising the majority of these

infections (9.3% of all patients) [4]. However, some published series note even higher rates of surgical site infection, up to 20–25% [34]. Notably, the rates of fascial dehiscence appear to be decreasing with more contemporary studies. A recent NSQIP review of cystectomies performed 2005–2012 identified a rate of dehiscence of 3.2%, lower than historical series with rates up to 8.9% [35]. The single institution review of MSK experience recorded a rate of fascial dehiscence requiring reoperation of 0.4% [4].

Management of superficial wound complications is straightforward. Wound seromas may be treated conservatively or with removal of skin clips (if placed at time of surgery) and drainage. Superficial wound infections are treated with drainage and antibiotics tailored to skin flora. Finally, superficial wound dehiscences can be allowed to heal by secondary intention, with daily or twice daily gauze packing of the wound. Literature regarding management of fascial wound dehiscence is limited. These are typically managed with reoperation and fascial closure. Complex repairs or patients with decreased fascial quality may require intraoperative assistance from general or plastic surgeons at each institution. In some cases, the closure may necessitate use of mesh sheets or even mesh strips used to perform sutured repairs [36]. Engagement of the wound and ostomy continence nursing services (if available) at each institution can be quite helpful.

There has been significant recent interest in preventing superficial wound complications via changing operating room procedures. These "bundles" of interventions were reported initially in the colorectal surgery literature, and were successful in reducing surgical site infections by >50% [37]. The bundle included several practices including an emphasis on evidence-based antibiotic prophylaxis, a separate closing tray of instruments, and changing of gloves by operating room staff prior to closure. Study of similar bundles interventions in both the gynecologic and urologic literature has shown similar positive results [38, 39]. One bundle studied at the Cleveland Clinic by Vij et al. was used in several major urologic procedures including cystectomy, and included preoperative/intraoperative antibiotics, specific skin preparation protocols, glove change and wound irrigation prior to skin closure, and new sterile closing instruments. This study demonstrated reduction in risk of superficial wound infection from 3.6% to 1.4% [39].

Negative-pressure wound therapy has also been explored in the literature for other surgical specialties as a method to decrease wound complications. These dressings have been studied in the fields of orthopedic surgery, general and breast surgery, cardiac surgery, spinal surgery, and vascular surgery with positive outcomes [40]. No data are currently available in urologic populations, but a recent meta-analysis of this vacuum dressing in laparotomy incisions for general and colorectal surgery cases found significantly decreased rates of surgical site infection [41]. While not yet specifically studied in the cystectomy population, initial data suggest a promising avenue of study.

Genitourinary Complications

Not surprisingly, genitourinary complications can occur commonly after urinary diversion, as the normal path of urine flow is disrupted and a new reservoir is created. The complications within this category are diverse and include renal failure, urinary leak, urinary obstruction/stricture, long-term renal deterioration, and electrolyte disturbances.

Renal failure, or acute kidney injury (AKI), occurs quite frequently after cystectomy, with studies demonstrating an incidence between 10% and 30% of patients [42, 43]. This frequently occurs as a result of fluid loss and fluid shifts perioperatively. One element of the current ERAS protocols includes optimization of intraoperative fluid management to avoid fluid overload. The particular methods of fluid management vary, including colloid administration, restrictive fluid administration, fluid administration directed at specific hemodynamic parameters, and use of vasopressor agents to maintain blood pressure. Regardless of method, all strive to minimize intravenous fluid administration. Not surprisingly, this

can increase the incidence of AKI. In a retrospective analysis of restrictive fluid and vasopressor administration during cystectomy, a restrictive approach to fluids independently of vasopressor was predictive of AKI postoperatively [44]. In many cases, the AKI will resolve with fluid resuscitation. However, this must be done carefully, with specific attention paid to the patient's clinical fluid status as well as any cardiac comorbidities to avoid fluid overload. Concurrently, the care team should review the patient's medication list, to both identify nephrotoxic agents as well as adjust any medication dosing accordingly. Adequate urinary drainage should be confirmed in all patients, and any catheters, stents, or tubes in the urinary system should be carefully irrigated to ensure patency. The clinician should also rule out urine leak with intraperitoneal absorption, which may be followed by evaluating outputs of the surgically placed drain. If renal failure persists or progresses despite adequate fluid resuscitation, consideration should be given to imaging with renal ultrasound to evaluate for hydronephrosis to rule out urinary obstruction. Finally, consultation with nephrology colleagues will assist with evaluation of any medical causes of AKI.

A ureteroenteric anastomotic leak is recognized in about 2–4% of patients following urinary diversion [4, 45], although the true incidence is likely hard to define as some early leaks may be subclinical. Leaks are often clinically evident, presenting as increased output from surgical drains or rising serum renal function indices from reabsorption across the peritoneum. Additional signs may include gastrointestinal ileus (with associated abdominal distention, nausea, and/or vomiting), wound discharge, or leukocytosis, fevers/sepsis. The diagnosis is confirmed by testing drain fluid for creatinine. No defined cutoff has been published for drain creatinine relative to serum creatinine, but in general, the value should be at least 2–3 times the serum creatinine to establish a leak. Imaging may be helpful to help localize the leak and identify any undrained collections. Imaging options include computed tomography with delayed phase images or a "loopogram"or "pouchogram", which utilizes plain film images as contrast is injected into the urinary diversion. Of note, while many providers routinely measure drain output for creatinine, the use of routine imaging to detect urinary leaks is unnecessary [46–49].

If ureteral catheters or stents are in place, the management of an early leak will be conservative and utilize the drains placed during surgery. In addition, the drainage of the urinary diversion should be optimized. A stomal catheter should be placed into ileal conduits, and the catheter within continent diversions should be frequently assessed for patency. The patient can then be monitored closely, with attention on clinical status, drain/urine outputs, and laboratory values. In the event of persistent leak, we favor proximal urinary diversion with placement of diverting percutaneous nephrostomy tubes [50]. The area of leakage can be monitored for resolution with antegrade nephrostogram and/or loopogram/pouchogram/neobladdercystogram. If none of the above methods adequately manage the urine leakage, then operative repair may be considered. A publication by Brown et al. illustrates algorithms for managing urine leaks [51].

Some surgeons do not routinely place ureteral catheters when performing ureteroenteric anastomosis citing that no definitive benefit has been documented in the literature with respect to urine leaks [52, 53]. A prospective, randomized trial in Switzerland randomized patients with or without stenting at the time of ureteroenteric anastomosis. While there was early evidence of urine leakage in the group without stenting, this difference had disappeared by day 7, and nonstented patient required surgical revision for urine leak [52]. With recent increased interest in robotic-assisted cystectomy and urinary diversion, a recent report highlighted intracorporeal ureteroenteric anastomoses without ureteral stenting. This procedure was performed in 10 patients (20 renal units) without any ureteroenteric urine leaks noted [54].

The incidence of ureterointestinal strictures is quite variable based on both the anastomosis technique and the length of follow-up used. However, rates in the literature range dramatically between 2% to over 20%. In most cases, ureteral stricture occurs secondary to ureteral ischemia or periureteral fibrosis and occurs

within 1–2 years of follow-up. However, long-term follow-up is required as rates do increase even beyond the first 2 years. Often, ureteroenteric obstructions are asymptomatic and as such are discovered incidentally on follow-up imaging or laboratory studies [55–59].

Preventing ureterointestinal stricture at the time of the initial urinary diversion has key importance. As these likely occur as a result of ischemia, it is vitally important to minimize the mobilization and devascularization of the ureter during the dissection, as well as minimize direct handling of the ureter when possible. This will limit damage to the small arterioles that provide blood within the periureteral adventitial sheath. Additionally, one should take special note during routing the left ureter underneath the colon mesentery, as any excessive angulation or tension on the ureter can facilitate stricture formation.

The method of performing ureterointestinal anastomosis can have significant impact on the stricture rate. Nonrefluxing anastomoses have been used to decrease risk of renal deterioration over time, but are associated with significantly higher (at least two-fold) rates of ureterointestinal stricture. One analysis with long-term follow-up demonstrated stricture rates of 13% in nonrefluxing anastomoses and 1.7% in direct refluxing anastomoses [57]. Further, investigators have also looked at ureteral stenting and its effect on strictures. The aforementioned randomized trial in Switzerland noted strictures only in the stenting group; however, the overall number of strictures was small and difficult to make true conclusions [52]. Finally, the impact of robotic surgery has also been studied with respect to stricture rates. An early comparison of robotic versus open surgery from Vanderbilt University demonstrated no significant difference between stricture rates amongst groups. However, the overall stricture rate of 9.4% (8.5% open vs. 12.6% robotic) is relatively high compared to historical studies, and the median follow-up in the study was short [60]. Another series of robotic urinary diversions demonstrated similarly high rates of stricture (13% overall) with longer follow-up [61].

Management strategies for ureterointestinal strictures include endoscopic (antegrade and retrograde) as well as open surgical approaches. Endoscopic approaches can be performed by urology or interventional radiology, and generally involve incision and/or dilation of the stricture segment. The rates of success in several endoscopic series managing postdiversion ureteroenteric strictures is in the 30–60% range [61–65]. As endoscopic management is significantly less invasive than open revision, this is often the initial therapy of choice for relatively short ureteroenteric strictures. Of note, the patients who derived the best benefit from endoscopic management were those with short, distal strictures (<2 cm), and preserved kidney function prior to intervention. The series described by Wolf et al. found that no patient with kidney function <25% on the side of intervention had a successful result [62]. Open surgical repair has a very high success rate (80% or higher) and should be considered the gold standard for repair of ureteroenteric strictures [65, 66]. However, these procedures are significantly more invasive and require technical expertize. Some surgeons with expertize in robotic surgery have reported on repair of ureteroenteric strictures using the robot; studies are small but demonstrated similar perioperative outcomes to open surgery [61]. Of note, regardless of the approach, the excised length of ureteral segment must be sent as a pathologic specimen to rule out malignancy. Finally, the surgeon should be prepared to use a segment of the GI tract if necessary to bridge any distance between the healthy proximal part of the ureter and the urinary diversion. Small bowel, colon or the appendix may be useful grafts to complete these revisions.

Replacing the urothelium of the bladder with intestinal mucosa can result in significant differences in absorptive properties of various electrolytes and other substances. This can result in long-term consequences for the patient that the urologist should be aware of to manage appropriately. The specific bowel segment drives the particular disturbances, and the fewest abnormalities in patients with ileum and colon diversions make these the most common bowel segments used.

Given the limited use of stomach or jejunum in current practice, the effects and management of their use will not be covered here. When colon and ileum are exposed to urine, there is increased absorption of ammonium chloride, which over time leads to hyperchloremic metabolic acidosis. In patients with impaired renal function, this can manifest clinically as lethargy, anorexia, weight loss, and over time the acidosis will lead to bone demineralization and osteopenia. Given the increased urine dwell time, these manifestations can be magnified in patients with continent diversions. As such, patients with impaired renal function (creatinine levels >2.0 mg/dl or glomerular filtration rate <35 ml/min) are less optimal candidates for continent diversions.

The incidence of acidosis in a series of patients with continent diversion was approximately 20% at 1 year, but this rate subsequently decreased to 7.3% at 2 years [67]. Chronic acidosis results in both vitamin D deficiency as well as resorption of calcium from bone as an acid-base buffer, and these factors combined with decreased intestinal absorption of calcium can result in osteopenia [68–71]. The treatment for symptomatic metabolic acidosis in these patients includes alkalinizing agents, hydration, and, in the case of a continent diversion, minimizing urine dwell time. With respect to bone health, serial use of DEXA scan to monitor bone mineral density has not been studied in this population, but deserves further investigation. Treatment of these patients should begin with correction of their acid-base status as above. However, those patients that do not show remineralization of the bone should be managed with supplementation of both calcium and Vitamin D [72–74].

Removing bowel segments from continuity also results in a few significant malabsorption states. In particular, the terminal ileum absorbs bile salts, fat-soluble vitamins (A, D, E, and K), and vitamin B12. In the case of excessive lengths of ileum used (e.g., continent cutaneous reservoir or orthotopic neobladder), the patient may then be at risk of vitamin B12 deficiency, dehydration, and steatorrhea. Intraoperatively, the surgeon should strive to leave as much terminal ileum as possible to avoid B12 deficiency, as deficiency can cause neurologic derangements and anemia. The depletion of B12 was thought to be a slow process that can take several years to develop symptomatic levels [75]. However, we have seen depletion occurs relatively early after diversion and it is the practice of the authors to monitor B12 levels on a yearly basis beginning at the first year after urinary diversion.

Lymphatic Complications

Historically, lymphatic complications (i.e., pelvic lymphoceles) after pelvic lymph node dissection in conjunction with radical cystectomy have not been commonly observed. The reported rate in the MSK complication series is <0.1% of cystectomies. The true incidence of lymphoceles may be higher; however, given that most are asymptomatic [4]. However, over the past few decades, surgeons performing cystectomies are performing lymph node dissections more frequently and the dissections are more extensive. This trend is largely based on data suggesting improved oncologic outcomes related to higher lymph node yield at cystectomy [76–79].

Increasing the extent of lymph node dissection has resulted in increased rates of lymphoceles. A recent European, randomized Phase III trial of extended versus limited pelvic lymph node dissection in cystectomy patients demonstrated an increased rate of lymphoceles in the extended pelvic lymph node group [80]. At 30 days, rates of lymphoceles requiring drainage were 3.4% in the limited dissection and 7.6% in the extended dissection group, with $p = 0.08$. At 90 days, lymphoceles remained stable in the limited dissection group at 3.4% but increased to 8.6% in the extended lymph node dissection group, $p = 0.04$. This is in line with other studies demonstrating that 8.3% of readmissions within 30 days were related to lymphoceles [81]. Importantly many pelvic lymphoceles do not require intervention, especially if found incidentally and/or are asymptomatic. Lymphoceles that result in discomfort, lower extremity edema, or become secondarily infected may require treatment. Further, prolonged lymphoceles may result in venous stasis

and increased theoretical risk for venous thromboembolism. In these cases, intervention is warranted. Initial management should be consultation with interventional radiology for aspiration and drain placement. Once the drain is in place, lymph drainage can be monitored, and removal of the drain is considered once output is minimal or if outputs remain persistent or the collections large in size, injection of various sclerotherapy agents may be considered [82, 83].

Cardiopulmonary Complications

Despite improvements in safety over the past decades, cystectomy and urinary diversion remain as major surgical procedures. Accordingly, the morbidity related to cardiac and pulmonary complications can be significant. This becomes even more relevant as the field expands indications for cystectomy to include patients that are older with additional comorbidities. Together, cardiopulmonary complications can occur in up to 20% of cystectomies [4], although this figure will vary depending on definition used.

Management of cardiac complications centers on early recognition and involvement of the appropriate medical teams within the institution. While cardiac complications most frequently occur in the elderly, comorbid population, preoperative optimization by internal medicine, cardiology, or geriatrics services, in order to identify modifiable risk factors and reduce risk should be considered in all patients. The reader is referred to published risk calculators, such as the Revised Cardiac Risk Index (RCRI), as well as guidelines published by the American College of Cardiology and the American Heart Association regarding preoperative evaluation [84, 85]. A group from the Cleveland Clinic devised a helpful algorithm incorporating these risk stratification tools in cystectomy patients to appropriately refer patients for preoperative medical evaluation while avoiding unnecessary referrals for low-risk patients [86].

The specific management of pulmonary complications (e.g., atelectasis, pneumonia, failure to wean supplemental oxygen) is beyond the scope of this chapter and may require consultation with the medical or pulmonary service at each institution. However, it is important to briefly mention the benefit of early ambulation in prevention of pulmonary complications. Early ambulation is an important component of most if not all enhanced recovery protocols. While ERAS protocols overall have been shown to reduce hospital length of stay and complication rates [87], the heterogeneity of these protocols limits direct conclusions about early ambulation in the cystectomy population. However, a small Australian study of patients undergoing abdominal surgery found that each day without mobilization increased risk of pulmonary complications threefold [88].

Thromboembolic Complications

Venous thromboembolism (VTE) is a risk associated with all major surgical procedures, but the risk is further increased when malignancy is present [89]. Within urology, radical cystectomy has the highest risk of VTE compared to both nephrectomy and prostatectomy [90, 91], and neoadjuvant chemotherapy may be contributed to the risk of VTE [92, 93]. A review of VTE complications in cystectomy patients revealed rates ranging from 3% to 11.6% after cystectomy [94].

Prevention of VTE after radical cystectomy is paramount. The AUA Best Practice Statement regarding prevention of VTE in urologic surgery provides recommendations based on age, minor versus major surgery, patient history, and malignancy. Most patients undergoing cystectomy will fall into the high- or very-high-risk categories. Preventative recommendations in this group include pneumatic compression devices and perioperative low-dose unfractionated heparin, or low-dose low-molecular weight heparin [95]. However, several studies have shown that >50% of VTE events occur after hospital discharge, which suggests a need for extending the prophylaxis regimen beyond the inpatient admission [91, 93, 96–98]. A study from the University of Chicago by Pariser et al. examined an extended prophylaxis regimen after cystectomy. Patients were given unfractionated heparin during

admission followed by low-molecular weight heparin (enoxaparin) at discharge for 28 days. Comparing to a historical cohort prior to the change without postdischarge prophylaxis, overall VTE rates dropped from 12% to 5%, with postdischarge VTE rates dropping from 6% to 2% [99]. Importantly, no excess bleeding complications were noted with this regimen. This finding is consistent with other Level I evidence regarding extended pharmacologic prophylaxis in abdominal and pelvic cancer surgeries [100]. Given these data, many centers have incorporated extended pharmacologic prophylaxis into their postoperative protocols.

The frequency of patients with VTE diagnosed prior to radical cystectomy has increased with the more widespread use of neoadjuvant chemotherapy. A retrospective review from MSKCC found that 16% of cystectomy patients experienced VTE occurring during the preoperative chemotherapy regimen [101]. It is important to consider the use of an inferior vena cava (IVC) filter in a subset of these patients perioperatively, as propagation or embolism of an existing clot may result in a pulmonary embolism. Indeed, in the MSKCC series, 11% of patients had IVC filter placed within the study period [101]. Regardless, a difficult question will arise postoperative with respect to the time to restart anticoagulation, with competing risks of further VTE development versus postoperative bleeding. This decision must be based on the surgeon's assessment of the operation itself as well as the individual patient risks of continuing to withhold anticoagulation. However, the EAU guidelines on thromboprophylaxis note that approximately 50% of cumulative bleeding risk occurs in the first day after the operation, and almost 90% of this cumulative risk occurs within the first 4 days postoperatively [102]. As such, in most cases it will be possible to restart anticoagulation within the first week; however, precise timing will be at the discretion of the surgeon and the medical specialty team.

The studies in the urologic literature for extended pharmacologic prophylaxis have used low-molecular weight heparin as the intervention of choice. However, this medication is renally cleared, which necessitates special consideration in the cystectomy population. Many patients preoperatively will have glomerular filtration rates precluding use, and a significant portion of patients will have acute kidney injury in the immediate postoperative period. Up to 30% of patients will experience acute kidney injury postoperatively, and this development of acute kidney injury predisposes to further chronic kidney disease [43]. A review of cystectomy patients at Fox Chase Cancer Center demonstrated that 43% of patients have declining glomerular filtration rate after surgery, and 13.0% of patients who would have qualified for low-molecular weight heparin at discharge would have subsequently had decline in kidney function to levels that might have produced supratherapeutic levels of anticoagulation [103]. Based on the variations encountered in patient comorbidity and postoperative course, a decision to give extended thromboprophylaxis must be individualized. Further, there remains a need for study of alternative anticoagulants in cystectomy population. There is literature to suggest that other low-molecular weight heparins are safer in populations with renal failure, although this review was not specific to either surgical patients or patients with malignancy [104]. A new class of direct oral anticoagulant, the factor Xa inhibitors, has received interest recently given the ease of administration. These have been tested in the orthopedic surgery space as prophylaxis, but have not yet been studied in urologic surgery populations [94].

Stomal Complications

Stomal complications are a significant source of morbidity for patients, with subsequent negative impacts on quality of life after cystectomy [105]. Further, stomal complications are one of the more common causes for reoperation. A review of ileal conduit patients at the Cleveland Clinic found that 5% of all cystectomy patients required revision due to stomal complications [106]. Several stomal related complications may occur and include stomal stenosis, necrosis, stomal prolapse, and stomal retraction.

A significant type of stomal-related complications is the parastomal hernia. Parastomal hernias are frequent complications with a reported incidence ranging between 5% and 65% [107–113]. Reasons for the heterogeneity include the length of follow-up as well as the method of diagnosis (clinical or radiographic), and consequentially it is difficult to compare rates between series. While hernias present clinically with a protrusion around the stoma itself, the clinical definition itself can be highly variable based on prospective or retrospective collection, clinician or patient reporting, and how the examination is performed. The majority of hernias are noted to occur within the first 2 years after surgery [114–116]. The most appropriate clinical definition requires a palpable defect or bulge adjacent to the stoma either supine with legs extended or upright with Valsalva. If radiologic criteria are added into the criteria, the definition will include any intraabdominal content that protrudes along the ostomy [117].

The benefits of adding radiologic criteria to the definition of parastomal hernia are objectivity, decreased impact on diagnosis of body habitus, reproducibility across trials, and the ability to measure changes over time. A helpful classification system was devised by Moreno-Matias et al. [118]. This system has subsequently been used successfully in both a randomized trial setting [119] as well as across multiple retrospective studies [107, 120]. In this system, a Type 1 parastomal hernia demonstrates a hernia sac with prolapsed bowel forming the stoma. A Type 2 parastomal hernia contains abdominal fat or omentum herniating through the defect created by the stoma. Finally, a Type 3 hernia contains herniated bowel loops other than that forming the stoma [118]. Importantly, the radiographic classification system shows appropriate concordance between the parastomal hernias noted on imaging and clinical symptoms [120].

While many patients with parastomal hernias are asymptomatic, a significant proportion will undergo repair either electively for symptoms or emergently for bowel compromise or bowel obstruction. Ripoche et al. reported long-term follow-up of 782 ostomy patients (median follow-up 10.5 years) and noted high rates of symptomatology, 75% of patients, as well as obstructive episodes in up to 15% [121]. A series of ileal conduit patients at Indiana University reported overall hernia rates of 29%, with subsequent surgical repair in 45%. These repairs were related to abdominal discomfort in 58%, bowel obstruction or strangulation in 15%, partial small bowel obstruction in 15%, or elective reasons in 12% [108]. Finally, a series at MSKCC of 384 ileal conduit patients reported that 24% of patients had a parastomal hernia on exam, with 40% being symptomatic. Of note, 81% of patients were prescribed an abdominal belt or binder as initial treatment. In total, 17% of patients were referred for possible surgical repair, and only 9% of the overall series underwent surgical repair [107].

Given the significant effects on quality of life related to parastomal hernias, efforts to reduce their occurrence have substantial importance. The etiology of parastomal hernias is multifactorial, with both technical factors and patient factors contributing. Retrospective studies have demonstrated several independent risk factors on multivariate analysis, including obesity, female gender, poor nutrition, and stoma aperture size [107, 120, 122, 123]. One method to prevent parastomal hernias from the time of the index operation is the placement of parastomal mesh. There have been several prospective, randomized trials published in the general surgery and colorectal surgery literature of potential benefits of parastomal mesh placed at the time of stoma creation [119, 124–127]. All but one study reported significant reductions in both clinical and radiographic parastomal hernia rates, with one study, Vierimaa et al., demonstrating a significant reduction in clinical parastomal hernias (14.3% vs. 32.3%) but no difference in rates of radiographic parastomal hernias (51.4% vs. 53.1%) [124]. The longest available follow-up of these colorectal studies is reported by Janes et al., who updated their series with follow-up out to 5 years. In these patients, the parastomal hernia rate was reported at 13% in patients receiving

prophylactic mesh versus 81% in patients with standard surgery [128].

While the use of prophylactic mesh in the ileal conduit population has not yet been reported in a randomized trial, there are series published to provide initial data. Styrke et al. published a consecutive series of 114 patients with prophylactic mesh placed at the time of ileal conduit diversion. In this study, investigators report a parastomal hernia rate of 14% at a median follow-up time of 35 months. Importantly, there were no mesh-related complications during the study period [129]. At MSKCC, we began to selectively offer prophylactic mesh placement in high-risk patients in 2013. Initial results demonstrated both safety and early efficacy, and our surgical technique has been described previously [130]. The question of whether parastomal mesh improves outcomes in patients undergoing radical cystectomy and ileal conduit diversion is currently under study investigation as part of a phase III randomized trial, with inclusion of both robotic and open cystectomy cases.

Stomal stenosis is seen in both ileal conduits and continent catheterizable channels. Regardless of diversion type, they can occur secondary to chronic ischemia of the conduit/channel, narrowing of the fascial aperture, retraction of the stoma, or due to local skin scarring. Over time, stenosis can lead to poor drainage or difficulty with catheterization, which can subsequently increase the risk of recurrent infections or renal deterioration. For ileal conduits, historical rates of stomal stenosis have been reported as high as 20–25%, but more contemporary series demonstrate much lower, such as the series by Frazier et al. reporting 3% stomal stenosis rate [131]. Of note, historically reported rates of stomal stenosis have been significantly lower with Turnbull loop stomas as compared to an end-stoma approach, although conflicting data are available [132, 133]. With respect to continent catheterizable channels, incidence of stenosis is varied given the multiple methods as well as the varied patient populations receiving them, but a series of long-term follow-up in Indiana pouches by Holmes et al. noted ~15% rate of stomal stenosis [134]. Managing stomal stenosis can involve simple procedures such as a circumferential releasing incision or Y-V plasty, but depending on the severity can require intraabdominal exploration and release/revision of the pouch.

Complications Specific to Continent Diversion

Continent diversion options (both orthotopic and continent catheterizable diversions) increase the complexity of the reconstruction as attempt is made to recapitulate the unique characteristics of the native bladder. There are several complications unique to the continent diversion that must be considered.

Orthotopic neobladders have demonstrated their safety and excellent functional outcomes in both men and women. Unlike the experience with radical prostatectomy in which bladder neck contractures are relatively commonly reported in the literature, rates of neobladder-urethral strictures range between 2.9% and 9% [135, 136]. Patients may present with obstructive voiding symptoms, urinary retention, or commonly new onset of worsening urinary incontinence. Some patients may be asymptomatic due to the lack of sensation of fullness in the neobladder and only be diagnosed by identifying an elevated postvoid residual volume. Treatment options include cystoscopy with dilation, transurethral incision of the contracture, and transurethral resection of the bladder neck. Comparative studies are lacking, although overall success in endoscopic treatments has been reported at 37%, a rate which remains stable with repeat procedures [137]. Of note, adjuvant clean intermittent catheterization was associated with significantly higher success rates (58% vs. 32%), and is recommended after endoscopic treatments to improve outcomes and ensure adequate emptying of the reservoir [135, 137].

Pouch stones are seen in both continent cutaneous diversions as well as orthotopic diversions. It is thought that rates are higher in continent cutaneous diversions for two reasons: higher

residual volumes as well as more bacterial colonization. Our practice is to perform at least yearly imaging in patients with continent diversions to rule out stones. As most are radio-opaque, they should be visible on plain film imaging. Conservative options for preventing stone formation in prior stone formers include increasing fluid intake, maximizing emptying of the diversion, or potassium citrate medical therapy [138, 139]. Once identified, stones will need to be managed surgically, based on size. Smaller stones can be managed with endoscopy or shock wave lithotripsy, while open or percutaneous approaches may be needed for larger stones. Of note, anatomical considerations may also push the surgeon toward open or percutaneous approaches, as some continent cutaneous diversions are dependent on continence mechanisms that can be damaged by endoscopy.

While uncommon, pouch rupture can be a serious complication that deserves consideration in any previously diverted patient who presents with acute abdominal pain. The cause is most commonly acute or chronic overdistention of the pouch, although additional risk can be related to catheter trauma. The diagnosis is made with imaging, either cross-sectional imaging or fluoroscopy, although computed tomography allows for delayed phases which may provide additional diagnostic information. Management is dependent on clinical status. If the patient is clinically stable without signs of sepsis, supportive management with close observation and maximal pouch drainage is appropriate. However, if the patient presents with septic symptoms or has an acute abdomen on examination, open repair must be performed. Drainage of the reservoir with an indwelling catheter may be attempted in patients with small defects and low outputs from abdominal or pelvic drains. However, proximal diversion of urine via nephrostomy tubes should be considered early in the course of an ill patient or when the extravasation is significant.

Difficult catheterization in a continent catheterizable channel can provoke significant anxiety in patients and also predispose to pouch rupture or further damage to the catheterizable limb. Rates of this complication are difficult to generalize given differences in types of channels created as well as variable definitions. A review of children with catheterizable channels found difficult catheterization quite common, occurring in 20% of channels [140]. If a patient presents with complaints of difficult catheterization, endoscopy is recommended to delineate the location and type of difficulty. The surgical repair necessary will vary pending this evaluation. Outcomes of revisionary surgery for continent channels have been published, although notably the indication for pouch and type of channel was quite heterogeneous. Pagliara et al. reported patency rates of 66% at a median 19 months after revision, and unfortunately channel incontinence after revision was 40% [141].

Finally, urinary incontinence can occur with cutaneous or orthotopic continent diversions. With respect to orthotopic diversion, urinary continence depends on several factors, including maintenance of intact external urinary sphincter, pelvic floor, age, prior pelvic surgery, prior pelvic radiation and adequate urethral length. Preoperative voiding function can have a strong impact on postoperative status. Day-time and night-time continence are considered separately, but continence at both times will continue to increase over the first year to 2 years after surgery [139, 142]. Overall continence rates vary in the literature based on the definition used, but in general at least 85–90% of patients will be using $\leq$1 pad per day [143–148]. Nocturnal enuresis is significantly more problematic, particularly in the older population. Early postoperative night-time continence has been reported at 45–65% [147, 149] but can be expected to increase even beyond the second year after surgery. Some have reported good experience oral imipramine as a medication to improve night-time continence [150].

Incontinence with a continent cutaneous reservoir can be quite bothersome to the patient, and typically occurs secondary to high pressures within the pouch or leakage from the constructed continent valve mechanism. Before any repair is considered, it may be useful to perform urodynamics to assess actual capacity and compliance of the pouch. For patients who are not surgical

candidates or prefer not to undergo an additional procedure, an external collection bag (e.g., ostomy appliance) or indwelling catheter may be used rather simply. Endoscopic bulking procedures can also be considered, although open surgical repair is the most effective treatment. Surgical options include reinforcing Lembert sutures around the valve mechanism, augmentation of the pouch, and reconstruction of the channel.

Conclusion

Despite many improvements in the care of the cystectomy patient, postoperative complications remain quite common. Fortunately, the vast majority of postoperative complications after radical cystectomy are low-grade in nature. Postoperative complications can occur in many organ systems, and have significant impact on the patients' quality of life. Urologists must thoroughly understand the management of these complications to provide the best care to these patients. Further, many of the complications discussed here can be prevented or mitigated with various strategies in the perioperative period. Incorporating these evidence-based interventions into practice along with meticulous attention to detail intraoperatively will continue to reduce the morbidity of this operation.

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Incontinent Urinary Diversion

17

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Introduction

Urinary diversion (UD) after radical cystectomy (RC) is one of the most challenging procedures in urological surgery due to the technical complexity and the high rate of potential perioperative complications [1]. The three most common types of UD are incontinent and continent abdominal wall UD (Ileal or colonic conduit, cutaneous ureterostomy, continent pouches), urethral diversions or neobladders, and rectosigmoid diversions. Any form of UD has its specific problems. In this context, surgeons must continue to refine their surgical technique of RC and UD to provide the utmost safety for the patient. Incontinent urinary diversion (IUD) is still the most popular type of reconstruction after RC. The conduits (using a segment of the distal ileum, although in a few cases can be constructed from other parts of the gastrointestinal tract) and the cutaneous ureterostomy (CU) are the most widespread techniques. A recent review has assessed the trends in the use of different techniques of UD (incontinent and continent); results revealed that from a population of 27,170 patients who were submitted to RC, 23,224 (85%) underwent an incontinent diversion. Moreover, conclusions revealed a decline of 12.1% in the use of continent diversion even among high volume and academic centers [2]. In Sweden, Ileal conduit (IC) increased from 55% in 1997 to 72% in 2005, and the use of continent diversion decreased from 38% to 23% during the same period.

Patient Preparation

Despite advances in surgical care, the incidence of postoperative complications following RC remains high. Even in the absence of

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complications, major surgery is associated with a 20–40% reduction in physiologic and functional capacity. This reduction in physiologic reserve is experienced as a greater level of fatigue 6–8 weeks after hospital discharge. The elderly and others with limited metabolic protein reserves are the most susceptible to the negative effects of operative stress. Furthermore, many bladder cancer patients undergo adjuvant chemotherapy, which, together with the operation, has prolonged physical, functional, nutritional, and psychological effects [3].

Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery after operations by maintaining preoperative organ function and reducing the stress response following surgery. ERAS involves interventions in key elements in the preoperative, intraoperative, and postoperative phases of surgical care [4].

The ERAS Society published guidelines for perioperative care after RC for bladder cancer. They identified 22 ERAS single items and provided recommendations. At our institution, we have a robust BC program and we have developed an ERAS protocol using the 22 items, as well as an individual pre-habilitation program [5].

Preoperative patient education and patient motivation are cornerstone elements of our ERAS protocol. Keeping patients involved and reinforcing perioperative goals throughout the process help reduce patient anxiety and increase compliance to meet surgical care goals. We provide an instructional book to our patients at the preoperative clinic visit, which is reviewed in detail with the patient. The book includes information such as what is ERAS, preoperative expectations from optimizing nutrition, carbohydrate loading, minimizing "nothing by mouth" time, and guides on urinary diversion management [6, 7].

We offer 3–6 weeks of pre-habilitation before elective BC surgery to improve postoperative outcomes and reduce complications rates. Prehabilitation initiatives should start as early in the surgical pathway as possible. Preoperative exercise, preoperative nutrition, smoking cessation, alcohol cessation, anemia, and psychological support are key elements of our ERAS protocol. We also offer lung training exercises to our patients to reduce postoperative pulmonary complications.

In the case of iron deficiency anemia, we administer intravenous iron. Preoperative functional capacity predicts postoperative morbidity, mortality, and functional recovery. In the preoperative setting, the functional reserve of our patients is measured with the 6-minute walking test. Our training program includes aerobic interval training and resistance training unsupervised at home. Training will be tailored and constantly adapted according to the actual condition of the patient. Besides, patients will be informed about the importance of their physical condition concerning the postoperative course and they are encouraged to adhere to the training program. Our ERAS protocol allows clear liquids and carbohydrate loading up to 2 hours before surgery. Preoperative carbohydrate loading to maintain "the fed state" reduces postoperative insulin resistance, thirst, hunger, and anxiety. Also, we are omitting mechanical bowel preparation in our ileal conduit and neobladder urinary diversion population.

Surgical Techniques

Cutaneous Ureterostomy

Introduction

Cutaneous ureterostomy (CU) is probably the simplest urinary diversion procedure and among the first-ever described [8]. By 1935 it was considered the UD with the best chances of survival due to the high incidence of complications associated with diversions using bowel segments in the pre-antibiotic era [9]. Though nowadays the complications associated with bowel use in the urinary diversion are much lower, CU remains the diversion with less "procedure-independent" associated complications [10] and the lowest morbid risk [11], making it best suited for fragile individuals. Advantages of CU are the lack of bowel anastomosis with reduction of the operative time and the postoperative paralytic ileus (POI), a common complication after UD. These

advantages have been confirmed in the study published by [12], with prolonged POI observed in 25.7% in the IC group vs 5.7% in the CU group; and the duration of surgery is 226 min in the IC group vs. 150 min in the CU group. Interestingly, there was no difference in major complications classified as Clavien–Dindo grades III–IV except for urinary leakage from the ureter-ileal anastomosis (14.2%).

Indications

- Diversion in patients where the bowel cannot be used
- Diversion in frail patients with high surgical risk or limited life expectancy [12]
- Temporary diversion in children with severe hydronephrosis while awaiting definitive repair [13]

Limitations and Relative Contraindications

- Obese patients [14]
- Short ureteral length
- Poorly vascularized ureter

Surgical Technique

Multiple variants of the technique have been described throughout history, most of them focusing on reducing the stenosis rate and improving patient comfort by improving the stoma.

These variants may be combined with a transureteroureterostomy if desired, with the advantage of having only one stoma, but with the additional risk of urine leak and ureteral stenosis [15]. It is important to take into account that blood supply may be diminished after passing the ureter through the abdominal wall; therefore, preservation of periureteral tissue and avoiding tension in the anastomosis are key factors. Obese patients are challenging because the ureter maybe only long enough to exit under the rib cage making it hard to apply a urine-collecting device; in such cases an ileal conduit may be preferable.

Steps

1. Stoma site: Ideally the stoma site should be marked preoperatively it may be single or dual and may be placed at the level of the umbilicus [16, 17] or a few centimeters lateral to the umbilicus in the pararectal space, ideally in a zone without creases and at least 5 cm below the costal margin [18, 19], similar to an ileal conduit stoma.
2. Incision: Any incision used for the prior procedure (e.g., pelvic exenteration or radical cystectomy) may be used or adapted; if there is no prior incision, a Gibson incision may be used to localize the ureter.
3. Once the ureter is located, dissect (preserving periureteral fat), ligate and transect the distal end, and mark it with a stay suture. Dissection is carried out upwards until the ureteropelvic junction is reached, to avoid angulation or kinking (as a general rule, about 8 cm of ureteral length are needed to reach the skin without tension) [19]. This is repeated at the contralateral kidney if applicable.
4. A skin incision is made according to the planned stoma technique (see below) and subcutaneous tissue removed, anterior and posterior rectus sheaths are incised in a cross fashion (to avoid external compression of the ureters), and muscle fibers are bluntly separated [14]. The diameter of the tunnel should allow at least the insertion of an index finger.
5. Both ureters are pulled through 1.5 cm above skin level, spatulated, sutured together medially (at the vertex), and then anastomosed to the skin with a 5/0 resorbable interrupted suture. A 6 or 8 Fr ureteral catheter is placed in each ureter and these may be fixed to the skin.
6. Additionally, if there is tension in the ureter and ureteral retraction is worrisome, a nephropexy may be performed.

Ureterocutaneous Anastomosis Variants

V-Flap technique [20]:

- Incise the skin in a “V” or “U” shape, draw the ureters at least 3 cm above skin level, spatulate the ureter, suture the apex of the skin to the vertex of the spatulated ureter using a 5/0 absorbable suture, and apply 5 or 6 additional interrupted sutures to attach the ureter the skin, creating a small nipple.

Double-barreled (Z-plasty) [20]:

- Incise the skin in a "Z" shape and bring both ureters to skin level, spatulate them, and suture each apex of the skin to the vertex of the ureter in a similar fashion to a Wallace II anastomosis [21, 22].

Toyoda technique [23]:

- A circular skin flap is removed at the desired stomal site. The ureter is brought through the tunnel and its distal end is cut longitudinally to make a "fish-mouth" opening. The epidermis and dermis are dissected from the adjacent skin area that will become "the bed" to suture the ureteral edges.

Complications

- Ureterocutaneous stricture (stomal stenosis) with an incidence of 13% up to 57%, being more frequent in the left side [24, 25], contemporary series report tubeless CU in >80% of cases [25, 26]
- Skin irritation around stoma
- Ureteral retraction

Follow-Up

- Ureteral stents may be removed at 1–3 weeks postoperatively [14].
- An ultrasound should be performed at days seven and 28, and monthly thereafter for 3 months, and then at the physician's discretion.
- Creatinine levels should be monitored closely during the first 3 months.
- Ensure ureteral patency and advise the patient to consult if there is no output in 12 hours.
- If stomal stenosis develops, a permanent ureteral catheter is recommended, with periodical changes every 1–3 months.

Ileal Conduit

Ahmed S. Elsayed, Ahmed A. Hussein, and Khurshid A. Guru

Indications

Bladder cancer (BC) represents the first indication to perform an ileal conduit (IC); however, other conditions such as neurogenic bladder dysfunction, refractory idiopathic detrusor overactivity, chronic inflammatory conditions (interstitial cystitis, tuberculosis, and other infectious diseases with bladder affectation and post-radiation bladder contraction), congenital anomalies (congenital bladder neck obstruction, exstrophy of bladder), complex or refractory bladder fistulas, and urinary re-diversion have been described [27, 28]. In these cases, the purpose of performing an IC is to control intractable urinary incontinence and avoid the progressive renal function impairment due to high bladder pressures. The IC represents the technique of choice for incontinent diversion in patients who underwent RC for BC [29]. The technique was first described by Vergengen and de Graeuve in 1909 [30], and since then, it has been modified to improve patient outcomes and quality of life [31]. Since the introduction of continent orthotopic urinary diversions (OUD), these have become the gold standard in some specialized centers [32]; however, recent studies show that the ileal conduit remains the most used urinary diversion after cystectomy for BC [2], possibly due to ileal conduit being easy and quick to construct, minimizing the risk of complications.

Patient Selection

The selection of each involves considerations related to oncological control, health status performance, technical feasibility, and quality of life. Therefore, classical contraindications have been proposed to perform an orthotopic continent urinary diversion, which allows us to identify those patients suitable to an IC or other non-continent urinary diversions (Table 17.1) [33, 34]. The main oncological concern to perform an OUD is prostatic urethra involvement by urothelial carcinoma in men, which has been described as an important predictor of urethral recurrence after cystectomy [35]. In women, the involvement of the bladder neck has been described as a predictor factor of urethral recurrence, which is

Table 17.1 Contraindications for orthotopic urinary diversion

Absolute contraindications	Relative contraindications
Urethra affected by urothelial carcinoma	Locally advanced disease
Impaired renal function	Need for adjuvant chemotherapy
Impaired hepatic function	Inflammatory bowel disease
Physical or intellectual limitations to perform self-catheterization	Short life expectancy
Unmotivated patients	Prior pelvic radiation
	Urethral pathology

why it should be considered during decision making [35]. However, it has been suggested that the performance of an OUD represents a protective factor of urethral recurrence; however, some authors suggest that these observations may be due to a selection bias because a major proportion of patients underwent IC have advanced tumor stage, prostatic urethral disease, or extensive CIS [33]. The patients with locally advanced stages and nodal metastases represent poor candidates to perform an orthotopic urinary diversion due to the difficulty that would involve the treatment of a local recurrence (surgery, radiotherapy) in the urinary reservoir [35, 36]. Therefore, it has also been suggested that the creation of a continent urinary diversion may delay the beginning of adjuvant chemotherapy due to a higher postoperative stay in the patients who underwent OUD [37]. Regarding the health status, the presence of chronic kidney disease represents a formal contraindication to perform an OUD, due to the absorptive surface the hydrogen ions of urine are absorbed and accumulate in blood conditioning the development of chronic metabolic acidosis and its consequences [38]. Therefore, to perform an IC in patients with chronic kidney disease represents the technique of choice since its absorptive surface is not sufficient to generate this complication. On the other hand, hepatic insufficiency also represents a contraindication to performing OUD; therefore, these patients are candidates for IC, as the absorption of ammonium from urine can increase blood levels, causing hyperammonemia encephalopathy and even hepatic coma [39]. The patients with inflammatory bowel disease are poor candidates to perform an OUD due to (1) the possibility of recurrence of the disease in the urinary reservoir, (2) impossibility of easy monitoring of the intestinal mucosa, and (3) increased risk of second neoplasia [40]. Another consideration to take into account for patient selection to IC is life expectancy; patients with a short life expectancy are candidates who underwent IC.

On the other hand, those patients who present some physical or intellectual limitations to perform self-catheterization should preferably undergo an IC. Likewise, the patients with an anatomical (strictures) or functional urethral pathology (vesico-sphincter dyssynergia) are poor candidates to perform an OUD and the IC represents a good option. Likewise, the motivation of the patients to provide sufficient care and their expectations on quality of life are factors to be taken into account [33].

Open Surgical Technique

The construction of an ileal conduit involves the following steps:

I. Ileal segment isolation and ileo-ileal anastomosis
II. Dissection and spatulated of ureters
III. Ileo-ureteral anastomosis
IV. Stoma confection

Figure 17.1 shows a schematic representation of the surgical field and anatomical landmarks in IC surgery.

Previous bowel preparation has failed to show an advantage in complications terms [41]. Moreover, the preoperative marking of the stoma site has shown to improve the planning of the ideal location for placement of the stoma, as well as the familiarization of the patient with care [42]. Once RC and pelvic lymphadenectomy are performed, the selection of a segment of terminal ileum of approximately 15 cm, located 20 cm proximal to the ileocecal valve, is carried out [31]. The proximal and distal ends of the future ileal conduit are usually marked with polyglactin

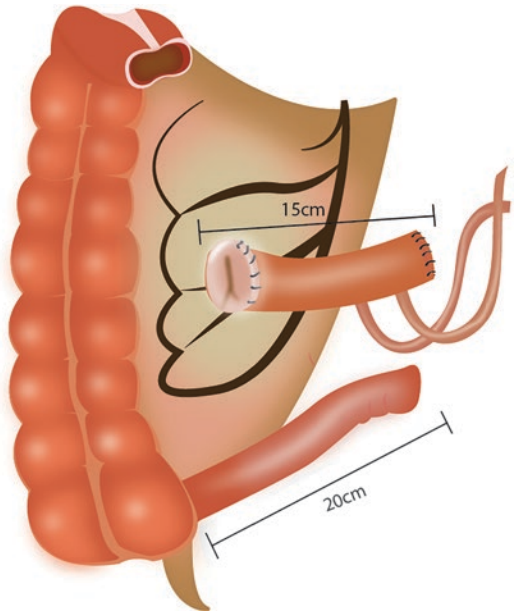

Fig. 17.1 Anatomical landmarks of ileal conduit surgery. During ileal conduit surgery, a 15 cm ileal loop located 20 cm proximal to the ileocecal valve is utilized. (From Subiela, González-Padilla, Castellarnau Uriz, Breda, Palou, and Rodríguez Faba)

stitches for better identification; after that the vascular arcades (branches of the superior mesenteric artery) are identified classically using transillumination of the mesentery. The vascular arcades have a vertical orientation to the mesenteric border of the ileum; once they are identified, then a delicate dissection of mesentery is performed in order to clamp both ends of the ileal conduit without compromising the vascularization. After that, the bowel is incised, the loop of IC is reserved, and the ileo-ileostomy is performed using a hand-sewn or stapled anastomosis. After that, the mesenteric window of the ileo-ileostomy is closed using 3–0 polyglactin suture. During the dissection of both ureters, the left ureter needs a more proximally extended dissection than the right ureter and a retro-sigmoidal tunnel must be performed to transpose the left ureter to the right side (usual site of stoma).

To avoid kinking and ischemia of the ureter, the left ureter should be without tension but not excessively mobile in the retro-sigmoidal tunnel. After the dissection of both ureters, the terminal ureteral segments should be sent to histological examination; then a spatulation of ureters must be performed. The ileo-ureteral anastomosis could be performed using different techniques; in the classical Nesbit technique improved by Bricker [31], the ureteral ends are spatulated and anastomosed separately in the antimesenteric side of the conduit. In Wallace variants, the ends of the ureters are widely spatulated and then sutured "head to head" (Wallace I) or "head to tail" (Wallace II) [22], and then directly anastomosed to the proximal end of the ileal segment. When the ileo-ureteral anastomosis is performed, ureteral catheters are placed (usually 8Ch uni-J), which must subsequently be fixed to avoid its migration. The stoma creation begins with a circular incision in the previously marked skin (frequently in the lower right quadrant of the abdomen). Thereafter, the layers of tissues are dissected until the aponeurosis of the rectus muscle and a cruciform incision in the anterior aponeurosis of the muscle is performed, then a blunt dissection in the depth of the muscle is carried out, creating a channel wide enough for the ileal segment to be free and avoid conduit stricture or ischemia, following the distal end of the conduit is externalized to the skin (2–3 cm), it is fixed to each quadrant of the cruciform incision of the aponeurosis with 4–0 polyglactin by the serosa of IC, then the mucosa of the conduit is sutured to skin with 4–0 polyglactin achieving the eversion of mucosa of ileal conduit.

Intracorporeal Surgical Technique

The key principles of intracorporeal ileal conduit urinary diversion are the same as open surgery. The port configuration is similar to the standard 6-port placement used during robotic assisted radical cystectomy (RARC). An extra 15 mm short suprapubic port may facilitate bowel anastomosis. Placing the ports an inch higher may facilitate bowel manipulation.

A. Isolation of the Bowel Segment and Creation of the Marionette Stitch

A 12 cm bowel segment is identified approximately 15–20 cm proximal to the ileocecal valve. A silk suture on a straight needle is introduced through the abdominal wall and

Fig. 17.2 Marionette stitch. (From Elsayed, Hussein and Guru and illustrate steps in an intracorporeal ileal conduit)

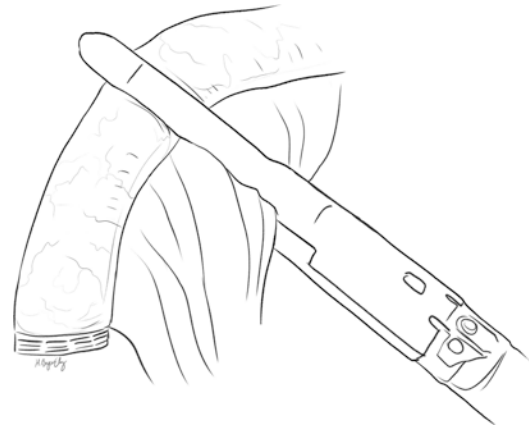

Fig. 17.3 Isolation of the conduit. (From Elsayed, Hussein and Guru and illustrate steps in an intracorporeal ileal conduit)

passed through the small bowel and back through the abdominal wall as a stay suture "Marionette technique" [43]. The marionette suture is not tied and is controlled by an instrument for dynamic retraction (Fig. 17.2).

The hook cautery is used to develop two mesenteric windows with a wide base, at the beginning and end of the future conduit. An endovascular stapler is used to divide the conduit from the rest of the ileum (Fig. 17.3). Indocyanine green (ICG) can be injected and the FireFly® technology may be used to ensure adequate blood supply of the future conduit and ureteric ends [44].

B. Preparation of the Conduit and the Ureter

An enterotomy is made at the caudal end of the future conduit (single or double based on the reimplantation technique). Then using the 4th arm to hold the Hem-o-lok on the caudal end of the ureter, a small snip is made and the ureter is spatulated. The same procedure is repeated on the contralateral side.

C. Ureteroileal Anastomosis

Retroperitonealization of the left ureter is achieved by crossing it to the right side through the mesentery of the sigmoid colon.

(a) Wallace technique

The appropriate length of the ureter is used (avoiding tension or redundancy). Both ureters are aligned together using the 4th arm. Both ureters are spatulated. The adjacent inner ends of the ureters are sutured together in a running fashion forming the Wallace plate. This is followed by ureteroileal anastomosis using 4/0 Vicryl suture in a continuous fashion (Fig. 17.4). Before completion of the ureteroileal anastomosis, an 8.5 Fr single J stent or a feeding tube is passed.

(b) Bricker

The appropriate length of the ureter is used (avoiding tension or redundancy). Each ureter is sutured on its corresponding side of the conduit (Fig. 17.5). One side of each ureter is sutured and then an 8.5 Fr single J stent or a feeding tube is passed before completing the other side.

D. Stent Placement

An enterotomy is performed at the proximal end of the conduit. An 8.5 Fr single J stent or an 8 Fr feeding tube is passed through the laparoscopic suction device utilizing the assistant's port and then through the ureteroileal anastomosis. The stent is secured to the conduit using a 3/0 chromic catgut suture to prevent dislodgement.

E. Completion of Ureteroileal Anastomosis

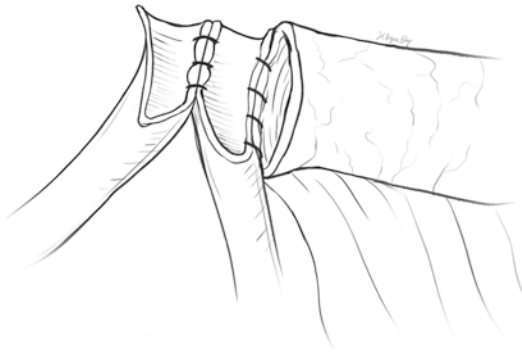

Fig. 17.4 Wallace ureteroileal anastomosis. (From Elsayed, Hussein and Guru and illustrate steps in an intracorporeal ileal conduit)

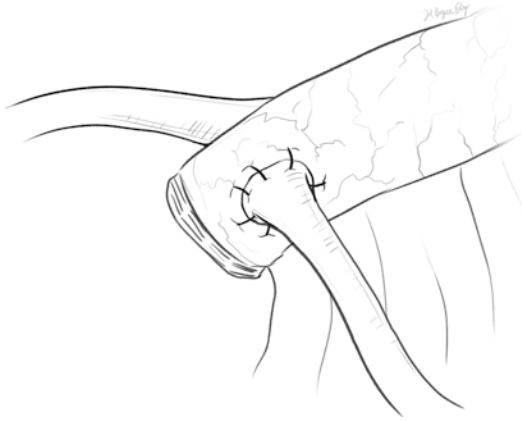

Fig. 17.5 Bricker ureteroileal anastomosis. (From Elsayed, Hussein and Guru and illustrate steps in an intracorporeal ileal conduit)

The Hem-o-lock and the distal ureteric ends are cut. Using a continuous 4/0 Vicryl suture, the ureteroileal anastomosis is completed.

F. Retroperitonealization of the Conduit

The peritoneal fold adjacent to the conduit is used to cover it and the ureteroileal anastomosis (Fig. 17.6).

G. Re-establishment of the Bowel Continuity

An extra 15 mm short suprapubic port is placed. The 4th arm is used to approximate the two sides of the ileum together. Using the monopolar hook, 2 enterotomies are made on the proximal and distal ileal limbs. Ensuring that the anti-mesenteric sides of the bowel are properly aligned, two sequential side-to-side

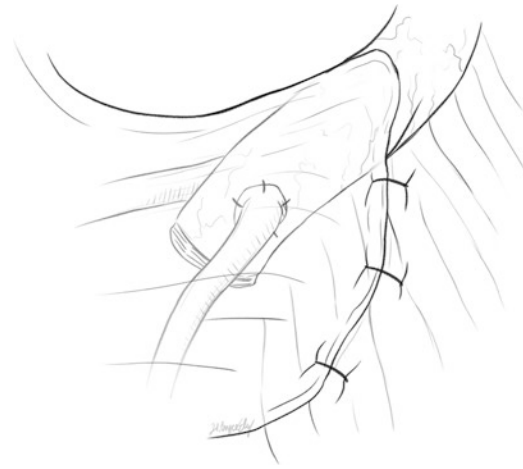

Fig. 17.6 Reperitonealization of the conduit. (From Elsayed, Hussein and Guru and illustrate steps in an intracorporeal ileal conduit)

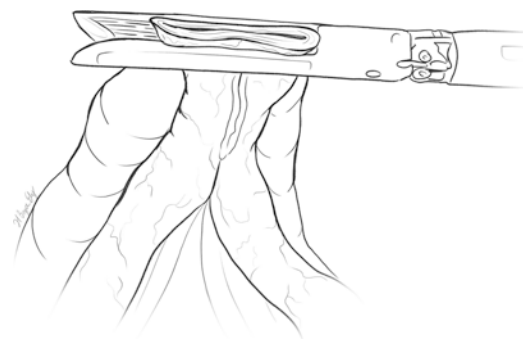

Fig. 17.7 Re-establishment of the bowel continuity. (From Elsayed, Hussein and Guru and illustrate steps in an intracorporeal ileal conduit)

bowel reanastomoses are performed using an Endo GIA stapler. This is followed by closure of the intestinal stump using another load applied transversely (Fig. 17.7). This is followed by closure of the mesentery using silk sutures to prevent internal hernia.

H. Delivery of the Conduit

The robot remains docked and a circumferential skin incision is performed in the planned site of the future conduit. Skin is removed and the fat is mobilized until reaching the rectus sheath. A cruciate incision is formed in the rectus sheath and four 3/0 Vicryl anchoring sutures are placed. A clamp

is introduced through the rectus muscle to grasp the marionette stitches and deliver the conduit through the rectus muscle to the skin surface.

About 5 cm of the conduit are delivered above the skin surface. The anchoring sutures are sutured to the base of the conduit, followed by the edge. Simultaneous tightening of all of the sutures will invert the conduit inside out. Lastly, the conduit edge is sutured to the skin surface.

Complications

The incidence of complications for ileal conduit patients is about 66%; near to 60% of these complications are stoma-related and the risk increase with the time after surgery [45]. Classically, complications in IC patients have been described as early (<90 days postop) versus late (>90 days postop) (Table 17.2). Early complications such as POI, bowel obstruction, enterocutaneous fistula, anastomotic leaks, wound infections, conduit necrosis, and pyelonephritis occur in more than 50% of patients; and late complications such as bowel obstruction, ureterointestinal strictures, stomal prolapse, stomal stenosis, stomal retraction, parastomal hernias, and metabolic disturbances have been described in 28–81% of patients [34]. Postoperative ileus is one of the most common complications; it has been described in 20–30% in most series [46]. Most patients recover bowel function with conservative management (nasogastric tube and prokinetics drugs); parenteral nutrition should be established in case of prolonged ileus (>7 days) and currently Alvimopan has been shown to be a useful agent to accelerate the recovery of gastrointestinal function after radical cystectomy [47, 48].

Table 17.2 Complications after ileal conduit

Early complications (<90 days)	Late complications (>90 days)
Postoperative ileus	Ureteroileal stricture
Bowel obstruction	Stoma stenosis
Enterocutaneous fistula	Stoma retraction
Bowel anastomotic leak	Parastomal hernia
Urinary leak	Metabolic disturbances
Ileal conduit necrosis	
Metabolic disturbances	

Bowel obstruction occurs in 0.7–14.9% after ileal conduit and must be differentiated from postoperative ileus since it can be a life-threatening condition [46]. Enterocutaneous fistula is a rare complication after IC; conservative approach (parenteral nutrition, antibiotics, somatostatin analog) followed by definite surgical intervention is the treatment modality in most cases [45]. Anastomotic bowel leak has been described in 1–5%; this is a life-threatening condition and laparotomy is required in most cases [49]. The necrosis of IC is a rare and potentially life-threatening complication. This is manifested by the darkening and retraction of the stoma; the acute case represents a surgical emergency [45]. Urinary leakage occurs even in 5% of patients with any urinary diversion [45]. A prospective randomized controlled trial showed that the use of stents of the ureteroileal anastomosis resulted in a lower rate of urinary leak [50]. Urinary leaks can be managed conservatively; If necessary a percutaneous drainage or bilateral nephrostomy tube to divert urine flow might be placed for non-draining leaks. Ureteroileal stricture occurs in 1.3–10%, the median time to diagnosis reported is 7–25 months after surgery. Although the treatment can be endourologic, the surgery is more effective [51]. In some cases, the stricture may be due to tumor recurrence; therefore, surgical resection and systemic treatment should be considered in these patients [36]. Stoma complications are the most frequent indication for reoperation after cystectomy. Stomal stenosis has been described even 25% of IC patients as a result of chronic ischemia, narrowing of the aponeurosis, and changes in the skin due to chronic dermatitis, the treatment is the surgery based on the cause of the stenosis [52]. Parastomal hernia occurs even in 17.1% [53]. Different studies have described that female gender, high BMI, low preoperative albumin, and previous laparotomy are independent risk factors. Surgical correction is indicated when the hernia increases in size, distortion of the abdominal wall with a problematic coupling of the stoma bag or abdominal pain [54]. Several surgical techniques have been described to correct a parastomal hernia with a global recurrence rate of 50–70% [53]. According

to data derived from gastrointestinal surgery, the use of prophylactic mesh at the time of stoma creation seems to decrease the risk of parastomal hernia [47]; however, there are no randomized trials of prophylactic mesh placement at the time of ileal conduit.

Follow-Up

Follow-up strategy after ileal conduit diversion must be oriented to investigate possible upper urinary tract changes, infectious complications, metabolic changes, and the development of secondary malignancies in the ileal segment. The most important change in the upper urinary tract is the ureterohydronephrosis (UHN) and obstruction following ileo-ureteral anastomotic stricture with the consequent loss of renal function [55]. An appropriate study to detect UHN is the ultrasound while the associated obstruction component can be estimated using MAG-3 renal scan. Some patients may present UHN without an obstructive component due to reflux, which can lead to renal function impairment. Infectious complications are common, and ileal conduit urine is bacteriuric in most cases; therefore, clinicians should decide to begin antibiotic coverage when the patients have symptoms [56]. The patients who underwent urinary diversion can be present with metabolic changes during follow-up, such as malabsorption, hyperchloremic metabolic acidosis, stone formation, Vitamin B12 deficiency, and bone demineralization. However, due to the development of these complications depend on the length of the intestinal segment and the time that the urine is in contact with the mucosa, only 10% of patients with ileal conduits will have metabolic disturbances. Therefore, the monitoring of these alterations should be based on the symptoms and the risk of the patient who who underwent IC [57]. The incidence of secondary malignancy in ileal conduit patients is unknown. The typical latency period for developing cancer in an intestinal segment used for urinary diversion is more than 10 years and the follow-up is not standardized [58]; however, a simple digital exam of IC could give information about the presence of mucosal abnormalities. Finally, all patients with an IC should be to undergo at least an annual inspection of the stoma to evaluate the appearance of frequent stoma-related complications that alter the quality of life.

Other Incontinent Diversions

Jejunal Conduit

The jejunum has the advantage that it avoids the use of irradiated ileum or colon. However, the use has been limited as 40–50% of the patients suffer an electrolyte imbalance known as jejunal conduit syndrome (highest water permeability) [47].

The method of constructing the jejunal conduit consist of locate the stoma anteriorly in the left flank and its optimal position is determined preoperatively for all patients. The left ureter is transected as it crosses the iliac vessels. The right ureter is transected in the pelvis, 2–3 cm below the crossing of the iliac vessels, or higher in patients treated with radiation. The shortest possible jejunal loop (10–12 cm.) is isolated about 15–25 cm from the ligament of treitz. The ureterojejunal anastomosis is performed according to Wallace and stented. A prophylactic oral electrolyte replacement consisting of 4 g sodium bicarbonate is also recommended [59, 60].

The major complications with the use of jejunum are electrolyte abnormality and water loss. However, the resulting hypochloremic, hyponatremic, and hyperkalemic metabolic acidosis, generally accompanied by dehydration, usually responds to increased salt and fluid intake. Nowadays jejunum is rarely used today because of the great consequences of fluid shifts, and this method should be considered only when no other option is viable.

Colonic Conduit

Classical reports revealed that ileal and colon conduit diversions have similar outcomes compared to other conduits, especially in the pediatric population. Moreover, colon conduit was considered to be superior to ileal because of the thicker musculature, infrequent peristalsis, and the need for less intraperitoneal manipulation [61]. Regarding the technical feasibility, ileal diversion remains to be the most frequent seg-

ment used in the majority of hospitals. The decision to use the colon is usually based on the condition of the ileum or distal ureters as a result of pelvic irradiation or prior surgical intervention, the length of ureter resected at the time of operation, or the presence of inflammatory bowel disease in the terminal ileum. Among the advantages of the colon conduit are minimal stomal stenosis, little residuum, less electrolyte disturbance, and availability for high and low diversions. Specifically in a series of 30 patients treated with a very high dose of pelvic irradiation (>65 Gy.) transverse colon conduit urinary diversion resulted to be associated with a 37% complication rate and 20% of reoperation [62].

Conclusions

Despite the different surgical techniques described for continent urinary diversions and incontinent urinary diversions, especially ileal conduit remains to be one of the preferred diversions in many centers. The theoretical low risk of postoperative complications, as well as the technical feasibility, contributes to this trend in use.

Furthermore, specific educational and enhanced recovery programs and conducted by anesthesiologists, and estomatherapists are highly important to improve patient acceptance. Other IUDs as CU have gained acceptance in selected cases (advanced age, comorbidities, and limited life expectancy). The rest of IUDs are nowadays very uncommon and only used in selected cases.

Acknowledgments Naif A. Aldhaam, Hannah B. Ely

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Continent Cutaneous Urinary Diversions

18

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Patient Selection

In selecting a urinary diversion following radical cystectomy, it is critically important to manage expectations for the patient. Having a keen and in-depth understanding of each type or urinary diversion allows the patient to better able to select an option with little or no associated regret. To achieve this, it is important to discuss both advantages and disadvantages of each approach so the patient can have as realistic understanding of lifestyle changes that may be associated with each type of urinary diversion. In discussing diversion options, they should be categorized into one of three groups. Option one includes the non-continent ileal conduit urinary diversion. The clear advantage to the patient for this option relies mainly on its simplicity. It carries with it the least number of postoperative complications and is associated with the quickest recovery. Patients should understand that if their goal is to simply get back to their baseline quality of life as quickly as possible, an ileal conduit would be the best choice. Most elderly patients or those with significant medical comorbidities would likely choose this option. For younger patients or those who feel they cannot tolerate an external appliance and stoma, then a continent urinary diversion would be indicated. The second option, then, for urinary diversion would be an orthotopic neobladder. There are many variations of orthotopic urinary diversions which will be discussed in another chapter. However, it is, again, important for patients to understand the advantages as well as the limitations of this option. The greatest advantage of this group of diversions is the fact that urine will come through the urethra and patients will void "normally." Of course, the word "normally" needs to be qualified further and this brings one to the greatest disadvantage of this type of diversion which is urinary incontinence. For men, patients will have both daytime and nocturnal incontinence for approximately 3–4 months. With pelvic floor rehabilitation and Kegel exercises, most men will have reasonably good daytime urinary control and not require any urinary pads or diapers. Nocturnal incontinence, however, tends to linger and more than 85% of men will experience leakage at night. This can be managed with awakening with an alarm 1–2 times per night or sleeping with a pad/diaper. Occasional use of an artificial urinary sphincter or penile clamp can also be utilized. Nocturnal incontinence, however, remains one of the biggest disadvantages in patients following an orthotopic urinary diversion. In addition, approximately 10% of men and 25% of women require intermittent

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self-catheterization following an orthotopic diversion. For patients who cannot deal with these issues, then the third category of urinary diversion would be an option which is a continent cutaneous urinary diversion. In discussing this option with patients, it is always helpful for them to see the different types of 14F catheters that they will require to catheterize their pouch. For a continent cutaneous urinary diversion, most patients typically catheterize themselves 4–5 times per 24 hours. The major advantage of this approach is that there is no urinary incontinence day or night from the urethra. No pads or diapers would be required. There can be occasional moistness/mucous at the stoma, and very rare cases of significant urinary leakage can occur. The real disadvantage is that they will always require catheters wherever they may be. During the first year after surgery for any type of urinary diversion, there appears to be a greater risk of urinary tract infections, but the frequency tends to decline after the first year. Patient preparation and education is fundamental prior to the procedure as it helps to establish appropriate expectations. Patients who meet the criteria and decide to proceed with radical cystectomy and continent cutaneous urinary diversion meet with specialized nurses who explain what a continent cutaneous diversion is, how it functions and what the postoperative care involves. Across the literature it is recommended that preoperative counseling and education could reduce anxiety, ameliorate wound healing and postoperative recovery, and minimize complications [1].

Patient selection is the key to success for any type of urinary diversion. Giving a patient a realistic understanding of life with a urinary diversion is critical. It can be quite helpful for patients to speak with other patients who have the different types of diversions. The use of educational videos and tutorials for patients and their families can be of great value and should be utilized in any practice performing these procedures. In Fig. 18.1 we depict a simplified image of a continent cutaneous urinary diversion that can be used for patient education.

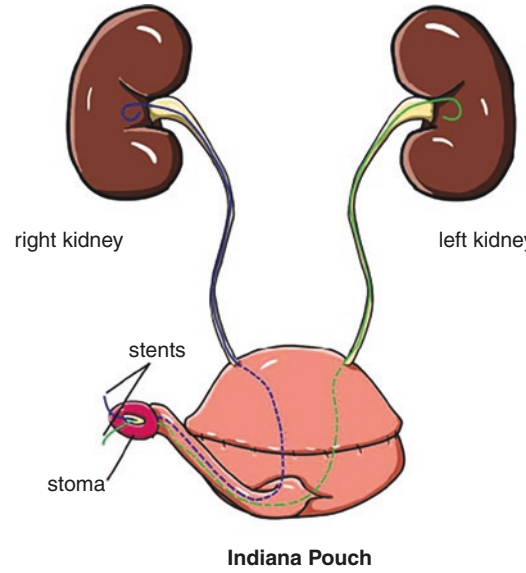

Fig. 18.1 Indiana pouch schematic that can be used for patient education

Patient Preparation

All patients need to undergo preoperative workup and medical clearance prior to their surgery. Patients who are on anticoagulation for cardiac or other reasons are advised to see their primary care physician or cardiologist to provide appropriate perioperative instructions for anticoagulation. At our institution, the patients are on a clear liquid diet for 48 hours prior to surgery and a detailed list of what they can eat is provided. A mechanical preparation that includes Go-lytely™, fleet enemas, and mineral oil is employed the day before surgery. Each patient scheduled to undergo a cutaneous continent urinary diversion should be marked preoperatively by a stomal nurse in case there are unforeseen intraoperative findings that obligate the surgeon to convert to ileal conduit. The location of a pouch stoma is flexible and can be placed in the umbilicus, a skin fold, or under the bikini line.

Patient counseling and education continues beyond the procedure. Upon discharge from the hospital, patients have close follow-up appointments with trained practitioners who teach them how to take care of their stoma, flush the pouch,

remove any mucus, and manage their tubes. A patient will leave the hospital with a suprapubic pouch catheter as well as a 14fr catheter in the stoma, both of which drain the pouch to gravity for an additional 2 weeks. During this 2-week postoperative time period the patient will irrigate each tube three times per day with sterile saline or water. In addition, each patient will stay on a prophylactic dose of lovenox for 3 weeks after leaving the hospital. A package of printed instructions and troubleshooting of common issues should be given to all the patients so they can refer to it at any time.

Surgical Techniques

Numerous techniques have been described for the creation of a continent cutaneous urinary reservoir that stores urine at low pressure and can be drained with clean intermittent catheterization. These techniques can be differentiated by the segment of bowel used to create the pouch and the catheterizable limb of the pouch. An ileal segment, the right colon, the transverse colon, or a combination of small and large bowel can be used to create the pouch. In general, the catheterizable limb of the pouch can be made by ileum or the appendix. The two most preferable stoma locations are the umbilicus and the right lower quadrant.

In 1993, Bissada described the characteristics of an ideal continent cutaneous urinary diversion [2, 3]. These include: (1) adequate volume, low-pressure reservoir with good compliance, (2) reliable continence mechanism, (3) ease of catherization, (4) good cosmetic appearance, and (5) simple construction without uses of excessive length of bowel. A discussion of all the described continent cutaneous urinary diversions is beyond the scope of this chapter. However, we provide a summary of the different techniques as they have been described by experts in the field. This chapter primarily focuses on the Indiana pouch as well as the use of appendix as these are the most commonly performed continent cutaneous urinary diversions performed today.

Indiana Pouch

The Indiana pouch was originally described as a continent pouch made by terminal ileum and right colon that utilizes the ileocecal valve to create a continence mechanism [4]. Indiana pouches reportedly have good continence rates ranging from 72% to 97% in the published series [5, 6].

Upon completion of the radical cystectomy, the right colon is fully mobilized proximal to the hepatic flexure and is divided at the junction of the right and middle colic arteries using a bowel stapler to ensure that blood supply will not be compromised. The last 12–15 cm of the terminal ileum is divided with a stapler and the mesentery is separated along the avascular plane of Treves using a vessel-sealing device. A side-to-side anastomosis is performed between the terminal ileum and the right colon using a bowel stapler. Due to the proximity of the bowel anastomosis to the pouch, we make a practice of covering the staple line with omentum to prevent any fistula formation postoperatively.

The classic Indiana Pouch utilizes a segment of tapered ileum as the catheterizable limb with the ileocecal valve and a high volume, lower pressure pouch aiding in continence. There have, however, been many modifications of this technique. Selection of the appendiceal stoma versus the tapered ileal segment depends on whether the appendix is present and has adequate length to reach the abdominal skin. In addition, the appendix needs to be able to accommodate a 14F red rubber catheter as well. In cases where the appendix can be utilized, the segment of the right colon along the antimesenteric border is detubularized and a trough is made in the taenia overlying the cecum. Afterward, windows of Deaver are created in the mesentery of the appendix and the appendix is buried in the trough of the cecum. The sutures are passed through the mesenteric windows to ensure that the blood supply is not compromised. A 14F silicone Foley catheter is serially inserted through the appendix and ease of passage is assessed. Once the appendiceal tunnel is created, the pouch is formed by colon folded

with a hand-sewn globular configuration. 2.0 Vicryl sutures are utilized to close the pouch in a running and interrupted double layer closure. If the appendix is utilized, the ureters are then reimplanted into the segment of terminal ileum in a refluxing, Bricker technique. Single J ureteral stents are passed up into the collecting system and brought out through a stab wound in the pouch. If the classic Indiana Pouch is performed with tapered ileum, then the ureters are brought into the pouch and anastomosed to the pouch in a widely spatulated fashion using 4.0 Vicryl sutures. Stents are then passed up the kidneys as previously stated. The ileocecal valve is typically reinforced with interrupted 3.0 silk sutures to tighten up the region, so a palpable "pop" is appreciated as the limb is catheterized. This step can insure a greater likelihood of continence. In cases that the appendix cannot be used, a modified Indiana pouch can be constructed using tapered ileum with or without the ileocecal valve as the catheterizable limb. A detailed discussion of all the techniques is beyond the scope of this chapter. However, we provide a brief summary of the most common types of pouches in Table 18.1 for completeness.

Upon construction of the pouch, its integrity should be tested with saline and confirmed. Furthermore, the valve mechanism and its continence should be tested intraoperatively to ensure easy passage of the catheter. If there is difficulty catheterizing the pouch during surgery, then postoperative catheterization by the patient is expected to be challenging. At the end of the case, the patient should have a large-bore catheter (24–28F) for direct pouch drainage (suprapubic catheter) and smaller draining catheter via the continence tunnel. The use of ureteral stents has been questioned by many urologists in the past, but we recommend their use to ensure ureteral patency in the immediate postoperative period. Stents are typically removed once tolerating regular diet.

Overall, surgeon's experience and preference dictate the type of continent cutaneous urinary diversion performed.

Table 18.1 Types of continent cutaneous urinary diversions

Type of CCUD (year)	Continence mechanism	Description
Ileal CCUD		
Kock pouch (1982) [7]	Intussuscepted ileal nipple	Double folded U-shaped configuration of ileal segment
Double T-pouch (2001) [8]	Tapered efferent ileal limb	Proximal ileal segment used for the anti-reflux mechanism and the site for ureteroenteric anastomosis. W-shaped configuration
Mansoura pouch (2004) [9]	Serosa-lined extramural valve	W-shaped ileal reservoir with ureters implanted through serosa-lined extramural tunnels
Ileocecal CCUD		
Lundiana pouch (1977) [10]	Ileal nipple sutured to the rectus fascia	Detubularized segment of right colon with the ureters implanted through submucosal tunnels
Mainz pouch (1983) [11]	Intussuscepted terminal ileum	Antimesenteric opening and spherical reconfiguration of the ileocecal segment with the ureters implanted through submucosal tunnels
Modified Mainz pouch (1992) [12]	Appendix embedded into the caecal pole	Similar to Mainz pouch
Indiana pouch (1985) [4]	Tapered ileal segment and ileocecal valve	Similar to Mainz pouch but ureters are implanted along the tenia libera
Florida pouch (1987)[a] [13]	Ileocecal valve and double plication of the efferent segment	Spherical pouch made by cecum and right colon including the hepatic flexure
Miami pouch (1988)[a] [14]	Tapered ileal segment and reinforced with proximal sutures	Cecum and right colon including the hepatic flexure, opened antimesenterically and configured in U-shape
Charlston pouch (1989) [15]	In situ appendix	Spherical pouch made by detubularized segments of the terminal ileum and right colon

Table 18.1 (continued)

Type of CCUD (year)	Continence mechanism	Description
Colonic CCUD		
Mainz pouch III (2000) [16]	Tailored bowel segment incorporated into the anterior pouch wall	U-shaped reservoir made by transverse and upper ascending or descending colon

CCUD continent cutaneous urinary diversion
[a]Could be classified as colonic pouches too

Robotic Approach for Continent Cutaneous Urinary Diversion

Creation of an intracorporeal continent cutaneous urinary diversion is not commonly performed. The most common approach is to perform the radical cystectomy and mobilization of the right colon robotically and then convert to an open procedure for the urinary diversion part. Goh et al. described a robotic intracorporeal approach for Indiana pouch creation [17]. Overall, this technique replicates the steps of the open procedure robotically. During the procedure, the bowel is detubularized with robotic scissors and the side-to-side ileo-colonic anastomosis is performed with the intracorporeal stapler. The detubularized colon is folded with a hand-sewn approach to a spherical configuration. The extraction site is used to taper the efferent ileal limb and to perform reinforcement of the ileocecal valve. The final stoma is matured through a port site.

Prevention and Management of Complications

Overall, patients with continent cutaneous urinary diversion reportedly have no difference in complication rates compared to patients undergoing an ileal conduit or orthotopic neobladder urinary diversion [18].

One out of three patients that undergo continent cutaneous urinary diversion will develop a significant decline in their renal function [6]. The major causes leading to impaired renal function include recurrent urinary tract infections, reflux nephropathy, nephrolithiasis, prerenal azotemia, stricture of the uretero-intestinal anastomosis, or a combination of those.

Low storage and emptying pressures are crucial to minimize urine reflux from the pouch to the renal pelvises, which lead to pressure induced kidney damage. To ensure a low-pressure system, the surgeon needs to detubularize the bowel segments used for pouch creation and fashion the pouch into the shape of a sphere following the principles of Laplace's law [19]. The patient will need to perform frequent pouch catheterizations throughout the day and pouch irrigation for mucus removal. Maintaining a non-distended, mucous free pouch can minimize the extent of urine reflux and the predisposition to ascending urinary tract infections. In addition, keeping the pouch empty and mucous free will diminish the chance of developing pouch calculi.

Patients with continent cutaneous urinary diversions are at high risk for stone development. This is especially true for patients who have chronic bacteriuria with urease-producing organisms and hydronephrotic kidneys with compromised drainage that leads to urine stasis. For these reasons, patients need to be treated promptly with antibiotics when their urine cultures grow urease-producing bacteria (proteus, ureaplasma, and staphylococcus aureus) even if they remain asymptomatic. Patients with nephrolithiasis and continent cutaneous urinary diversion can either be observed or undergo procedures for stone management (Table 18.2) [20].

Uretero-enteral anastomotic strictures constitute another common complication, ranging from 3% to 10% in the literature, and are independently associated with a decline in renal function [6, 21]. Standard management includes surgical revision of the anastomosis with reimplantation of healthy ureter to the bowel and is successful 80% of the time [22]. An attractive alternative that has been described over the past few years is antegrade endoscopic management, with durable results up to 30% [23]. The use of appendix as the catheterizable stoma likely gives better continence than tapered ileum, but is associated with a slightly higher rate of stomal stenosis requiring revision of dilation as compared to tapered ileum.

Table 18.2 Diversion-related complications and suggested management

Complication	Management
Hydronephrosis Obstructive Non-obstructive	Conservative management Percutaneous nephrostomy
Ureteroenteral anastomosis stricture	Percutaneous nephrostomy and nephroureteral stent Surgical repair and re-anastomosis
UTI/pyelonephritis	Oral/IV antibiotics Percutaneous nephrostomy Nephrectomy
Stomal stenosis	Dilation Surgical repair
Urolithiasis Pouch Ureter/kidney	Observation Percutaneous nephrostomy Intracorporeal lithotripsy/ lithopalaxy ESWL PCNL
Pouch perforation	Conservative management Surgical repair
Parastomal hernia	Conservative management Surgical repair

UTI urinary tract infection, *IV* intravenous, *ESWL* extracorporeal shockwave lithotripsy, *PCNL* percutaneous nephrolithotomy

Metabolic and electrolyte derangements occur non-specifically with any urinary diversions that involve contact between urine and bowel [24]. The management for other common complications related to continent urinary diversions is summarized in Table 18.2.

Urinary Tract Monitoring

After radical cystectomy, the urethral remnant in men and the upper urothelial tracts constitute sites of cancer recurrence. Urethral tumors occur in 1.3–13.7% depending on the series. Many risk factors have been described in the literature, but the most prevalent ones are positive urethral margins, prostatic involvement, and cutaneous urinary diversion [25]. Upper urinary tract recurrence takes place in 4–10% of the patients and constitutes the most common site of late recurrence [26]. Risk factors include noninvasive and multifocal disease as well as positive ureteral or urethral margins at the time of cystectomy [27]. Upper tract recurrence is mostly diagnosed based on symptoms (62%) compared to follow-up investigations (38%) [28].

The National Comprehensive Cancer Network guidelines recommend CT or MR abdomen-pelvis with urogram protocol every 3–6 months for the first 2 years and annually thereafter. Furthermore, urine cytology and urethral wash cytology are recommended every 6–12 months for the first 2 years and as clinically indicated thereafter [29]. The American Urological Association and the European Association of Urology recommend cross-sectional imaging (CT or MRI) at 6–12-month intervals for 2–3 years and then annually. Despite the fact that most clinicians acquire urine cytology every 6–12 months, the guidelines do not routinely support the use of urine cytology or other urine-based tumor marker for early detection of disease recurrence [30, 31].

The guidelines do not report an exact time for clinicians to stop following up patients that remain disease free after 5 years. A risk-adapted schedule that takes into consideration patient prognosis, comorbidities, and goals of care should be implemented in order to provide individualized follow-up schedule.

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Orthotopic Bladder Substitution

19

Divya Ajay, O. Lenaine Westney, Ahmed S. Elsayed, Ahmed A. Hussein, and Khurshid A. Guru

Introduction

Radical cystectomy followed by urinary diversion is considered the gold standard in the treatment of muscle-invasive bladder cancer without detectable metastasis [1]. In 2018, bladder cancer was the sixth most common type of cancer with 81,190 new cases in the United States [2]. Approximately, 30% of these patients will develop muscle-invasive cancer during their lifetime and those who undergo surgery must manage a urinary diversion for the rest of their lives. Life is indisputably different after a cystectomy and varies depending on the type of urinary diversion. This surgery is associated with significant changes in urinary and sexual function, body image and interpersonal relationships, psychosocial stress, financial demands, and subsequently the quality of life.

The orthotopic continent diversion ("neobladder") can help patients avoid a stoma and permit urethral voiding. But, for a variety of reasons the incontinent ileal conduit remains more popular. In the United States, in 2006, only 19.5% of patients underwent a continent urinary diversion [3].

An orthotopic continent diversion is an internal reservoir anastomosed to the native urethra that relies on the patient's functional external striated sphincter for continence. Reservoirs are typically constructed from a large piece of ileum that is detubularized and reattached to the urethral remnant and ureters. The proof of concept was first demonstrated in dogs by Guido Tizzoni and Alfonso Poggi [4]. Camey and Le Duc first used intact ileum and then detubularized ileum for the Camey II reservoir, making pioneering advances in the field [5, 6]. Since then, multiple types of orthotopic bladder substitution techniques have been described including Hautmann pouch, hemi-Kock pouch, Studer neobladder, T-pouch, etc. [7–10] Reservoirs using stomach, jejunum, and cecum have been utilized; however, due to severe metabolic abnormalities they have slowly fallen out of favor [11, 12]. This chapter will focus on the use of the ileal orthotopic bladder substitution as performed in our institution.

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Indications and Contraindications

An orthotopic neobladder is technically more challenging than an ileal conduit; this can translate to a longer operative time and more involved postoperative management. In general, patients with renal or liver impairment, poor compliance to the training regime or catheterization, inflammatory intestinal disease, cancer at the prostatic apex or bladder neck, urethral stricture disease, and pre-existing urinary incontinence are not candidates for an orthotopic neobladder.

Urethral Margin

The risk of urethral recurrence after a neobladder is reported at 5–10% and occurs in the first 3 years postoperatively [13]. A high risk of urethral recurrence is a contraindication to a neobladder, but predicting this can be challenging. Multifocal disease, carcinoma in situ, ureteric disease, and urothelial cancer at the distal prostatic urethra are considered risk factors for urethral recurrence. An intraoperative frozen section of the resected urethral margin is considered sufficient to proceed with a neobladder by most centers.

Age and Motivation

We do not use a strict age cut-off for a neobladder; however, in general, patients above the age of 70 will opt for an ileal conduit due to less time and work intensive post-operative course and shorter intraoperative duration. The patient's motivation, commitment, and comprehension of the required postoperative are far more important than age when considering eligibility for a neobladder.

Sphincter and Urethral Quality

The ability to void urethrally depends on the function of the native urethra and sphincter. Patients with baseline incontinence or urethral stricture disease are poor candidates for neobladder. Management of urinary incontinence with a neobladder is challenging and will be discussed below.

Gender

Orthotopic neobladders were initially limited to men, with the flawed impression that women have a higher risk of local recurrence and voiding dysfunction with a neobladder. However, with an improved understanding of the female rhabdoid sphincter mechanism and early detection of bladder cancer, orthotopic reservoirs are becoming more common in female patients without other contraindications [14].

Patient Preparation

Preoperatively the patient's serum electrolytes and chemistries are checked to ensure no baseline abnormalities. Full informed consent is obtained including discussion of the possibility of alternative urinary diversion options in case technical or oncological factors make orthotopic diversion inappropriate. The wound/ostomy service places a stoma site marking. Broad-spectrum antibiotics are used preoperatively.

Preoperative bowel preparation is not routinely used in patients. It causes varying degrees of dehydration and may delay the return of bowel function. A randomized control trial has demonstrated it is safe to omit bowel preparation and is not associated with bacterial overgrowth [15].

Surgical Technique

Open Studer Neobladder

We perform an open orthotopic neobladder in a manner similar to that described before [8, 13], with modifications. Equipment needed is listed in Table 19.1. Our institutional technique with specific tips and tricks is described below.

Table 19.1 Equipment for orthotopic neobladder

Instruments	22 and 24 Fr Greenwald Sounds Mosquitos labelled 12, 1, 3, 5, 6, 7, 9 and 11 Bookwalter retractor GIA 75 stapler × 3 loads and TA 60 with 1 load 9 inch smooth Gerald pick ups
Suture	2-0 Monocryl on UR-6 needle 3-0 silk 18" suture pop-offs 2-0 vicryl suture (SH or CT-2) 3-0 vicryl suture (SH) 5-0 chromic suture #1 PDS suture (needle) #2 vicryl suture needle) 5-0 vicryl on RB 1 needle
Tubes	26 or 28 chest tube Single J stents (7 Fr × 90 cm) 22 Fr Rusch catheter (2-way) 19 round blake drain

During the radical cystectomy and pelvic lymphadenectomy, a urethral margin and bilateral ureteral margins are sent for frozen section to ensure each is disease free.

A. Mesenteric length confirmation and placement of the urethral anastomotic stitches

Prior to starting the orthotopic diversion, a dependent portion of the distal ileum is brought down to the urethral stump to confirm ease of anastomosis. While there are maneuvers to address deficits of 1–2 cm, when a gap of 5 cm or greater is encountered, the diversion approach may need to be reconsidered.

With the kidney rest up on the operating room table and patient in the flexed positioned (as they were positioned for the radical cystectomy), we start by placing the urethral portion of the anastomotic sutures. 2–0 monocryl sutures on a UR6 needle are used, placed outside-in at the 12, 1, 3, 5, 6, 7, 9 and 11 o' clock positions (Fig. 19.1). Subsequently, the kidney rest can be lowered and some of the flex on the table reduced.

B. Bowel harvest and re-establishing continuity

After identifying the ileocecal valve, the first 20–25 cm of distal ileum is spared to avoid postoperative malabsorptive concerns. After evaluating the mesenteric arcades and the mobility of the bowel, a marking silk stitch is placed at the distal most portion of the ileum to be harvested. The entire length of the ileum harvested for the neobladder is between 55 and 59 cm. It is divided into three segments measuring 20–22 cm for the first two and 12–15 cm for the last segment, also referred to as the afferent limb. Marking silk sutures are placed to identify the three segments (Fig. 19.2).

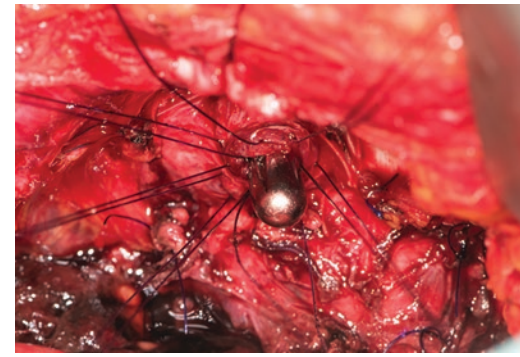

Fig. 19.1 Urethral anastomotic sutures

While harvesting the bowel, the distal portion of the mesentery is long and may transect mesenteric vasculature to help with neobladder mobility; however, we try to maintain a small proximal mesenteric window to maintain good blood supply to the harvested ileum. The mesentery is incised with a LigaSure (Covidien, Mansfield, MA, USA), and a stapled bowel anastomosis is performed. The staple line is imbricated with lembert sutures. The mesentery gap is not closed.

After replacing our retractors, a 5 mm incision is made just distal to the afferent limb along the antimesenteric aspect of the ileum and the distal staple line is resected. The entire length of bowel is irrigated by placing a catheter tip syringe through the 5 mm incision and draining the fluid through the distal portion of the ileum.

C. Constructing the neobladder

To detubularize the bowel, the antimesenteric border is opened over a chest tube (Fig. 19.3) using cutting current for the seromuscular layer and coagulation electrocautery for the mucosal

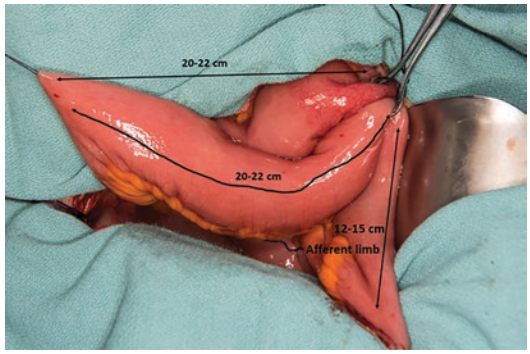

Fig. 19.2 Layout of ileum harvested for neobladder

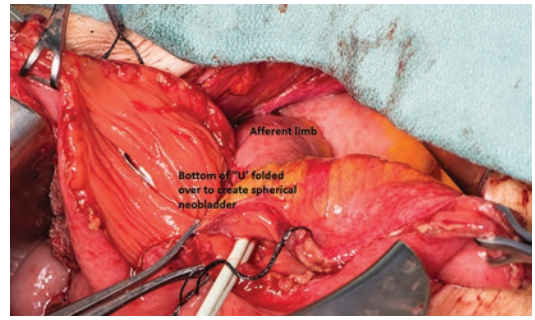

Fig. 19.4 Creating the spherical shape of the neobladder by folding over the bottom of the "U" ileal configuration to meet the distal portion of the afferent limb

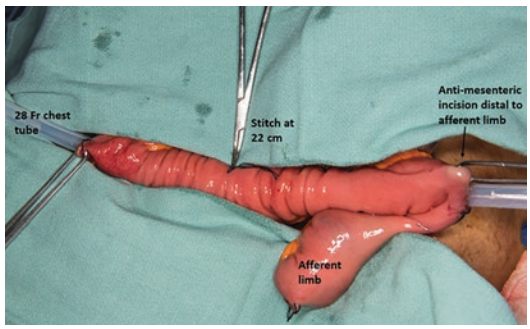

Fig. 19.3 Opening the anti-mesenteric border over a chest tube

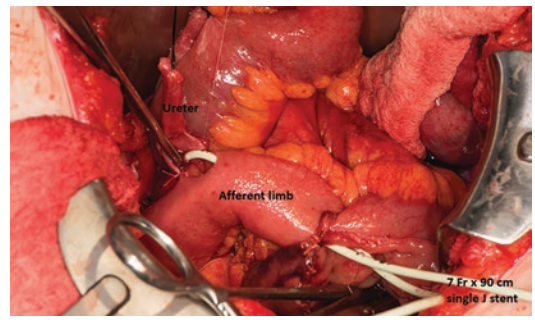

Fig. 19.5 Anastomosing the ureters to the afferent limb and passing the stents through the afferent limb

layer. The ileum is now reconfigured into a U shape (Fig. 19.1). The posterior wall is closed with 3–0 vicryl in a running locking fashion taking full thickness bites on the bowel.

Next, the spherical shape of the neobladder is created by folding over the dependent portion of the "U" to meet the distal portion of the afferent limb (Fig. 19.4).

D. Ureteroileal anastomosis

The left ureter is adequately mobilized and transferred to the right either behind the sigmoid mesentery (or in some cases through it) at the level of the aortic bifurcation. The ureters are spatulated depending on the caliber and diameter of the native ureters. The ureters are anastomosed to the most proximal portion of the afferent limb end-to-side fashion. We use interrupted 5–0 vicryl suture on an RB 1 needle for this anastomosis. 7 Fr single × 90 cm single J ureteral stents are placed into the ureters and brought out past the afferent limb (Fig. 19.5). It is held in place by a 5–0 chromic suture to the mucosal surface of the neobladder.

E. Ileourethral anastomosis

The right and most dependent portion of the neobladder is used for the urethral anastomosis. A 24 Fr Greenwald sound is used to size the opening (Fig. 19.6). The remaining anterior wall of the neobladder is closed with 2–0 vicryl running locking sutures. The stents are brought through the antimesenteric portion of the anterior neobladder. They are secured again with a 5–0 chromic purse string suture.

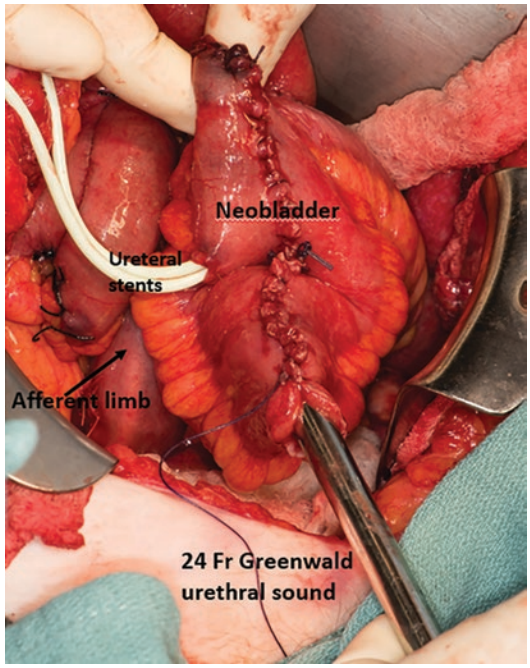

Fig. 19.6 Sizing the ileourethral anastomosis

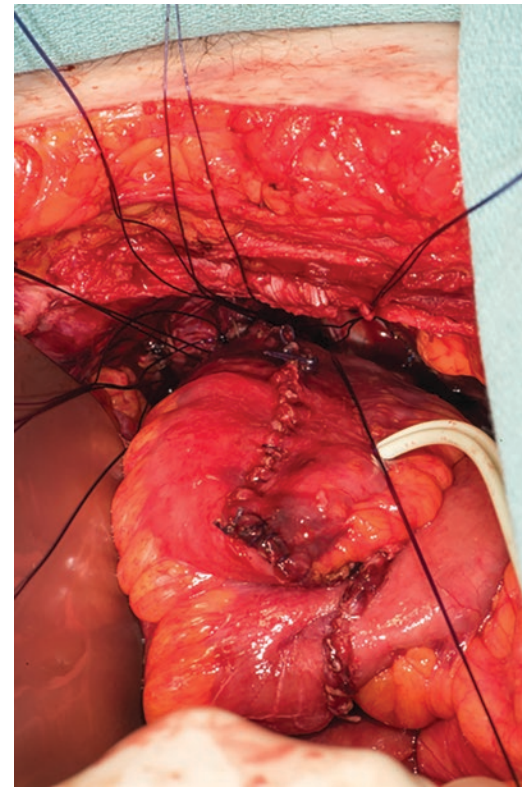

Fig. 19.7 Neobladder to urethral anastomosis

The corresponding urethral anastomotic sutures are placed on the inferior portion of the neobladder along the right suture line. Alternatively, the right side of the pouch can be closed fully with a separate 20–24 French aperture in the most dependent location. After placing the posterior sutures, a 22 Fr Rusch catheter is placed in the bladder with 10 cc in the balloon (Fig. 19.7). The anastomosis is tested by filling the 22 Fr Rusch catheter with normal saline.

The stents are brought out in the right lower quadrant and an ostomy bag placed over them. A 19 blake drain is placed in the vicinity of the neobladder being careful to avoid placing it over any anastomoses. The bowel is run to carefully checking for injuries and the omentum if present is brought over the neobladder. The fascia is closed with #1 PDS suture with #2 vicryl internal retention sutures (for neoadjuvant chemotherapy patients). The skin is closed with 4–0 monocryl or staples (Fig. 19.8).

Other Technical Issues

(a) *Nerve-Sparing*

Nerve-sparing can play a crucial role in determining the return of continence.

If the tumor is not locally advanced, a nerve-sparing technique should be attempted. This can be bilateral if permissible, or unilateral if there is lateralized disease. In some cases, authors advocate against performing an orthotopic neobladder for patients who cannot undergo nerve-sparing surgery [16].

In women, the paravaginal nerve fibers are preserved by dissecting along the anterolateral paravaginal plane no further dorsal than the 2 or 10 o'clock position [17].

(b) *Ideal Characteristics*

To preserve upper tract function and minimize metabolic disturbances, the neobladder

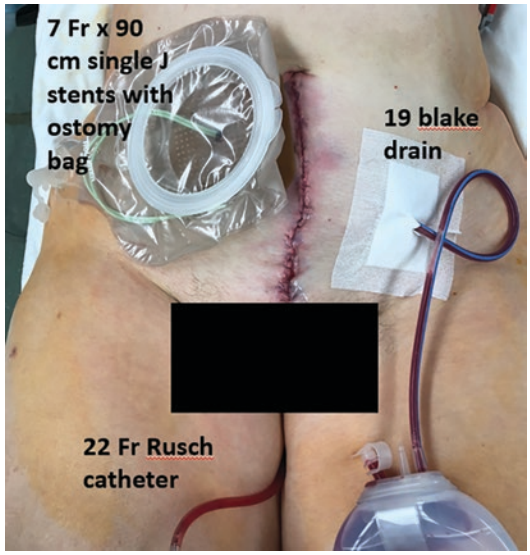

Fig. 19.8 Postoperative appearance with all catheters and drains. Rusch Catheter (Teleflex Medical, Wayne, PA)

must be low pressure (<15 cm H_2O), with adequate capacity (~500 cc) and must empty to completion (residual <100 cc) four to five times a day.

Higher internal pressure in the reservoir may overcome the external sphincter mechanisms to maintain continence and could potentially cause upper tract deterioration with reflux nephropathy. Detubularization of the intestinal segments limits the ability of the bowel to generate a peristaltic wave, which can also contribute to incontinence. Complete voluntary control of voiding with good emptying minimizes the likelihood of absorption of urinary waste products and resulting metabolic complications.

(c) *Site of Outlet*

It is essential that the entero-urethral anastomosis should be watertight, well-vascularized with good mucosal opposition. Some authors advocate for the site of the urethral stump to be button-holed at the most dependent portion of the reservoir [17, 18] and others anastomose the lowest portion of the suture line of the reservoir to the urethra [19–21].

We have consistently had excellent outcomes with the non-buttonholing method of using the inferior portion of the suture line for the urethral anastomosis. Button-holing may decrease the blood supply to the part of the ileum beyond the buttonhole, increasing the risk of stricture and anastomotic complications. Our data did, however, show a slight increase in the rate of anastomotic leak at the 12 o'clock position at the 3-week cystogram [22].

(d)*Robotic/Laparoscopic*

Urologists have been early adopters of minimally invasive surgery with robot-assisted laparoscopic prostatectomies and partial nephrectomies becoming the norm. However, the adoption of robotic radical cystectomy and intracorporal orthotopic diversion has been less popular.

Multiple authors described laparoscopic radical cystectomies between 1992 and 1995 [23]. However, it was not until 2002 before Gill et al. described the pure laparoscopic radical cystectomy with an intracorporal neobladder [24, 25]. The robotic-assisted laparoscopic cystectomy was first described by Menon et al. in 2003 [26].

Multiple configurations and techniques of intracorporal robotic neobladders have been described since including the U-shaped [27], Y-shaped [28], W-shaped [29], pyramid-shaped [30], Padua ileal bladder [31], and the Florence intracorporal neobladder (FloRIN) [32] to list a few.

Recent randomized controlled studies have found comparable oncological outcomes between open and robotic radical cystectomies [33, 34]. However, these were not powered to compare intracorporal versus extracorporal diversions and outcomes of the same. A few retrospective studies have shown that intracorporal diversions can be performed safely with comparable outcomes to extracorporal diversions, but no specific benefits are noted [35–37]. With similar outcomes, much higher costs, and longer operating room times, currently intracorporal orthotopic neobladders are difficult to justify.

The following section, authored by Ahmed Elsayed, Ahmed Hussein, and Khurshid Guru, describes the technique for intracorporeal W neobladder.

Intracorporeal W-Neobladder

Ahmed S. Elsayed, Ahmed A. Hussein, and Khurshid A. Guru

Intracorporeal urinary diversion (ICUD) provides benefits including smaller incisions, reduced pain, decreased bowel-related complications, and a decreased risk of fluid imbalances. ICUD has mainly been adopted for ileal conduits. Intracorporeal orthotopic urinary diversion was adopted at a slower pace, given the heightened technical complexity, steeper learning curve, and longer operative time. Continent urinary diversions have been associated with an improved quality of life compared to conduit diversion. Here, we describe our intracorporeal W-neobladder technique step by step.

Our technique for intracorporeal W-neobladder was previously described [38]. The port configuration is similar to the standard 6-port placement used during RARC. An extra 15 mm short suprapubic port may facilitate bowel anastomosis. Placing the ports an inch higher may facilitate bowel manipulation.

A. Retraction suture

A 45 cm bowel segment is identified approximately 15–20 cm proximal to the ileocecal valve, and a W-configuration is set up. There are four "limbs" of the W configuration, and two limbs combine to make a "trough" on each side of the W. The most dependent parts of the right and left trough are maintained in place with sutures to the Foley catheter using 2/0 silk sutures. The catheter will act as a dynamic retractor until the neobladder-urethral anastomosis is performed (Fig. 19.9).

B. Forming the W configuration

Proximal ends of both right and left troughs are kept in place using stay sutures. These sutures keep the W orientation and facilitate manipulation of the bowel and construction of the neobladder. They mark the end of the pouch and the beginning of the chimney on each side.

Fig. 19.9 Formation of W configuration. (From Elsayed, Hussein, and Guru and illustrate steps in the intracorporeal W-neobladder)

C. Detubularization the bowel

The right trough is detubularized using hot scissors a few millimeters away from the mesenteric border (to provide a wider bowel surface area for the construction of the neobladder-urethral anastomosis later on). Detublarization can be done while providing traction using the assistant's suction device. We prefer to open only one trough at a time to avoid spillage of the intestinal contents and maintain orientation. Traction by the bedside assistant using the Foley catheter and by the fourth arm on the proximal trough sutures helps to stretch the bowel segment as well. The adjacent bowel edges of the detubularized right trough are sutured together in a running fashion using 3/0 V-Loc sutures. Suturing is done in a continuous fashion with tightening every three throws. The same steps are repeated for the left trough.

D. Construction of the posterior plate

The right and left trough are sutured together in the midline to form the posterior plate of the neobladder (Fig. 19.10).

E. Neobladder-urethral anastomosis

The traction sutures are released from the Foley catheter. Two 3/0 V-loc sutures are used and suturing is started at the 6 O'clock position. The dependent part of the posterior plate of the neobladder is anastomosed to the urethra in an end-to-side fashion (Fig. 19.11). Sutures can be reinforced by including some periurethral tissue. To facilitate the urethral anastomosis, Trendelenburg position can be reduced or flattened, pneumoperitoneum pressure reduced, or perineal pressure applied.

F. Suturing anteriorly around the catheter

The urethral-neobladder sutures are continued anteriorly over a 22 Fr hematuria catheter until the 12 o'clock position, folding the right and left edges around the urethra. Suturing is completed, closing the caudal 2/3 of the anterior surface of the neobladder (Fig. 19.12).

G. Bowel division

Ten centimeters are left for the chimney proximal to the stay sutures. An Endo GIA vascular stapler is used to divide the neobladder from the bowel on each side (Fig. 19.13).

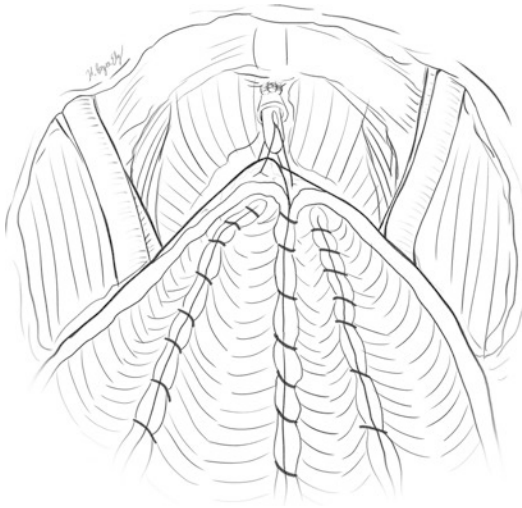

Fig. 19.10 Posterior plate of W neobladder. (From Elsayed, Hussein, and Guru and illustrate steps in the intracorporeal W-neobladder)

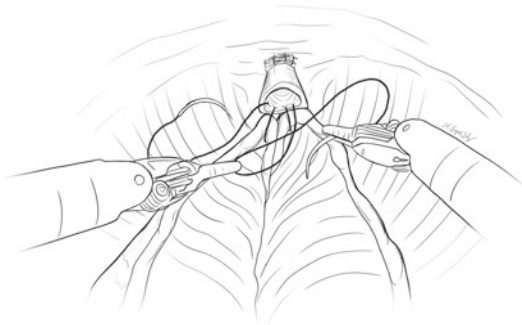

Fig. 19.11 Neobladder urethral anastomosis (posterior). (From Elsayed, Hussein, and Guru and illustrate steps in the intracorporeal W-neobladder)

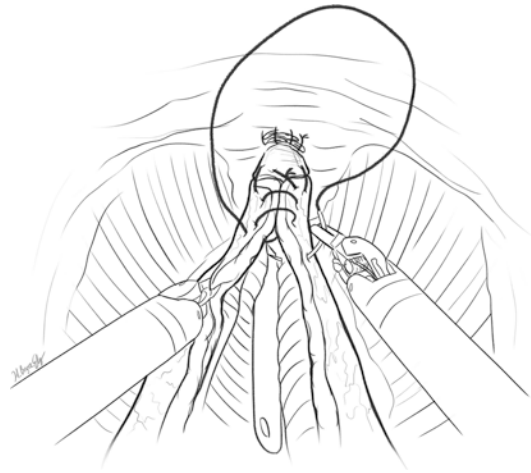

Fig. 19.12 Neobladder urethral anastomosis (anterior). (From Elsayed, Hussein, and Guru and illustrate steps in the intracorporeal W-neobladder)

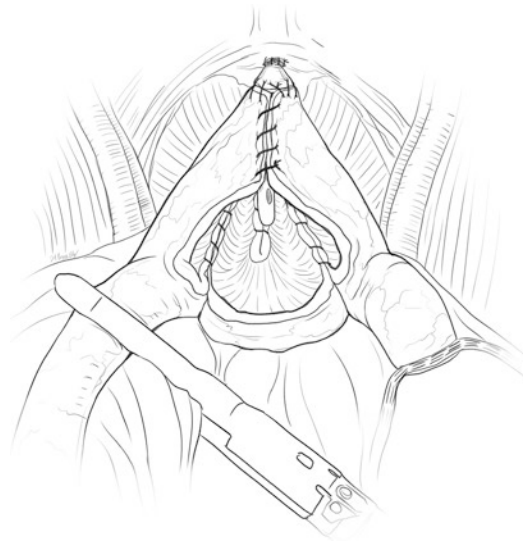

Fig. 19.13 Bowel division. (From Elsayed, Hussein, and Guru and illustrate steps in the intracorporeal W-neobladder)

Bowel continuity can be restored now or after the construction of the neobladder.

H. Ureteroileal anastomosis

The ureter is partially transected and spatulated anteriorly, and the staple line is removed from the chimney. Appropriate length of the ureter is used (avoiding tension or redundancy). End-to-end (at the staple line) or end-to-side (to an enterotomy in the chimney) ureteroileal anastomosis is performed in an interrupted or continuous fashion using a 4/0 Vicryl sutures. The Hem-o-lock and the distal ureteric ends are cut and sent for final pathology. The ureteroileal anastomosis is performed on one limb followed by the passage of the stent before the other limb is sutured. An 8.5 Fr single J stent is passed through the catheter and through the ureteroileal anastomosis. The stent is secured to the neobladder using 2/0 Chromic catgut to prevent dislodgement. Stents can be sutured to the neobladder to facilitate removal later on at the time of catheter removal. The ureteroileal anastomosis in then completed (Fig. 19.14).

I. Closure of the anterior plate of the NB

The remaining suture from the anterior wall is lifted up by the fourth arm. The posterior flap is rolled over the anterior plate as a "cigarette box." The two limbs are sutured from lateral to medial, giving the neobladder a globular configuration (Fig. 19.15).

J. Re-establishment of the bowel continuity

Please refer to "Intracorporeal Ileal Conduit Urinary Diversion" chapter.

K. Omental coverage

The omentum is straightened and anchored to cover the anterior aspect of the neobladder (Fig. 19.16).

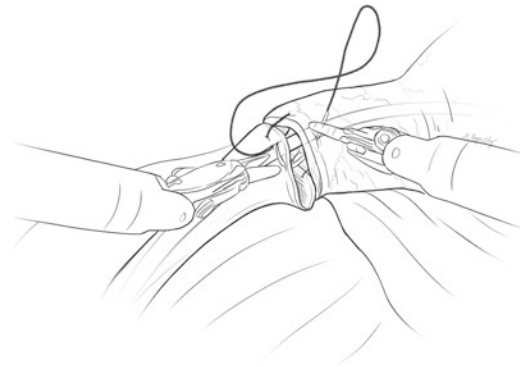

Fig. 19.14 Ureteroileal anastomosis. (From Elsayed, Hussein, and Guru and illustrate steps in the intracorporeal W-neobladder)

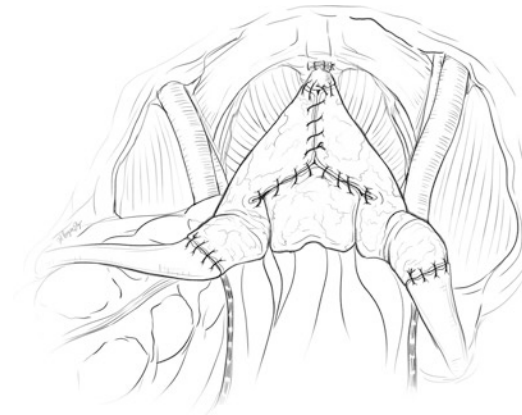

Fig. 19.15 Anterior plate of the neobladder. (From Elsayed, Hussein, and Guru and illustrate steps in the intracorporeal W-neobladder)

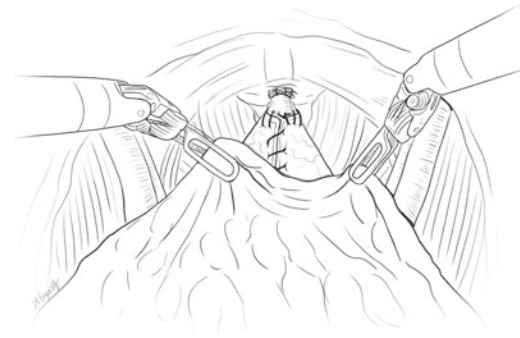

Fig. 19.16 Omental coverage. (From Elsayed, Hussein, and Guru and illustrate steps in the intracorporeal W-neobladder)

Postoperative Management

Following the enhanced recovery protocol, patients are managed postoperatively with cautious parental fluid replacements, oral alvimopan (Entereg, Cubist Pharmaceuticals, Inc., Lexington, Massachusetts) while reduced of bowel function, gradual advancement of diet and

minimal use of narcotic pain medications [39, 40]. Serum electrolytes, bicarbonate level, and osmolality are monitored regularly.

Stents are maintained for 5–7 days. The drain is removed once output falls below 300 per day. It is usually checked for creatinine to ensure no urine leak prior to removal. The 22 Fr catheter in the neobladder is irrigated with normal saline three times a day to evacuate the mucus in the bladder. This is initially done by the nursing staff and starting postoperative day three, by the patient or their family members. A cystogram is performed at 3 weeks, and if no evidence of a leak, the catheter is discontinued. Patients are all taught to self-catheterize the neobladder and start with catheterizing every 2 hours. This is eventually weaned down based on their residual urine volumes.

Complications

Multiple large series have demonstrated the overall 30-day complications after a cystectomy and urinary diversion between 50% and 60% [41]. Bowel-specific complications are as high as 20% at a median of 1.5 years [42]. This number is not reported to be higher in patients undergoing orthotopic neobladder in comparison to those undergoing ileal conduits [43].

Management of Complications

1. *Voiding Dysfunction*

   The normal mechanism of voiding in patients with a neobladder is coordinated straining (Valsalva maneuver) with pelvic floor relaxation [44].

   The improved quality of life attributed to the orthotopic neobladder can be severely diminished when patients have postoperative voiding dysfunction. Voiding dysfunction, in general, is defined as a failure to store and/or a failure to empty.

   A systematic review found 4–25% rate of incomplete emptying requiring clean intermittent catheterization, 13.3 ± 13.6% daytime incontinence and 15–40% nighttime incontinence [45].

   (a) *Urinary Retention*

   Postoperative urinary retention is more common in women. It may occur early; however, it is often reported later in the course, after years of good neobladder function and emptying. Up to 50% of patients have reported urinary retention at 5 years. While the etiology is unclear, experts believe it is a combination of:

   - A mechanical kink in the urethra-pouch anastomosis as the full pouch falls posteriorly during Valsalva maneuver
   - Inferior displacement of the bladder neck
   - Autonomic denervation of the urethral stump
   - Herniation of the pouch wall through the prolapsed vaginal stump
   - Disordered reinnervation resulting in the inability of the sphincter to relax [46, 47]

   Treatment of urinary retention is clean intermittent catheterization. Transurethral resection of the urethral fold and open reduction of the pouch size with anterior fixation to the abdominal wall have also been described. Intraoperative maneuvers including increased back-support of the pouch through omental packing behind the reservoir, suspension of the vaginal stump to the preserved round ligaments, and suspension of the reservoir dome to the back of the rectus abdominis muscles have been proposed to reduce the incidence of urinary retention.

   (b) *Urinary Incontinence*

   Suboptimal neobladder capacity and damage to the sphincter mechanism (directly or indirect neurovascular damage) contribute to urinary incontinence postoperatively. Advanced age, non-detubularized segments, colonic segments with stronger peristaltic waves and non-nerve sparing surgery are contributing risk factors [48]. Noctural enuresis affects up to 67% of patients initially but may resolve as the bladder capacity increases. Over-distension of the neobladder and

lack of afferent sensory feedback contribute to nighttime incontinence [45].

Technical factors like creating an ellipsoid or spherical configuration prevent injury to the pelvic floor; positioning the neobladder neck in the most dependent portion of the pelvis is essential in avoiding postoperative voiding dysfunction. Postoperatively, patients are advised to perform timed voiding every 2–4 hours with volumes less than 400 cc; aggressive intermittent catheterization titrated based on bladder residuals is performed to keep bladder volumes low. Since the bladder capacity continues to increase over the next 6–12 months, we wait to perform urodynamics or other evaluation on these patients until then [45]. There is no published guidelines or standardization of urodynamics studies in orthotopic neobladders; however, these studies can be helpful to assess capacity, compliance, bladder emptying, storage pressures, etc. [49]

If daytime incontinence with low Valsalva leak point pressure is demonstrated, urethral bulking agents or the artificial urinary sphincter can be used for treatment in men. Nocturnal enuresis can be addressed with behavioral changes like reduced fluid intake in the evening, medication adjustments, and timed voids at night. Medical management with anticholinergics has shown to have modest benefit [50, 51]. Desmopressin may be used with some benefit, but side effects have to be closely monitored [52].

In women, preservation of the posterior hypogastric nerves and autonomic nerves and functional integrity of the female striated urethral sphincter have been suggested play an important role in maintaining continence [53]. Treatment of new onset stress urinary incontinence for women can be treated with transurethral bulking agents or pubovaginal fascial slings [54].

2. *Metabolic Abnormalities*

Absorption of ammonium ion through the intestinal mucosa leads to hyperchloremic metabolic acidosis and disturbances in electrolyte metabolism in patients with orthotopic bladder substitution. Up to 31% of patients in one series were found to have metabolic acidosis at 1 month, but this improved to 22% at the end of 1 year [55]. Generally, those with normal baseline renal and hepatic function can compensate for the ongoing acid absorption. Additionally, the metabolic acidosis can be easily correct with oral sodium bicarbonate or potassium citrate administration. Main side effects of sodium bicarbonate include gastrointestinal disturbances and fluid retention from sodium intake.

3. *Vaginal Vault Prolapse or "Neocystocele"*

A pouchocele or neocystocele forms due to caudal migration and posterior prolapse of the neobladder with subsequent urethral kinking [47, 56]. This was demonstrated in a functional MRI study by Ghoneim et al. [47]. Others postulate that straining to empty the neobladder leads to the formation of the neocystocele [44]. Prophylactic technical maneuvers including urethral suspension, posterior omental or peritoneal flap interposition, anterior pouch fixation to Cooper's ligament and maximal preservation of paravaginal tissue, levator muscles, and pelvic floor fascia have been described to prevent caudal migration of the neobladder to prevent pelvic organ prolapse [57, 58]

Transvaginal repair of neocystocele or enterocele with vaginal vault suspension maneuvers have been successfully performed in a small group and even restored normal voiding in some patients [59]. The same group has also described augmentation with polypropylene mesh by the same group [59]. At our institution, we use human pericardium to perform robotic or open sacrocolpopexy in patients with post-neobladder pelvic organ prolapse with successful outcomes [60].

4. *Fistulae*

Neobladder to vagina or rectal fistulae are rare, reported at 1–3% [19, 61–63]. Neobladder-vaginal fistula patients present

with severe and immediate urinary incontinence after the removal of urethral catheters. Median time to presentation was 1 month [61]. Exam under anesthesia, neobladder endoscopy, vaginoscopy, attempt at cannulation of the fistulous tract, double dye test, cystogram are useful in diagnostic evaluation. Fistula formation may be secondary to inadvertent injury to the anterior vaginal wall during cystectomy, overlapping suture lines, interrupted tissue planes between the posterior bladder neck and vagina or compromised tissue vascularity between the urethra and anterior vaginal wall [64]. It has also been reported as a complication from collagen injections used for the treatment of stress urinary incontinence [65]. Neobladders are at particularly high risk of fistula formation due to multiple suture lines and placement adjacent to many newly resected surfaces.

Neobladder-vaginal fistula can be repaired either abdominally or transvaginally adhering to the same surgical principles as in any fistula repair, namely circumferential dissection of the fistulous tract, multiple layer closure, tension-free closure, non-overlapping suture lines, and the use of tissue interposition when possible [66]. Vaginal repair can be challenging because the patient's vagina is often atrophic and the wall of the neobladder is much thinner than the native bladder. While all studies report good success for repair of distal anterior vaginal wall; some studies show poor success rate with the repair of fistulas at the neobladder-urethral anastomosis [67–69]. Patients need to be counseled that the risk of rhabdosphincter injury and post-fistula repair stress incontinence is high [56]. An abdominal approach allows for omental interposition and is preferred in patients with severe vaginal atrophy or for large fistulae [62, 69]

Neobladder-enteric fistulae are reported at 1.5% of patients in large series [7, 70]. Like with neobladder-vaginal fistulae, urine leak and adjacent small bowel anastomoses are risk factors. Case reports described the use of nonsurgical management options including low-residue diet [71] or total parenteral nutrition [72], oral antibiotics, and continuous neobladder drainage. However, most cases are managed surgically [73].

5. *Ureteroileal Anastomotic Strictures*

Patients may develop malignant or benign ureteroileal anastomotic stricture after orthotopic neobladders. In general, malignant strictures from primary or recurrent malignancy respond poorly to endoscopic treatment, and require permanent drainage and open repair.

The incidence of benign strictures after radical cystectomy and urinary diversion is reported between 1% and 13% and usually present between 6 and 18 months post-cystectomy [17, 74]. The pathophysiology is likely secondary to ischemia and inflammation from compromised blood supply secondary to adventitial stripping, urine leak, prior radiation, acute trajectory, or tight tunneling under the sigmoid mesentery of the left ureter or anti-refluxing mechanism [74, 75].

The gold standard for treatment has been open surgical repair; however, due to the associated morbidity, minimally invasive techniques have been tried. Balloon dilation of ureteroenteric strictures has reported with success rate between 13% and 60% [75]. Acucise endoureterotomy and laser incision of ureteroenteric strictures have been attempted with 62 and 71% stent-free patency rates at 22 months follow-up. Patients with right-sided strictures, <1 cm in length with stent placement for >4 weeks had higher rates of success with endourological procedures [75, 76].

Open repairs with direct implantation or tissues bridge with boari flap or ileal ureters have a reported long-term success rate of 78% at 47 months follow-up [77].

6. *Sexual Dysfunction*

Similar to other pelvic extirpative surgeries, patients post-cystectomy and urinary diversion have significant sexual dysfunction.

Eighty percent of patients report sexual dysfunction after radical cystectomy and urinary diversion [78]. However, less attention has been focused on this in comparison to post-prostatectomy erectile dysfunction.

A systematic review by Modh et al. demonstrated that patients' advanced age, poor baseline erectile function, surgical factors like non-nerve-sparing surgery, and the use of incontinent urinary diversion were associated with worse post-cystectomy erectile dysfunction [79]. Patients who are offered a neobladder are generally younger, and it is likely, due to this selection bias, that neobladder patients have better recovery of erectile function postoperatively.

The etiology is likely multifactorial due to iatrogenic causes from neurovascular damage surgically and neoadjuvant chemotherapy, emotional, psychological, social concerns, and stigma associated with urinary diversions. In female patients, decreased clitoral sensation, decreased vaginal length and penetration, and body image factors contribute to 30–48% sexual dysfunction [80, 81]

Preoperative counseling is critical in managing patient expectations. Post-cystectomy erectile dysfunction in men can be treated with oral phosphodiesterase type 5 inhibitors, intracorporal injections, transurethral suppositories, vacuum-pump devices, and inflatable penile prosthesis. In women, oral phosphodiesterase type 5 inhibitors may increase clitoral sensation, blood flow, vaginal lubrication, and sexual satisfaction [80]. Sexual therapy and counseling is an important adjunct.

7. *Urolithiasis*

Patients with orthotopic neobladders are at an increased risk of urolithiasis due to metabolic, infectious, and structural causes [82].

Chronic metabolic acidosis leads to increased calcium excretion. The hyperchloremic metabolic acidosis is associated with bone loss, impaired renal calcium reabsorption, increased urinary calcium excretion, hyperoxaluria, and hypocitraturia, which increases the risk of stone formation [83].

Patients with orthotopic neobladders are prone to have asymptomatic bacteriuria. Patients colonized or infected with Proteus, Klebsiella, Pseudomonas, Enterococcus, and Staphylococcus have been reported in recurrent stone formers [84]. Bladder irrigation protocols and low-dose antibiosis can be used in patients with recurrent stones.

Stasis of urine from neobladder neck strictures, incomplete emptying, and refluxing ureteroileal anastomoses are important risk factor in post-neobladder stone formation. All anastomoses are performed with absorbable suture, because there is an increased risk of stone formation with the use of non-absorbable stapler, especially in patients who perform clean intermittent catheterization postoperatively [85].

8. *Bowel-Related Complications*

Early paralytic ileus and bowel obstruction is the most common bowel-related complications post-orthotopic neobladder. The incidence of paralytic ileus is reported between 1.58% and 23.5% in a systematic review [86]. Risk factors include age and increased body mass index. Chewing gum was associated with shortened time to flatus and bowel movements [87].

Delayed return of bowel function is not worse in patients who undergo orthotopic neobladder and in some series is associated with lower incidence of paralytic ileus in comparison to patients undergoing ileal conduit urinary diversion [88].

The use of a nasogatric tube and routine preoperative bowel preparation were associated with delayed return of bowel function. A 2008 Conchrane review studying paralytic ileus after any abdominal surgery in adults concluded that the peripherally acting μ-opioid receptor antagonist reduces time to flatus [89]. Erythromycin, cholecystokinin-like drugs, and cisapride were ineffective or had unacceptable adverse events. Intravenous lidocaine and neostigmine might have potential benefit [89]. In a randomized control trial,

laparoscopic or robotically performed surgery has shown early recovery of bowel function in comparison to open surgery [90].

Multiple intraoperative interventions have also been attempted to help expedite return of bowel function. A randomized control trial advocated for readaptation of the peritoneum showing hastened recovery of bowel function [91]. A retrospective study described suspending the stapled anastomotic portion of bowel on the posterior peritoneum so it does not fall into the pelvic cavity; this was shown to reduce early intestinal obstruction without increasing paralytic ileus [92].

Early commencement of solid diet intake has demonstrated improvement in return of bowel function. Time to stent removal has been investigated by one study concluding that in comparison to those whose stents were removed immediately after the ureteroileal anastomosis, those patients whose stents were removed 5–10 days after surgery had improved upper tract drainage and accelerated return of bowel function [93].

In our practice, we have used a standardized enhanced recovery program including the use of alvimopan preoperatively, preoperative carbohydrate loading, no bowel preparation, intraoperative goal directed fluid therapy, intraoperative use of exparel ™ for pain control, early resumption of diet, minimal use of narcotics, and early mobilization [94].

Conclusion

In appropriately selected patients orthotopic bladder substitution constructed from optimal length with meticulous technique is a urinary diversion option approximating physiologic voiding. The surgeon should be vigilant to monitor, evaluate, and manage postoperative voiding symptoms, bowel function, metabolic abnormalities, upper tract function, and quality-of-life issues.

Acknowledgment Naif A. Aldhaam, Hannah B. Ely.

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Neoadjuvant Chemotherapy

20

Brandon Bernard and Thomas W. Flaig

Introduction

Neoadjuvant cisplatin-based chemotherapy (NAC) followed by radical cystectomy is a recommended standard of care for muscle-invasive urothelial carcinoma (UC). The rationale for NAC includes early treatment of micrometastatic disease, with a higher compliance and successful administration than in the adjuvant setting, and an opportunity to study the in vivo response and gain a greater understanding of the biology of any given cancer. Disadvantages of NAC are that it relies on clinical stage alone and that treatment-related delays or progression during NAC may impact definitive and curative treatment (radical cystectomy).

Data in support of this approach include a clinical trial of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) for three 28-day cycles followed by radical cystectomy compared to radical cystectomy alone [1]. In this investigation, patients who received neoadjuvant MVAC showed a strong trend toward improved median OS (77 versus 46 months; $p = 0.06$), a reduction in risk of bladder cancer–specific death, and achieved a nearly 40% pathologic complete response (pCR). Additionally, roughly 85% of those with a pCR were alive at 5 years, compared to roughly 40–45% of patients that did not achieve a pCR. Another phase III trial compared 3 cycles of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) versus definitive local therapy alone [2]; this trial demonstrated a roughly 15% reduction in rate of death with neoadjuvant CMV at median follow-up of 8 years and an improvement in absolute OS of 6% at 10 years. Pathologic CR rate was similar as that seen with MVAC (33%) [3]. A 2003 meta-analysis confirmed the benefit of multi-agent NAC, demonstrating a 5% improvement in absolute OS and 7% improvement in disease-free survival [4].

Alternatives to MVAC include gemcitabine plus cisplatin (GC) for 4 cycles or dose-dense (dd) MVAC for 3–4 cycles. The use of GC in this setting was extrapolated from evaluation in the metastatic setting in which oncologic outcomes appeared similar compared to MVAC while those that received GC experienced less toxicity [5]. More recently, ddMVAC with growth factor support has emerged as an option for NAC, with trials in the metastatic setting showing a decreased risk of progression or death compared to conventionally dosed MVAC and with less toxicity [6, 7]; moreover, single-arm studies of neoadjuvant ddMVAC for localized UC have shown a significant association between pCR rate and risk of relapse or death [8, 9]. Furthermore, a

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cross-sectional analysis found neoadjuvant ddMVAC to be associated with a significantly higher degree of pCR compared to those that received GC [10].

There are currently no prospective, randomized data comparing neoadjuvant ddMVAC to GC or standard dose MVAC; however, results from the S1314 clinical trial (A Randomized Phase II Study of Co-Expression Extrapolation [COXEN] with Neoadjuvant Chemotherapy; ClinicalTrials.gov Identifier: NCT02177695), among others, will provide some initial insights into these regimens and provide information on the utility of predictive biomarkers to identify such patients. Lastly, other studies have explored the use of neoadjuvant immunotherapy, with early evidence suggesting a potential role for this strategy [11]. Additional prospective studies are required to define the role immunotherapy in the perioperative management of muscle-invasive UC.

Indications

As mentioned, NAC is the standard of care for localized, muscle-invasive UC (≥cT2), which is technically resectable (≤T4a). Staging requires muscularis propria (MP) sampling in the TURBT specimen to determine the T stage; thus, if no MP is in the sample or pT1 is found when clinical suspicion of muscle-invasive disease is high, strong consideration should be given to obtain a repeat TURBT for confirmation of stage. Definitive pathologic assessment, given the implications for treatment, is critical, with expert review/second review recommended if any uncertainty.

Next, for those diagnosed with localized disease cT2-T4a, the clinician must determine patient eligibility for receipt of NAC. Generally, contraindications to cisplatin-based chemotherapy include: performance status (Eastern Cooperative Group (ECOG) ≥ 2); renal function (CrCl <60 ml/min); hearing loss (≥ grade 2 as per Common Terminology Criteria for Adverse Events (CTCAE) version 4); peripheral neuropathy (≥ grade 2); and New York Heart Association (NYHA) class III heart failure (defined as: marked limitation of physical activity; comfortable at rest; less than ordinary activity causes fatigue, palpitation, or dyspnea) [12, 13]. In those with one or more of these conditions which is irreversible, it is often best to proceed directly to surgery without NAC and consider clinical trials for those with high risk of relapse based on pathologic staging at cystecomy. While level 1 evidence exists for the use of NAC in muscle-invasive UC, this applies to those eligible to receive cisplatin-based therapy, without substitution of other agents such as carboplatin. Ultimately, patients with comorbidities that make them borderline for NAC consideration, an in-depth discussion of the potential risks and benefits is needed, and shared decision-making utilized with respect to a final recommendation on neoadjuvant treatment. Hopefully, new predictive biomarkers may allow for a more personalized approach, clarifying which patients are most likely to benefit from NAC, while sparing those unlikely to respond from the toxicity of NAC and delay for surgery. Lastly, it should be mentioned that advanced numerical age should not be an absolute contraindication to NAC; rather, a combination of age, co-morbidities, performance status, and general fitness for NAC should all factor into the assessment.

Patient Preparation

Following the determination that NAC is indicated based on disease- and patient-specific factors, it is important that the patient have recent staging to ensure localized disease. Based on current guidelines, a computed tomography (CT) or magnetic resonance imaging (MRI) urography of the abdomen and pelvis, along with a chest imaging (CT or x-ray), is required [14]. Additionally, for those with signs or symptoms of bone metastases, a bone scan should be performed. While not necessary, a fludeoxyglucose-positron emission tomography (FDG-PET)/CT may help differentiate those cases where conventional imaging is equivocal and there is concern for

distant metastatic disease. In addition, for those that experienced a delay between TURBT and medical oncology assessment, a repeat TURBT is often beneficial to ensure the tumor is sufficiently de-bulked; it is surmised that a more minimal tumor burden may allow for greater chemotherapy penetrance and thus have a higher likelihood of pathologic downstaging at the time of cystectomy. As a general rule, a repeat TURBT should be considered before starting NAC if the procedure will be ≥8 weeks from chemotherapy start. Furthermore, if renal function is impacted by tumor-induced obstructive uropathy, a ureteric stent or percutaneous nephrostomy tube should be placed to assess for renal recovery and potential candidacy for cisplatin. Lastly, for patients that are to receive MVAC, a baseline cardiac function assessment should be obtained to document baseline left ventricular ejection fraction (LVEF); knowledge of an impaired LVEF would make GC a preferred choice.

Other practical considerations include placement of central venous access for those receiving MVAC, given the higher volume of intravenously administered drugs with this regimen, and due to the vesicant nature of doxorubicin and vinblastine with risk of extensive soft tissue damage should extravasation occur. Furthermore, in those centers with access to clinical pharmacists and/or dedicated nursing staff, it is beneficial for patients to receive formal chemotherapy teaching prior to receiving the first cycle. Lastly, ensuring patients are counseled on the optimal approach for antiemetics during chemotherapy is imperative to ensure optimal management of nausea and vomiting and thus minimizing the risk of worsening renal function through decreased intake of fluids.

Selection of Agent

As indicated, there is no clear evidence for the superiority of GC over ddMVAC in this setting and both remain reasonable options. While data suggest that ddMVAC may be superior to other regimens in terms of clinical outcomes and tolerability, at present both regimens are acceptable as NAC. Gemcitabine plus cisplatin may be given in either 4- or 3-week cycles; in practice, many providers utilize 4 cycles of GC given every 21 days given the tolerance of this dosing schedule and the ability to receive surgery more quickly [15]. It must be stressed that no studies have shown carboplatin to be non-inferior to cisplatin-containing NAC regimens; moreover, data suggest reduced efficacy of this agent in the metastatic setting [16]. Thus, carboplatin should not be substituted in the NAC setting if a patient is deemed cisplatin-ineligible. If cisplatin is contraindicated, the patient should proceed directly to radical cystectomy, or consider a clinical trial. Should renal impairment, hearing loss, or neuropathy develop during NAC, one may consider dose-reducing the cisplatin versus foregoing subsequent cycles and proceeding straight to surgery. For those who develop modest worsening of kidney function in the midst of NAC, one may consider changing to split-dose cisplatin over days 1 and 2 instead of the standard dosing of cisplatin on 1 day (see below: Administration). Note that in those with more advanced heart failure (NYHA class ≥ III), NAC should be avoided entirely due to the need for intravenous fluid with all regimens (largely due to the inclusion of cisplatin) and risk for causing volume overload.

Administration

Once a regimen is selected, informed consent obtained, adequate organ function confirmed, chemotherapy teaching conducted, and central access addressed (as appropriate), NAC may start. While a cycle of GC may be given in 3- or 4-week intervals, many practitioners employ a 3-week cycle, for reasons mentioned previously. Here, both drugs are administered on day 1 and the gemcitabine alone on day 8 of each cycle. Dose-dense MVAC is administered every 2 weeks with granulocyte-colony stimulating factor (G-CSF) support given 24 hours after the last chemotherapy. In those with borderline renal function at baseline or with deterioration during NAC, cisplatin may be administered in a split dose approach, either on days 1 and 2 or 1 and 8; however, it is unknown if

efficacy is compromised with this approach. Significant volumes of intravenous fluids are typically administered before and after cisplatin to ensure optimal hydration and for renal protection. Anti-emetics, both as same day premedication and as schedule take-home medication, are given with each cycle as supportive care. With NAC, the aim is for completion of 4 cycles of GC or 4 cycles of ddMVAC prior to radical cystectomy. Generally, surgery should be planned for 3–6 weeks after the completion of NAC, based on a patient's hematologic and clinical recovery. Examples of NAC regimens, including dosing and supportive care, are shown in Table 20.1.

Management of Side Effects

Common and rare but serious side effects seen with NAC drugs and their treatment options are presented in Table 20.2. Patients should be counseled on the risk of these side effects during the informed consent process. Additionally, common and general side effects with either regimen include fatigue, nausea and vomiting, cytopenias, rash, alopecia, anorexia, and the risk of febrile neutropenia; these should be described to all patients. Patients should be made aware that, should symptomatic anemia develop, a red blood cell transfusion may be recommended. Note that a complete list of all potential side effects from the drugs is extensive and it is suggested the reader consult the most recent FDA-approved package insert for the individual drugs if further information is desired.

Table 20.1 Examples of neoadjuvant chemotherapy regimens

NAC regimen	Dose & cycle interval	Supportive care
ddMVAC[a]	Methotrexate (30 mg/m^2 D1) Vinblastine (3 mg/m^2 D1) Doxorubicin (30 mg/m^2 D1) Cisplatin (70 mg/m^2 D1) 1 cycle = 14 days; 3–4 total cycles	Pre-hydration: 1 L NS over 1 hour Pre-medications: palonosetron 0.25 mg IV once; dexamethasone 10 mg IV once; fosaprepitant 150 mg IV once Post-hydration: 4 g $MgSO_4$, KCL 20 mEq in 1 L NS over 1 hour Pegfilgrastim 6 mg SC (D2)
GC	Gemcitabine (1000 mg/m^2 D1, 8) Cisplatin (70 mg/m^2 D1) 1 cycle = 21 days; 4 total cycles	Pre-hydration: 1 L NS over 1 hour (D1) Pre-medications: palonosetron 0.25 mg IV once (D1); dexamethasone 10 mg IV once (D1, 8); fosaprepitant 150 mg IV once (D1) Post-hydration: 4 g $MgSO_4$, KCL 20 mEq in 1 L NS over 1 hour (D1)

[a]Note: an alternative dosing schedule, with chemotherapy split over 2 consecutive days per cycle, is used by some based on the original clinical trial design [7]

There are no restrictions with regard to diet, work, and exercise, and generally patients should be encouraged to continue to participate in their normal routine/activities if they feel well enough to do so. That said, taking precautions when patients are at greatest risk for neutropenic fever (between days 7 and 12 following NAC) is prudent, and it is suggested patients apply a commonsense approach to reduce their risk (including avoiding crowds, known sick contacts, and maintaining good hand hygiene). It should be noted, however, that most cases of neutropenic fever are secondary to a patient's endogenous bacteria, while the majority of pathogens are never identified and patients recover with empiric antimicrobial treatment. All patients should have a thermometer at home and be aware to seek emergent medical assessment should they develop a fever of ≥100.4 °F (38 °C), shaking chills or similar, while on therapy.

Currently, the improvement in supportive care drugs – anti-emetics and G-CSF, specifically – allows for most patients to manage acute toxicities and complete the desired 4 cycles. It is important to recognize that cisplatin is classified as having high emetogenic potential by both the NCCN and the American Society of Clinical Oncology; therefore, ensuring adequate "as needed" and scheduled drugs to prevent both acute and delayed emesis, including an neurokinin-1 receptor antagonist (NK-1RA), serotonin receptor antagonist (5-HT3 RA), and steroids, is critical [17, 18]. Additionally, ensuring patients have adequate breakthrough anti-emetics (e.g.,

Table 20.2 Side effects of interest with neoadjuvant chemotherapy and potential remedies

Drug	Specific toxicities	Prevention/treatment
Methotrexate	Mucositis	Baking soda rinse; mouthwash (may contain local anesthetic, antihistamine, steroid, antacid, and/or antifungal)
	Acute kidney injury	Hydration; urine alkalinization
	Cellular toxicity	Leucovorin rescue (for overdose)
	Hepatotoxicity	Supportive care
Vinblastine	Peripheral neuropathy	Dose-reduction; gabapentin/pregabalin; capsaicin cream
	Constipation	Sennosides; stool softeners
	Diarrhea	Hydration; anti-diarrheal agents
	Headache	Non-opioid analgesics
	Extravasation	Use of central line; heat/antidote
Doxorubicin	Cardiotoxicity	Baseline echocardiogram
	Extravasation	Use of central line; heat/antidote
Cisplatin	Nephrotoxicity	Hydration; avoid other nephrotoxic drugs; consider split-dose if GFR borderline
	Ototoxicity	Supportive care; hearing aids if indicated
	Peripheral neuropathy	Dose-reduction; gabapentin/pregabalin; capsaicin cream
Gemcitabine	Thrombocytopenia	Dose-reduction/delay
	Flu-like syndrome	Supportive care
	Rash (48–72 hours post-infusion)	Supportive care
	Pneumonitis	Discontinue drug; supportive care; glucocorticoids

It should be noted that this table is not exhaustive and that the reader should consult the current FDA-approved package insert for each individual drug for further details

metoclopramide or prochlorperazine) is required; olanzapine 10 mg orally nightly may also be used.

The standard use of G-CSF with ddMVAC (and selective use in those receiving GC at high risk for febrile neutropenia) has reduced the incidence of fevers, infections, hospital admissions, and any resulting complications; it also allows for a greater likelihood of being able to stay on schedule and complete treatment in a timely fashion and thus proceed to cystectomy more quickly. Should any regimen cause serious adverse events, or a delay in the next cycle of chemotherapy, dose-reduction should be considered, given the peri-operative nature of NAC with surgery remaining the most important and curative component of treatment.

Oncologic Monitoring

Depending on the regimen used, oncologic monitoring may be utilized during NAC to identify progression during treatment. In those receiving GC, cystoscopy and imaging between cycles 2 and 3 is performed by some providers, but there is no rigorous data to support this as a standard approach in all patients. In those patients with progression, NAC should be abandoned and the patient should proceed with cystectomy as long as staging indicates localized and resectable disease; those with stable disease or evidence of response should complete the remaining 2 cycles of chemotherapy. If ddMVAC is used, it is often not feasible or clinically useful to perform mid-treatment evaluations, as the entire treatment course is complete within 6 weeks. For both regimens, re-staging with imaging of the chest, abdomen, and pelvis should be performed preoperatively to confirm the absence of progression to metastatic disease.

Following surgery, all patients should enter into a surveillance program as per current NCCN guidelines to monitor for recurrence, with upper tract, abdominopelvic, and chest imaging every 3–6 months for 2 years, then yearly abdominopelvic imaging until 5 years post-cystectomy [17].

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21 Adjuvant Chemotherapy in Bladder Cancer

Walter M. Stadler and Brian L. Heiss

Indications

There is an approximately 50–65% overall survival at 5 years for all patients with muscle-invasive bladder cancer who undergo radical cystectomy alone [1, 2]. Patients with organ-confined, lymph node negative tumors have a 5-year survival of 60–75%, but 5-year survival drops to 45–50% when the tumor is non-organ confined with negative lymph nodes [1, 2]. When there is lymph node involvement, 5-year survival drops to ~30% [1, 2]. In order to improve on these numbers, chemotherapy regimens have been added perioperatively. Neoadjuvant chemotherapy has been shown to have an overall survival benefit, and its use is supported by level I evidence as described in the prior chapter. The benefit of adjuvant chemotherapy after cystectomy is not definitively settled and lacks level I evidence. Despite the lack of high-quality evidence, there is lower tier evidence supporting the recommendation for adjuvant chemotherapy for bladder cancer in select situations.

The potential advantages of adjuvant versus neoadjuvant chemotherapy include timely treatment of the primary, especially for patients who are unlikely to benefit from systemic therapy, and better pathologic staging information for patient selection. Although the former is a common concern for patients and clinicians, the level 1 data demonstrating a survival advantage with neoadjuvant chemotherapy demonstrates that this is not a relevant concern on a population level. This does not preclude the potential for an adverse impact in specific sub-populations of patients who do not benefit from the systemic therapy. Unfortunately, there are no validated biomarkers available to select patients most likely to respond. Chemotherapy after surgery does allow for a pathologic confirmation of the extent of disease. Imaging can underestimate the disease stage and in a retrospective analysis of over 700 patients, 36% of patients with T staging of organ-confined disease had non-organ-confined disease at the time of surgery [3]. Under the reasonable presumption that the relative benefit of systemic therapy is equivalent across various risk groups, the absolute survival benefit will be greatest in patients at highest risk for recurrence. The enhanced pathologic information thus allows for selection of patients who are at highest risk for recurrence and thus have the potential for the greatest benefit.

There are, nonetheless, several disadvantages to adjuvant therapy related to the challenges of a major surgery. About 30% of patients have severe complications and delayed recovery following cystectomy that preclude them receiving adjuvant chemotherapy [4]. Even if there are no

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absolute clinical contraindications to administering adjuvant therapy, the low accrual in multiple adjuvant trials as discussed below suggests that patients are reluctant to pursue this therapy in the context of the often prolonged and challenging recovery from cystectomy. Clinical development of novel adjuvant therapies is also challenged in terms of intermediate response endpoints. The effectiveness of neoadjuvant therapy can be assessed by pathologic responses in the cystectomy specimen, whereas adjuvant chemotherapy's effectiveness can only be assessed by time to tumor recurrence for the patient.

Despite these challenges, several trials have attempted to address the value of adjuvant chemotherapy (Table 21.1). Although none of the trials provide a definitive answer, several meta-analyses have attempted to address the value of adjuvant chemotherapy in bladder cancer. A Cochrane meta-analysis in 2006 is perhaps the most comprehensive. Despite combining data from multiple trials, the overall number of patients and events was still small. This analysis showed that the overall hazard ratio (HR) for all of the six included trials was 0.75 (90% confidence interval [CI] 0.60–0.96, $p = 0.019$) [5]. The absolute improvement in survival from all trials was 9% (95% 1–16%) at 3 years [5]. Trials that used a cisplatin-based chemotherapy regimen had an improvement to 11% (95% CI 3–18%) [5]. The authors concluded that with this evidence they could not make a definitive comment on the true effect of adjuvant therapy as the trials where limited in terms of low patient and event numbers. A later meta-analysis published in 2014 by Leow at el. pooled 945 patients from 9 RCTs and found that for overall survival, the pooled HR across nine trials was 0.77 (95% CI, 0.59–0.99; $p = 0.049$) [6]. This analysis provided further evidence for an overall survival benefit with adjuvant chemotherapy but is also not considered to be definitive.

The most recent prospective trial addressing the value of adjuvant chemotherapy is EORTC Intergroup trial 30994, which randomized patients to 4 cycles of adjuvant chemotherapy (either MVAC or gemcitabine/cisplatin) or to observation [14]. The investigators intended to recruit 680 patients but had to stop accrual early after only 284 patients. The trial did not show a statistically significant impact on survival, but the results were consistent with the aforementioned meta-analyses. The authors also performed an updated meta-analysis of the previous trials and added in their trial; this analysis also suggests an overall survival advantage of chemotherapy with a HR of 0.77 (CI 0.65–0.91, $p = 0.002$) [14]. The result was also similar to the Leow et al. meta-analysis.

Despite a lack of level I evidence, the aggregate of weaker evidence for adjuvant chemotherapy after cystectomy has led to its recommendation by the European Association of Urology (EAU) and the American Society of Clinical Oncologists (ASCO) in patients with pT3/T4 and/or pN+ M0 muscle-invasive bladder cancer [15, 16]. The National Comprehensive Cancer Network (NCCN) guidelines suggest giving adjuvant chemotherapy to patients with high-risk pathology who have not received neoadjuvant chemotherapy and is considered a 2a recommendation [17]. These guidelines specifically recommend using a cisplatin-based regimen.

As noted earlier, it has been difficult to accrue patients for adjuvant chemotherapy trials, largely due to the known toxicities of cisplatin-based therapies, but it appears that ongoing immunotherapy trials, for which toxicity is likely less, may not have this disadvantage. Depending on the results of those trials, the treatment recommendations for the adjuvant setting may change within the next few years.

Patient Preparation

With adjuvant chemotherapy, patients need to be selected carefully as the regimens are intensive and can be challenging for patients just after surgery, especially since cisplatin-based therapy is recommended. For patients to receive methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC), they should meet the following criteria: medically fit, ECOG <2 or Karnofsky performance status >70%, CrCl ≥60 ml/min, no evidence of hearing loss, peripheral neuropathy

Table 21.1 Selected adjuvant chemotherapy trials in bladder cancer

	Patients (ITT)	Adjuvant chemotherapy regimen	Duration of adjuvant chemotherapy	Recurrence (observation vs treatment)	Overall survival (observation vs treatment)	Notes
Skinner et al. (1991) [7]	102	Cyclophosphamide 600 mg/m^2 Doxorubicin 60 mg/m^2 Cisplatin 100 mg/m^2	Four 28-day cycles	3-year DFS 46% vs 70%.	Median OS 2.4 vs 4.3 years ($p = 0.0062$).	Stopped early because a planned analysis after 75 patients showed a benefit to the control arm ($p = 0.05$) and the decision was made to continue the trial for only 2 more years.
Studer et al. (1994) [8]	91	Cisplatin 90 mg/m^2	Three 28-day cycles	–	5-year OS 54% vs 57% ($p = 0.65$).	Stopped early because of poor accrual and an interim analysis showed the difference was smaller than expected.
Freiha et al. (1996) [9]	55	MTX 30 mg/m^2 Vinblastine 4 mg/m^2 Cisplatin 100 mg/m^2	Four 21-day cycles	No recurrence in 25% vs 48% Median PFS 12 vs 37 months ($p = 0.01$)	Median OS 36 vs 63 months ($p = 0.32$).	Stopped early because control arm performed better than anticipated.
Lehmann et al. (2005) [10]	49	MVAC or MVEC	Three 21-day cycles	PFS 13.0% vs 43.7% ($p = 0.002$)	Median OS 20.4 vs 35.1 months. 10-year OS 17.4% vs 26.9% ($p = 0.069$).	The trial intended to accrue 100 patients but was stopped after an interim analysis showed a marked difference in progression free-survival for the first 49 randomized patients.
Paz-Ares et al. (2010) [11]	142	Paclitaxel 80 mg/m^2 Gemcitabine 1000 mg/m^2 Cisplatin 70 mg/m^2	Four 21-day cycles	3-year recurrence rate 44% vs 73% ($p < 0.0001$)	Median OS 26 months vs not reached. 5-year OS 31% vs 60% ($p < 0.0009$).	Prematurely closed due to poor accrual.
Stadler et al. (2011) [12]	114	MVAC	Three 21-day cycles	5-year recurrence rate 20% in both arms (p-0.62)	5-year OS 85% in both arms.	Stopped early because an interim analysis of the first 110 patients demonstrated futility.
Cognetti et al. (2012) [13]	194	Gemcitabine 1000 mg/m^2 Cisplatin 70 mg/m^2	Four 28-day cycles	DFS 42.3% vs 37.2% ($p = 0.70$)	5-year OS 48.5% in both arms ($p = 0.24$).	Prematurely closed due to poor accrual and an interim analysis showing inadequacy of chemotherapy.
Sternberg et al. (2015) [14]	284	MVAC or gemcitabine plus cisplatin	Four cycles	PFS 31.8% vs 47.6% ($p < 0.0001$)	Median OS 6.7 vs 4.6 years. 5-year OS 53.6% vs 47.7% ($p = 0.13$).	Prematurely closed due to poor accrual.

≤1, and absence of congestive heart failure [15, 18]. In patients with a CrCl of 40–60 ml/min, it is also possible to use split-dose cisplatin where cisplatin 35 mg/m^2 is given on either days 1 and 2 or days 1 and 8. The other regimen that can be used is gemcitabine/cisplatin, which tends to be more easily tolerated than MVAC. Gemcitabine/cisplatin is reviewed in the next section.

If the adjuvant immune checkpoint inhibitor trials demonstrate benefit, there will clearly be a change in selection criteria for adjuvant therapy given the lower side effect profile of immune checkpoint inhibitors, although the rare life-threatening toxicities and frequent need for steroids to ameliorate toxicity will need to be considered. This will likely lead to the inclusion of more patients in adjuvant therapy compared to the number of patients that can be offered the currently recommended traditional chemotherapy. If immune checkpoint inhibitors are approved for adjuvant therapy, the predominant exclusion criteria will likely be preexisting autoimmune conditions.

Selection of Agent

The current recommendation for chemotherapeutic agents to be used in the adjuvant setting are methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin as the MVAC regimen. The other regimen that can be considered in selected patients is gemcitabine/cisplatin. MVAC and gemcitabine/cisplatin have similar efficacy in the metastatic setting as well as in the neoadjuvant setting, [19, 20]. Given that cisplatin requires adequate renal function that may be lacking in some patients, it is tempting to switch to carboplatin. But, it has been shown that chemotherapy regimens containing carboplatin are not as active as those containing cisplatin in the metastatic setting, and the recommendation is to use cisplatin and forego adjuvant therapy if there is a clinical contraindication to cisplatin [21].

With the approval of five immune checkpoint inhibitors for bladder cancer in the metastatic setting, there is great interest in exploring the effectiveness of these agents in the neoadjuvant and adjuvant settings. In the adjuvant setting, there are currently three ongoing multicenter, randomized phase III trials comparing a year of either an anti-PD1 or anti-PD-L1 agent against observation that should have results in the near future. These trials include the AMBASSADOR trial of pembrolizumab (NCT03244384), the IMvigor 010 trial of atezolizumab (NCT02450331), and the CheckMate 274 trial of nivolumab (NCT02632409). Obviously, if any of these does demonstrate an advantage, the relevant question will become whether it is more effective than cisplatin-based therapy in those patients who could tolerate it.

Administration

The MVAC regimen can be given as originally described or in a dose dense manner. The dose-dense regimen consists of methotrexate (30 mg/m^2 on day 1), vinblastine (3 mg/m^2 on day 2), doxorubicin (30 mg/m^2 on day 2), cisplatin (70 mg/m^2 on day 2), and filgrastim (240 mcg/m^2 subcutaneously on days 4–10). The regimen is repeated every 14 days and if toxicity permits, for 4 cycles. The gemcitabine/cisplatin regimen is given as follows: gemcitabine (1000 mg/m^2 on days 1, 8, 15) plus cisplatin (70 mg/m^2 on day 2), repeated every 28 days for 4 cycles, although a dose-dense regimen has also been described.

Management of Side Effects

Besides the standard management of chemotherapeutic side effects expected from these drugs such as nausea, vomiting, acute kidney injury, and myelosuppression, the urinary diversion created during the radical cystectomy needs to be kept in mind. The common urinary diversions created after radical cystectomy are the ileal conduit, continent ostomy (Indiana pouch), and the orthotopic neobladder. The ileal conduit is continuously draining urine to a pouch on the external abdominal wall. The continent ostomy is a

reservoir for urine constructed out of ascending colon and a small portion of ileum that is connected to the external abdominal wall that requires periodic catheterization to remove the urine. The orthotopic neobladder is constructed of ileum connected to the native urethra, and it requires emptying with periodic abdominal straining. The neobladder is not always fully emptied completely, which can lead to an increase in infection risk. Adjuvant chemotherapy in this situation would seem to be more prone to side effects related to infections, but a retrospective analysis, although small, showed that there is no higher incidence of risks between the ileal conduit group versus the neobladder group [22]. That being said, it is important for patients with neobladders to be mindful of trying to empty their bladders as much as possible and stay alert for any clinical signs of infection.

Oncologic Monitoring

For the first 2 years post cystectomy, NCCN recommends obtaining urine cytology every 6–12 months [17]. Urethral wash cytology every 6–12 months can be considered in patients with high-risk disease, which is defined as having a positive urethral margin, multifocal CIS, or prostatic urethral invasion. After 2 years, urine cytology and/or urethral wash cytology can be obtained as clinically indicated. Urine cytology can be difficult to interpret as the specificity is high at 94% but the sensitivity is low at 48% [23].

In terms of recommendations for laboratory testing, for the 1st year, renal function testing (electrolytes and creatinine), CBC, CMP, and LFTs should be evaluated every 3–6 months [17]. Monitoring renal function is especially important after adjuvant therapy with cisplatin. After the first year, renal function testing (electrolytes and creatinine), LFTs, and vitamin B12 should be checked annually until the patient is 5 years out. After 5 years, the recommendation is to check vitamin B12 annually. Vitamin B12 deficiency can be a complication arising from the ileal resection used for construction of the neobladder.

Defining and Evaluating Recurrence

In post-cystectomy muscle-invasive bladder cancer after adjuvant chemotherapy, the NCCN recommends a CT urogram or MR urogram to image the upper urinary tracts and obtain axial imaging of the abdomen and pelvis every 3–6 months for the first 2 years as well as a chest x-ray or CT chest every 3–6 months [17]. Alternatively, if metastatic disease is suspected, a PET/CT can be obtained but this is a category 2B recommendation. After the first 2 years, it is recommended to obtain an abdominal and pelvic CT or MRI with a chest X-ray or CT chest annually (or a PET/CT, again a category 2B recommendation, only if metastatic disease is suspected). Annual imaging starting after 2 years should be continued until the patient is 5 years out from cystectomy. For the span of 5–10 years out, a renal ultrasound should be obtained annually to evaluate for hydronephrosis. For patients at greater than 10 years out from cystectomy, imaging should be done as clinically indicated.

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Trimodal Therapy

22

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Indications for Trimodality Treatment

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Introduction

Trimodality treatment (TMT) of muscle-invasive bladder cancer (MIBC) comprises transurethral resection of the bladder tumour (TURBT) followed by radical radiotherapy (RT) with a concurrent radiosensitising agent. TMT followed by close surveillance for recurrence within the native bladder is an alternative strategy to upfront radical cystectomy (RC), allowing patients to preserve their native bladder. Both approaches can be preceded by neoadjuvant chemotherapy in fit patients. Historically RT was only employed in patients unfit for RC but, with improved radiotherapy techniques and the introduction of concurrent radiation sensitisers, more recent retrospective case series have shown equivalent results to RC cohorts [1–4].

Organ-sparing multimodality treatments, which reduce comorbidity without compromising cure, have an established role in breast, laryngeal and anal cancer. There is a growing consensus that for the patients with MIBC who wish to preserve their native bladder, TMT is an

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excellent option. Patient selection for TMT is key, giving patients the best chance of complete tumour response with low recurrence rates, in order to avoid salvage cystectomy.

Bladder cancer is predominantly a disease of elderly patients, a significant number of whom lack the physiological reserve to safely undergo major surgery and who may have multiple medical co-morbidities. In such patients, deciding their suitability for TMT rather than other treatments is a balance between choosing optimal treatment for cancer cure and tolerability.

The Case for TMT

In MIBC, RC with pelvic lymph node dissection has been considered the gold standard treatment for fit patients. However, around 50% of patients treated with RC develop metastatic disease within 2 years. The relative stasis in surgical outcomes compared to the advances in RT and radiation sensitisers has meant that bladder preservation has caught up in terms of efficacy. The SPARE trial, a UK randomised phase 3 trial of bladder preservation versus cystectomy, attempted to conclusively demonstrate non-inferiority of bladder preservation but was unable to effectively recruit patients for randomisation [5]. It is unlikely that randomised data will ever be obtained between the two modalities.

Comparison is therefore reliant on retrospective series, which are biased by patient selection (typically older patients in the trimodality cohort) and method of staging (histological staging available post-cystectomy whereas trimodality is radiologically staged alone). Various retrospective series have suggested an equivalence in treatments, for example, at a UK specialist centre [1] (Fig. 22.1). 5-year disease-specific survival for RC and RT (53.4% and 56.8%, respectively) showed no significant difference despite the RT cohort being significantly older (mean age 75 versus 68 years). This compared radiotherapy alone to RC, suggesting TMT may even be superior to RC.

A number of large published retrospective case series [1, 3, 4, 6] for patients receiving TMT

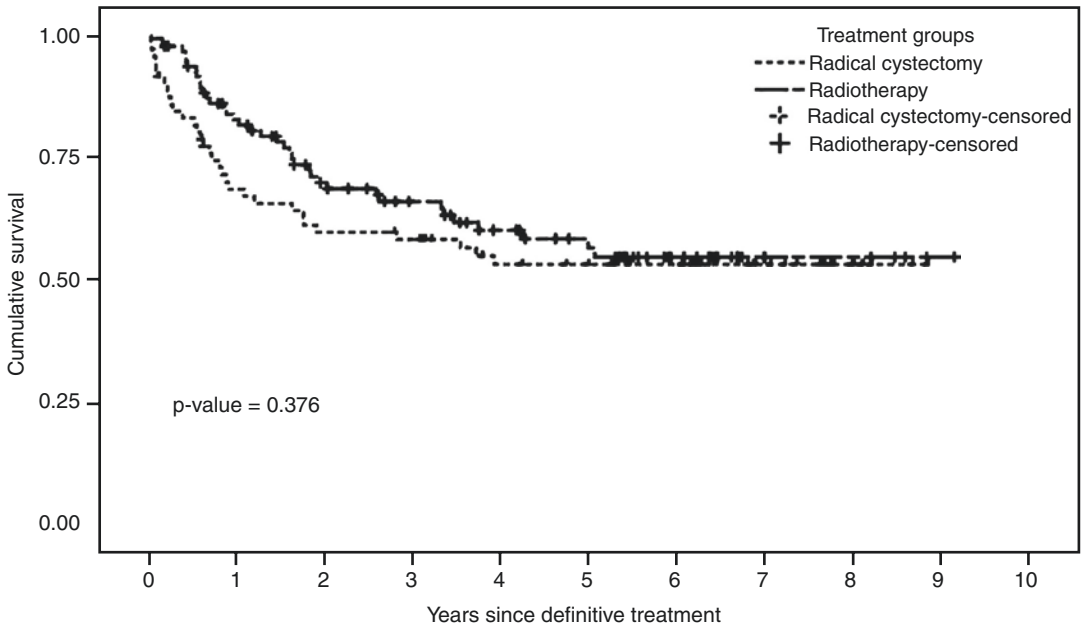

Fig. 22.1 No difference in disease-specific survival betwen radical radiotherapy and RC. Kaplan-meier cumulative survival curves for radical cystectomy and radical radiotherapy group, showing cause-specific deaths only, for 169 patients treated between 1996-2000 for MIBC at a large University teaching hospital in Leeds, UK. Five-year disease specific survival rates for the radical radiotherapy and radical cystectomy group were 56.8% and 53.4%, respectively. There was no statistically significally difference in CSS between the two treatment groups (log–rank test, p = 0.376). (Reprinted from Kotwal et al. [1]. Copyright (2008) with permission from Elsevier)

have reported outcomes equivalent to surgical series, such that it is now considered a reasonable option for patients fit enough for RC who choose to preserve their native bladder. UK guidelines from the National Institute for Health and Care Excellence (NICE) and others from the American Urological Association (AUA) and the National Comprehensive Cancer Network (NCCN) all recommend offering the choice of TMT to patients with MIBC who hope to retain their native bladder or are not fit for RC. [7–9]

Patients opting for treatment bladder preservation must agree to close surveillance after TMT.

Trials where first check cystoscopy was performed at around 6 months after TMT [10, 11] have shown high rates of complete response (CR) with residual disease in <20%. Earlier cystoscopy between induction and consolidation RT used in the RTOG trial protocols [3] resulted in lower rates of CR, with residual disease in 30%. Estimates of 5-year rates of muscle-invasive local recurrence requiring salvage cystectomy was around 10–15% [3]. Superficial recurrence can be managed with further TURBT or intravesicular BCG with 5-year rates of superficial local recurrence around 30% post TMT [3]. Amongst survivors at 5 years, around 80% will have an intact bladder following TMT [3].

Salvage cystectomy was historically considered to be a more difficult surgical operation than a primary radical cystectomy, with higher complication and mortality rates. However, in a large series of patients treated with cystectomy in Manchester between 1970 and 2005 [12], no significant difference was seen between radical cystectomy and a post-irradiation salvage cystectomy for 30-, 60- or 90-day mortality, early surgical complication rates or medical complications.

However, patients need to be aware that they cannot have an orthotopic neobladder with a salvage cystectomy.

Patient Selection for TMT

The patient-, tumour- and treatment-related factors which determine a patient's suitability for TMT are outlined in Table 22.1.

Patient Factors

Baseline Bladder Function

Good bladder function is a prerequisite for bladder-sparing treatment. If current bladder function is significantly impairing quality of life, TMT should be avoided.

Patients should be made aware that RT may reduce current bladder capacity, thus increasing symptoms of frequency and nocturia, but this is rare. The majority of patients manage well following RT (5.7% of patients with grade 3 or higher late genitourinary toxicity in a pooled analysis of RTOG trials [3]). Only very few patients require a cystectomy for poor post-RT bladder function.

TMT should be avoided in patients with a baseline bladder capacity of less than 100 ml, or if urinary frequency or nocturia is having a significant effect on quality of life.

Contraindications to Chemotherapy or RT

Most comorbidities such as severe cardiac, renal or liver disease which preclude chemotherapy (or RT) would also be barriers to RC. However, some conditions are specific contraindications to RT or chemotherapy. Long-term immunosuppression, e.g., after organ transplantion, chronic methotrexate use for autoimmune disease or in HIV, makes patients high risk for chemotherapy and would favour surgery. In the United States, the use of cisplatinum-based chemotherapy predominates and requires excellent renal function (EGFR >60 ml/min). In cases with inadequate renal function, alternative options include 5FU/MMC, gemcitabine or BCON (radiotherapy with concurrent radiation sensitisers carbogen and nicotinamide) [2, 10, 11].

The major contraindications for RT are inflammatory bowel disease where bowel sensitivity is dose-limiting, previous pelvic RT to radical doses and rare radiation hypersensitivity syndromes such as ataxia telangiectasia.

Patient Compliance

Choosing TMT requires patients to commit to long-term surveillance with imaging and cystoscopy to detect early recurrence.

Table 22.1 Factors influencing good candidates for TMT

	Good candidate for TMT	Poor candidate for TMT
Patient Factors		
Baseline Bladder Function	Good function	Poor function
	Volume > 200ml	
	No significant frequency or nocturia	
Contra-indications to RT	Nil	Inflammatory bowel disease
		Prior pelvic RT
		Radiation hypersensitivity syndromes (eg. ATM)
*Contraindications to chemotherapy**	Nil	Immunosuppression
		Impaired renal function (if platinum-based chemo)
Agrees to adhere to surveillance	Yes	No
Tumour Factors		T4b ‡
T stage	T2-T3	
	Consider T4a	
	High risk T1 in elderly	
Tumour Size	<5cm	>5cm ‡
Nodal disease	None	Present ‡
Associated Carcinoma in Situ	No	Yes
Tumour related hydronephrosis	No	Present - unilateral or bilateral ‡
Histological Type	Urothelial	Adenocarcinoma, Squamous cell, other
Treatment Factors		
Response to TURBT	Complete resection	Incomplete resection
Response to neoadjuvant chemotherapy	Good response	No response/progression ‡

*consider carbogen and nicotinamide (BCON)
‡Are poor prognostic markers regardless of treatment (RC or TMT). Not predictive markers for response to TMT

Tumour Factors

T Stage

TMT is recommended for T2-T4a disease, and also high-risk T1 disease in inoperable patients. Patients with T4b (invasion into pelvic side and or abdominal wall) have been excluded from major trials of TMTs. [2, 3, 10, 11]

Complete response rates fall with increasing tumour stage, so patients with T2/T3a tumours are better suited to TMT than T3b/T4a tumours which are at greater risk of local failure, although they can still be treated with TMT. The tumours greater than 5 cm is a poor prognostic feature so that some clinicians would favour RC on that basis [13].

Nodal Disease

The presence of nodal disease confers a worse prognosis, and these patients are recommended to undergo neoadjuvant chemotherapy followed by RC. The major trials using bladder sparing protocols, namely, BC2001, RTOG, BCON, [2, 3, 11] have excluded patients with nodal disease. Patients with nodal disease were included in the Erlangen series treated with bladder sparing treatment where complete response at 6-week cystoscopy was lower (53% CR rate) with nodal disease than in N0 patients (73% CR rate, $p = 0.3$) [14]. In N1 disease – given prognosis is poor regardless of treatment – optimum management is not clear and in practice TMT is often employed if patients express a strong preference.

Associated Widespread Carcinoma in Situ

The presence of carcinoma in situ is a poor prognostic factor for local recurrence of disease, so patients with widespread CIS are generally not considered for TMT as they may require BCG or salvage cystectomy.

Tumour-Related Hydronephrosis

Hydronephrosis, either unilateral or bilateral, related to bladder cancer, is a well-established marker of poor prognosis, including after RC [15]. In the RTOG 89–03 phase III trial comparing chemoRT +/− neoadjuvant MCV, the presence of hydronephrosis was associated with a significantly lower (38% to 64%, $p = 0.02$) complete response rate [16]. Most clinicians would therefore avoid TMT in this setting. However there is a lack of evidence that RC is a better treatment for these patients.

Histological Type

Trials of TMT have included exclusively or near exclusively urothelial bladder cancer. Therefore there is a lack of strong data to support TMT in rarer tumours, e.g. squamous cell carcinoma or adenocarcinoma.

Furthermore, the influence of the more recently described urothelial carcinoma (UC) variants, e.g. micropapillary, is also not clear. A retrospective series of 303 patients treated with TMT identified 66 patients with variants of UC (including 49 with squamous/glandular differentiation, 8 sarcomatoid, 3 micropapillary and 3 with neuroendocrine differentiation) and found no difference in disease-specific survival, overall survival or bladder-intact disease-specific survival between variant UC and pure UC. [17, 18] The study is limited by small numbers but certainly suggests patients with variant UC should not be excluded from TMT.

Treatment Factors

Transurethral Resection of Bladder Tumour (TURBT)

A visibly complete resection after TURBT is associated with a greater chance of success of subsequent TMT, with an odds ratio of 0.49 (95% CI 0.25–0.96, $p = 0.04$) [3]. However, those with an incomplete resection can still be considered. The BC2001 and BCON trials demonstrated goods outcomes despite 40% and 60% of patients, respectively, receiving no TURBT or incomplete resection at TURBT [2, 11].

Neoadjuvant Chemotherapy

Used before RC, cisplatin-based neoadjuvant chemotherapy has an established survival benefit of 5% at 5 years. In a meta-analysis the benefit from neoadjuvant chemotherapy was demonstrated to be independent of type of local treatment – radiotherapy or cystectomy [19], confirmed by the longer term results of the BA06 trial [20].

Inadequate response to initial neoadjuvant chemotherapy is a poor prognostic marker, and some clinicians would consider an immediate RC, though again there is a lack of evidence for RC as a better treatment in this group.

The Ideal TMT Candidate

In summary, the ideal TMT candidate would have good baseline bladder function, no contraindications to RT or chemotherapy and willing to adhere a programme of surveillance. They would have a T2-T3 tumour with no nodal disease, no hydronephrosis and no associated carcinoma in situ, and have had a good response to neoadjuvant chemotherapy and a complete resection on TURBT.

The presence of large or advanced disease, nodal disease, hydronephrosis or lack of response to neoadjuvant chemotherapy often leads to TMT being avoided in favour of RC. However these features are prognostic rather than predictive markers such that a case can be made for TMT despite them, in patients eager to retain their native bladder.

TMT in Patients Unfit for RC

Bladder cancer is predominantly a disease of the elderly with a median age of diagnosis at 73. The strong association between smoking and bladder cancer means patients are often also burdened with the cardiac and respiratory consequences of lifelong smoking. RC is a major surgery and tests the physiological reserve of the fittest patient. Ninety-day mortality rises significantly with increasing age, from 6.4% in patients aged 66–69 years to 14.8% in patients over 80 [21]. A

significant number of new MIBC diagnoses will therefore be assessed as unfit for RC. In these patients, TMT is the best available curative option.

The presence of patient, tumour or treatment factors (see Table 22.1) which reduce the likelihood of a complete response to TMT (e.g. hydronephrosis, carcinoma in situ, advanced T stage, incomplete TURBT) need to be interpreted differently in this setting. Without another curative treatment option, even a patient with factors suggesting a reasonably high risk of failure may be willing to undergo TMT and be able to tolerate the treatment. In fact a systematic review which compared outcomes in elderly and younger patients showed disease-specific survival worsening with age with RC but no difference in 5-year disease-specific survival in radiotherapy trials between those over and under 75 – supporting the use of TMT in this older cohort [22].

In frail patients with significant comorbidities, the decision may be made to compromise the chance of cure by avoiding chemotherapy or even reducing the irradiation dose in order to deliver a tolerable treatment. Getting the correct balance right between overly aggressive or excessively cautious treatment is challenging.

In MIBC patients >80 years old, Noon et al. [23] found the 5-year cancer-specific mortality was 59%, far higher than the 30.8% mortality from other causes. This implies an unmet need and under treatment of bladder cancer in this age group.

Patients not fit for cisplatin-based chemo are often not fit for RC either. A viable alternative is to receive either 5FU/Mitomycin C, weekly low-dose gemcitabine or concurrent carbogen and nicotinamide (BCON), which has demonstrated equivalent results to concurrent chemotherapy. An age-specific analysis compared patients over 75 receiving gemcitabine or BCON to younger patients [24]. As expected overall survival was worse in the older cohort; however, local progression-free survival and disease-specific survival were equivalent, demonstrating BCON and gemcitabine are effective well-tolerated treatments in this age cohort.

Furthermore, radical dose RT alone can still be curative for some patients. Kotwal et al. [1] demonstrated a 5-year overall survival of 34.6% and 5-year disease-specific survival of 56.8% in patients receiving radiotherapy alone. In the BC2001 trial, overall survival was 35% at 5 years in those receiving RT alone. [2]

In patients not fit for radical dose RT, palliative fractionation schedules should be considered, e.g. hypofractionated treatment with 21 Gy in 3 fraction on alternate days [25]. In Duchesne et al. [26], these patients had a 2-year overall survival of 19%, suggesting a lasting response in around one-fifth of patients even at these 'non-radical' doses.

A multi-disciplinary approach, alongside physiotherapists and dieticians, allows us to better optimise the patients in this cohort and identify those able to tolerate the more aggressive treatments.

Summary

Organ preservation through TMT for muscle-invasive bladder cancer has demonstrated its role as a valid first-line radical treatment in patients wishing to preserve their native bladder through numerous large retrospective series over the last 20 years. Patient, tumour and treatment factors associated with having a good response to TMT (Table 22.1) may assist clinicians in their recommendations to patients. Elderly patients unsuitable for RC need their suitability for TMT thoroughly assessed, with radiotherapy alone a viable alternative, and it is vital that stereotypes about age and comorbidities do not lead to under-treatment in this cohort.

Patient Preparation for Trimodal Therapy

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Initial Workup

All bladder cancer patients should be managed in a multidisciplinary setting.

Having taken a full history and performed a physical examination, baseline bloodwork should be sent to assess renal function status, as well as electrolytes and complete blood count, and careful consideration of comorbidity, performance status, and fitness for trimodality therapy (TMT).

All patients should have urine cytology sent and have bladder and upper tract imaging. In patients with hydronephrosis, ureteric stenting or nephrostomy should be considered if creatinine clearance is deranged, particularly if a platinum containing systemic therapy option is being considered, as well as baseline audiometry.

Maximal trans-urethral resection of bladder tumour (TURBT) should be performed prior to TMT. In order to identify the clinical stage and grade of disease, bladder muscle must be included in the pathology specimen. All visible tumours should be resected.

Patients with muscle-invasive disease should have local staging with a pelvic MRI or CT scan (with and without intravenous contrast and excretory imaging), as well as CT chest, abdomen and pelvis to assess for distant disease. Bone scan [27] should be performed if there is suspicion of bone metastases, such as pain or raised calcium or alkaline phosphatase.

Trimodality Bladder Preserving Strategy

There are no completed head-to-head randomised studies for radical cystectomy (RC) compared to TMT [28], but there are several series showing TMT has good results in carefully selected patients [29–31].

In order to be considered for TMT, patients must be accepting of long-term surveillance which includes surveillance cystoscopies which are three-monthly, then six-monthly after the second year, and then annually after 4–5 years.

Radiotherapy Preparation

Fiducial marker insertion may aid in identification of the tumour-bearing area within the bladder both for RT treatment planning and targeting, particularly in cases where there is little evidence of gross residual tumour after neoadjuvant chemotherapy and/or TURBT. Lipiodol, a radio-opaque contrast, that may be injected via direct cystoscopic guidance, has been used in this manner [32]. Typically, this may be more useful in parts of the bladder that are mobile and subject to volume change/deformation often above the bladder neck and trigone. When used, this should be injected around the tumour or previous TURBT scar. An alternative may be radio-opaque hydrogel, although performance of this material for this purpose was felt to be less ideal [33].

Patients should have a planning CT scan performed in the supine position with their arms on their chest with a comfortably full bladder if there is a desire to deliver maximal dose to the tumour-bearing areas within the bladder; otherwise, patients may have CT planning with an empty bladder. Tattoos (one anterior tattoo over the symphysis pubis and 2 lateral tattoos over the iliac crests) should be placed to aid patient set up at the time of treatment delivery. A maximum of 3 mm CT slice thickness should be used. Scan limits should include from at least the L2 vertebral body to below the ischial tuberosity/lesser trochanter.

Perioperative Chemotherapy – Concomitant Chemotherapy as Part of Bladder Preservation Therapy

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Introduction

There are a large number of trials showing that it is feasible and safe to add radio-sensitising agents to radiotherapy for bladder cancer. In the

main this has been based on agents used for the same purpose in other malignancies such as anal cancer [34] but in addition there are trials looking at radio-sensitisation strategies based on hypoxia modification. The rationale for these latter studies is that older hypoxia modification studies suggest a significant role for hypoxia in radio-resistance in a range of cancers including bladder cancer [35–37].

The field is further complicated by the emergence of different patterns of radiotherapy usage on either side of the Atlantic. In the United Kingdom, radiotherapy has historically been widely used for muscle-invasive bladder cancers, especially in older, less fit patients. In the main, treatment has been given as a single block, often with a degree of hypofractionation with schedules such as 52.5-55Gy in 20 fractions over 4 weeks being typical. Elsewhere, schedules based on 2Gy fractions became widely used with 64Gy in 32 fractions over 6.5 weeks being considered the standard of care. In North American centres, a different pattern of care emerged with bladder preservation being viewed as an alternative to radical cystectomy in younger, fitter patients with operable tumours. The North American pattern of care is based around an initial maximal trans-urethral resection of the bladder tumour (TURBT) followed by a block of around 4 weeks of radiotherapy to a dose of 40Gy in 20 fractions or equivalent. This is then followed by a further cystoscopy and if relevant tumour resection. Patients exhibiting a poor treatment response are then fast-tracked to cystectomy while the remainder proceed to a further block of radiotherapy to around 20–24 Gy in 2 Gy fractions or equivalent. This rather complicated model of care is summarised in Fig. 22.2 with the simpler UK pattern of care summarised in Fig. 22.3. It should in particular be noted that 'complete' TURBT is not a fixed part of the UK schedule and many patients in BC2001, for example, had only had a tumour biopsy [38]. The effect of including complete TURBT in case selection in North America is that higher stage patients are

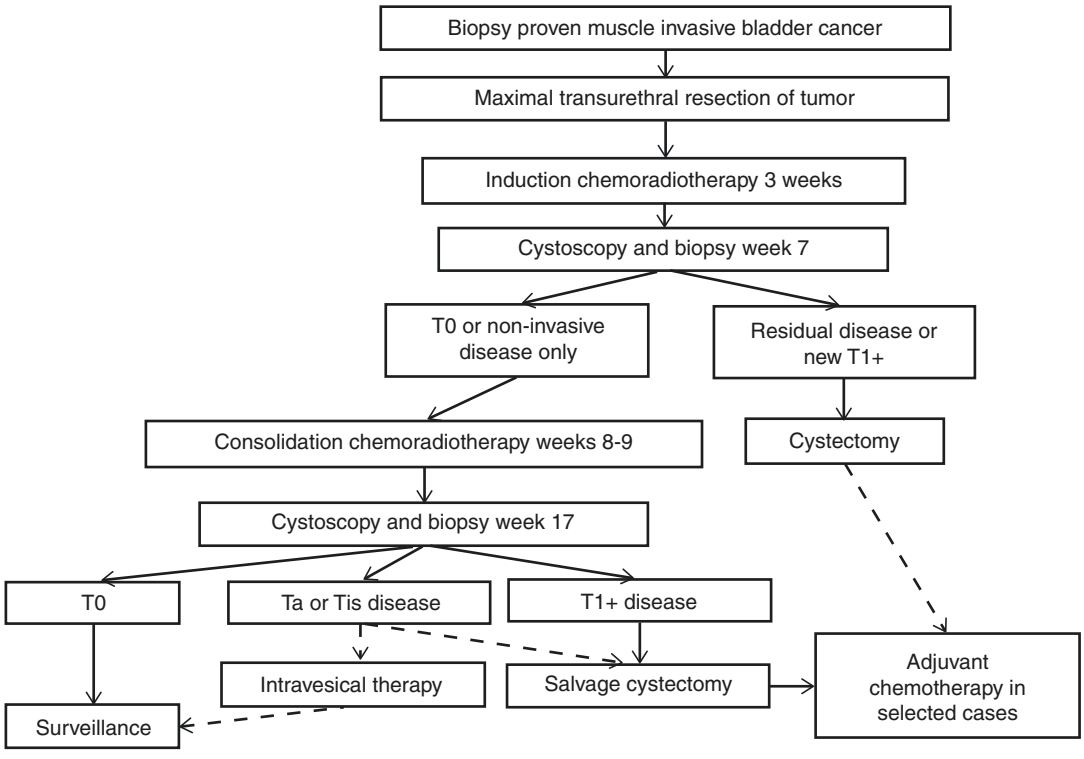

Fig. 22.2 Trimodality therapy

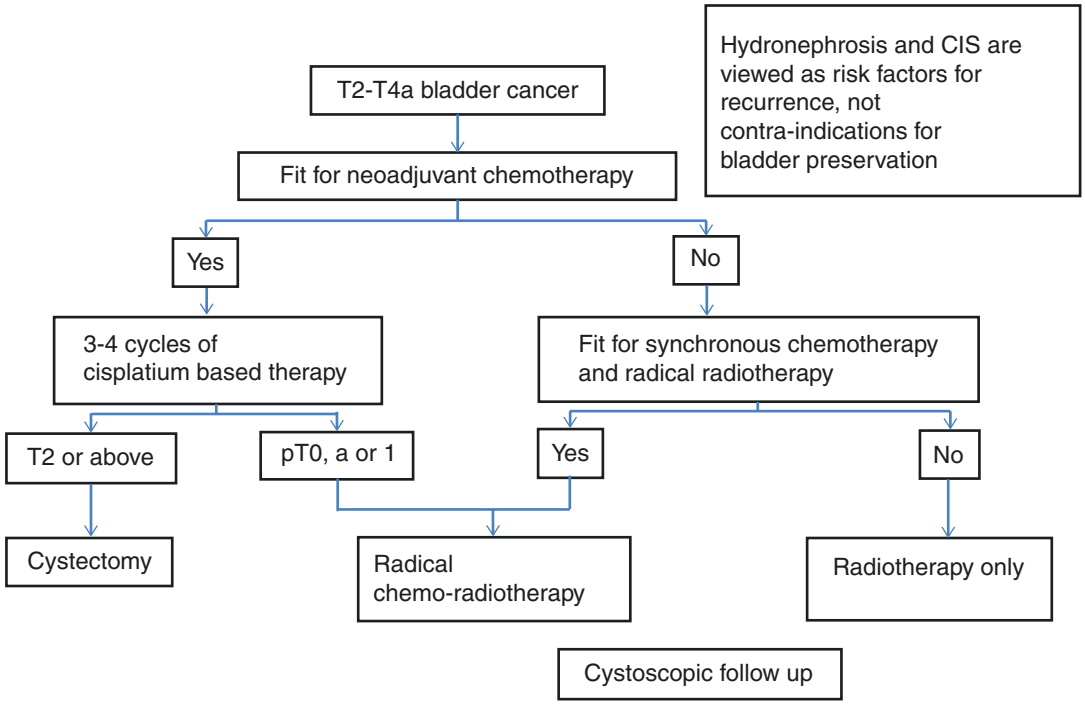

Fig. 22.3 UK radiotherapy practice

deliberately excluded from most chemoradiotherapy trials, in marked contrast to the UK-based studies. In practice, there are a range of ways to combine chemotherapy, radiotherapy and surgery as summarised in Fig. 22.4. All these combinations will be found in practice in proportions that show marked regional variations. There was (and remains) a strong surgical view that cystectomy is the standard of care and that bladder preservation should be viewed as experimental and these split dose schedules reflect in part the need to reassure surgeons that patients with radio-resistant tumours are not having definitive therapy deferred. The radiobiological rationale for this "split dose" approach is more questionable due to the risk of accelerated repopulation of tumour during the off-therapy interval. This surgical anxiety and reluctance to refer is reflected in the low rates of usage of radiation in North America under 10% of cases [39] compared to much higher rates of over 50% in the United Kingdom [40]. Interestingly, if one compares survival rates from registry series, the 5-year overall survival for muscle-invasive bladder cancer is remarkably similar between surgical and radiotherapy series [40, 41].

Due to the different underlying philosophy of treatment selection, the median age of UK radiotherapy patients is significantly higher than the cystectomy patients; for example, a registry-based series from Leeds reports a median of 75.3 years for radiotherapy vs. 68.2 for surgery [42]. In contrast, in studies such as the NCIC randomized trial of cisplatinum using split course North American trimodality therapy, the median age was 65 years [43]. In the more recent UK randomised studies comparing radiotherapy alone with radiotherapy plus 5-fluorouracil (5FU) and mitomycin C (MMC) [35, 44–48] or radiotherapy with hypoxia modification [36, 37, 49, 50], the median ages of subjects were 72–74 years, once again suggesting rather different patient selection criteria. This means comparisons of UK and North American outcomes with radiotherapy using fundamentally different irradiation protocols and very different case mixes are potentially as fraught as com-

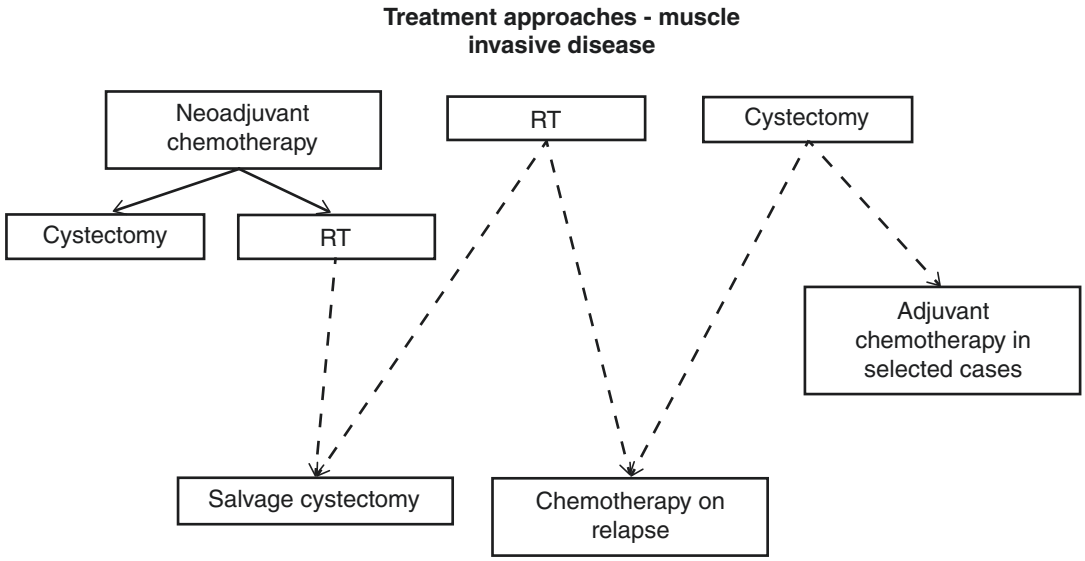

Fig. 22.4 Possible combinations of surgery, radiotherapy, and chemotherapy in bladder cancer care

parisons between radiotherapy and surgery with case mix being very hard to allow for. There are very few randomised comparisons within the bladder preservation literature. However, there are comparisons of both radio-sensitisers and radiotherapy schedules in the anal cancer literature, and these offer potential pointers to help define bladder cancer practice. The first of these relates to split course schedules with numerical dose escalation. In anal cancer, this does not appear to improve local control rates, but does increase toxicity (reviewed by Glynne-Jones et al. [51]). Schedules typically used in the United Kingdom are 55Gy in 20 fractions or 64Gy in 32 fractions as compared to 60Gy in 20 fractions or 74Gy in 37 fractions for prostate cancer where significant parts of the lower bladder will receive the full-prescribed dose. While whole organ tolerance doses for bladder with modern IMRT techniques are not known, it is clear from the prostate cancer literature that partial bladder doses well above those in standard use are well tolerated. Dose escalation in bladder cancer using modern IMRT/IGRT techniques combined with chemo-radiation is being tested in the UK RAIDER trial (ISRCTN: 26779187).

Choice of Agents

Cisplatinum

Cisplatin is an inorganic platinum agent (cis-diamminedichloroplatinum) that functions as an alkylating agent with antineoplastic activity. It forms highly reactive, charged, platinum complexes, which bind to nucleophilic groups (found on the guanine bases), inducing intrastrand and interstrand DNA cross-links. This promotes apoptosis and cell-growth inhibition. It is widely used as an anti-cancer chemotherapy agent alone and in combination. It forms the basis for many of the chemoradiotherapy schedules in use in bladder cancer. This may be traced back to the National Cancer Institute of Canada (NCIC) trial comparing split course radiotherapy with interim check cystoscopy with the same schedule combined with cisplatinum 100 mg/m^2 given 2-weekly × 3 during the initial 4 week block [43]. The trial showed no impact on distant metastatic spread but did show a substantial reduction in loco-regional failure (hazard ratio 0.5, 95% CI 0.29–0.86, $p = 0.036$). There are a number of issues with this study however. The first is the small sample size of 99 patients recruited at 11 Canadian centres over a 4-year period with a median age of 65 years

(range 43–75 years). This means the patients must have been highly selected and the upper age coincides with the median age at diagnosis in the United Kingdom and North America. Additionally, the very high cisplatinum dose would alone exclude at least 50% of patients in the UK practice on renal function grounds alone.

More recent North American schedules have stuck with cisplatinum, either alone or in combination, but at lower infused doses, reducing the toxicity and lowering the renal function threshold for participation. A range of combinations have been tested, with much of the work carried out via the group at Massachusetts General Hospital as summarised in Table 22.2 [52]. The relatively small numbers in each study and lack of large randomised series make the drawing of definitive conclusions difficult. The key features of the pooled data are the relatively young median age of 66 years compared to the median at diagnosis for bladder cancer of the mid-70s. Secondly, the low rates of high stage (T4 8.1%), hydronephrosis (16.7%) and high rates (66%) for complete resection at TURBT (a surrogate for low disease burden) mean that the series comprises relatively young patients with relatively favourable characteristics. With this in mind, the 5-, 10-, and 15-yr cumulative disease-specific survival rates of 64%, 59% and 57% stand in comparison with cystectomy series which will tend to have similar characteristics. The MGH series raises the obvious question of what would happen if one treated more 'typical' older bladder cancer patients with less favourable tumour characteristics with combination therapy.

Fluoro-Uracil (5FU)

5-FU is a clear, colourless or slightly yellow solution. It is an analogue of uracil, which is a component of RNA and is believed to function as an antimetabolite by means of intracellular conversion to the active deoxynucleotide. This activated deoxynucleotide interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. 5-Fluorouracil may also interfere with RNA synthesis by similar means. The drug has a long history of use as a radio-sensitiser, in particular in anal cancer but also in other diseases such as those of the upper aero-digestive tract. The most commonly used schedule in bladder cancer care is based on the protocols initially developed in anal cancer. These showed high complete response rates with acceptable long-term functional outcomes compared to radiotherapy alone [53, 54]. Based on

Table 22.2 Summary of Massachusetts General Hospital Chemoradiotherapy studies (Adapted from Efstathiou et al. [52])

Protocol	Neoadjuvant chemotherapy	Induction or concurrent	Consolidation or cystectomy	Adjuvant chemotherapy	Patients
MGH 180	MCV x2	CP + RT	CP + RT	None	50
MGH 880, RTOG 89–03 arm 1	MCV x2	CP + RT	Cystectomy or CP + RT	None	56
MGH 880, RTOG 89–03 arm 2	None	CP + RT	Cystectomy or CP + RT	None	45
MGH 930A	None	CP, 5FU, twice daily RT	CP, 5FU, twice daily RT	MCV × 3	21
RTOG 95–06	None	CP, 5FU, twice daily RT	CP, 5FU, twice daily RT	None	14
RTOG 97–06	None	CP, twice daily RT	CP, twice daily RT	MCV × 3	22
RTOG 99–06	None	CP, paclitaxel, twice daily RT	Cystectomy or CP, paclitaxel, twice daily RT	CP + gemcitabine ×3	45
Per protocol	Varied	Various	Cystectomy or varied consolidation	Various	95
				Total	348

these data our group set out to explore chemoradiotherapy schedules based on infused 5-FU.

Phase I and II studies showed good tolerability with a standard UK radiotherapy regimen of 55Gy in 20 fractions [47] so a phase III trial, BC2001 was set up and reported initial chemoradiotherapy results in 2012, updated in 2017 [38, 45]. With 49 months median follow-up, adding chemotherapy to full dose radiotherapy was associated with a 33% reduction in the risk of loco-regional recurrence with a reduction of almost 50% in invasive recurrence, a similar hazard ratio to that observed in the NCIC trial [43] but in a significantly older population. This benefit appeared consistent in pre-planned subgroup analyses and was not affected by prior neoadjuvant chemotherapy, suggesting that neoadjuvant and concomitant chemotherapy confer separate benefits on distant and local control, respectively. The improvement in loco-regional control was achieved with modest increases in acute toxicity that did not reach statistical significance with respect to grade 3 or 4 outcomes. We were particularly concerned that the more intensive therapy, particularly when given after neoadjuvant chemotherapy, did not result in impaired late bladder function. Late toxicity was measured using RTOG and LENT/SOM scales; neither measure showed a clinically significant increase with combination therapy. Likewise, we were unable to detect any significant impact on bladder volume. These results are thus consistent with the bladder preservation strategy described maintaining good posttreatment bladder function. This regimen thus forms the basis of one of the treatment cohorts in the current study. Finally, mature patient reported outcomes from BC2001 have now been published showing excellent preservation of all outcomes out to 5 years in the majority of patients [44, 55].

These schedules have a number of potential advantages compared to cisplatinum. Firstly, they are not dependent on renal function, a major problem in older bladder cancer patients with age-related renal function decline, often compounded by, for example, renal tract obstruction by tumour. Secondly, the agents have well-established safety profiles with good functional outcomes due to their long-term use in anal cancer [56]. Thirdly, although no comparisons with cisplatinum-based regimes exist in bladder cancer, these trials have been carried out in anal cancer. Although there is a perception that the "best" radio-sensitiser is cisplatinum – this view being very prevalent in the urological world – the head–to-head comparisons in anal cancer support the view that 5FU is in fact equally effective but with a much better safety and toxicity profile [57, 58]. In this context, as already noted, both the NCIC and BC2001 trials show similar hazard ratios for reduction in loco-regional failure of around 50% [38, 43].

Mitomycin C (MMC)

Mitomycin-C is a blue-purple crystalline powder and acts as an anti-tumour antibiotic. It is activated in the tissues to form an alkylating agent, which disrupts DNA in cancer cells by forming a complex with DNA, and also acts by inhibiting division of cancer cells, by interfering with the biosynthesis of DNA. It is typically given as a single bolus of 12 mg/m^2 on day 1 of the chemoradiotherapy schedule. Some protocols cap the dose at a total of 20 mg/m^2. There are no data with MMC monotherapy in bladder cancer, so all outcomes relate to the combination with 5FU, the data being summarised above. On the basis of the anal cancer data, it appears to be a key component of the radio-sensitisation regimen [58].

Carbogen/Nicotinamide

This has been explored in a series of trials and settings culminating in the BCON trial [49]. The principal problems with utilising this schedule are two-fold: the use of piped gas from a cylinder during the radiotherapy treatment; nicotinamide has no licence for this indication. That said, preclinical studies show that oral nicotinamide is well tolerated and reaches levels sufficient for radiosensitisation following oral administration [59]. Studies looking at outcome predictors based on the BCON trial suggest that the schedule works best in tumours with significant hypoxia, evaluated either via the presence of necrosis or via more complex profiling [60–63]. This is in contrast to the 5FU/MMC schedule which works

equally well in tumours with and without significant necrosis [64].

Gemcitabine

Gemcitabine is a pyrimidine nucleoside analogue in which hydrogen atoms in the 2′ carbon in deoxycytidine have been replaced with fluorine. It is a widely used intravenous cytotoxic drug in a range of cancers including bladder cancer where it has substantial single agent activity [65, 66] and is a key component of various combination therapies including with cisplatinum (in a number of variants) [67–69] and with carboplatin [66, 70–72]. It has been evaluated in a phase 2 trial with radiotherapy [73] with similar outcomes [74] to those seen with 5FU/MMC and nicotinamide/carbogen but in a non-randomised setting. The combination is well tolerated and easily administered.

Other Radio-Sensitisers

Cetuximab has been investigated in a non-randomised phase I/II trial alongside 5FU/MMC with or without neoadjuvant gemcitabine and cisplatinum. The combination was very well tolerated with all patients completing the full course of therapy and no dose-limiting toxicities seen [75]. Response rates were high with the 2-year rate of invasive bladder recurrence being >90%. More recently, a range of PD1/PDL1 pathway targeting monoclonal antibodies are being explored in trials including durvalumab with 5FU/MMC with 55Gy/20 fraction radiotherapy (phase 2/3; RADIO trial: ISRCTN 43698103); pembrolizumab, also with 5FU/MMC or gemicitabine or cisplatinum with either 55Gy/20 fraction or 64Gy in 32 fraction radiotherapy (phase 3: KEYNOTE-992 trial NCT04241185); NCT04186013 assessing 60 Gy in 30 fraction radiotherapy with atezolizumab × 3 (phase 2, non-randomised) and NCT03775265 also with atezolizumab but for a total of 9 doses and combined with chemoradiotherapy with the same choice of agents s KEYNOTE-992 (phase 3, randomised). It is noteworthy that all these trials use UK style single block chemoradiation rather than North American split dose schedules. These latter trials have the potential to transform the outcomes for patients with bladder cancer as these can lead to the licencing of IO drugs in the first-line curative setting; hence, results are eagerly awaited.

COVID-19

The recent COVID-19 pandemic has highlighted new potential concerns for patients with bladder cancer and potentially changes the risk-benefit ratio for surgery versus primary bladder preservation. UK experience has been that even at the height of the epidemic in London, patients could be treated in a COVID-secure environment with no detectable excess risk. Agents such as 5FU/MMC, as used in BC2001, can be administered without the need for even extended day case stays and no significant risk of drug-induced neutropenia and infection [38, 47, 48]. The IO agents also appear safe to use in the presence of COVID-19. At the time of writing, the long-term outcomes of the epidemic are not known; however, it seems possible that viruses like COVID-19 will become endemic with flare-ups rather like those seen with influenza. Techniques that are COVID-safe may thus become more attractive, especially when considering the risks of surgery in a relatively old, relatively unfit population as seen with bladder cancer as a smoking-related cancer [76].

Conclusions

Bladder preservation with a range of agents shows good loco-regional control with excellent toxicity profiles and no quality of life penalty from the addition of chemotherapy to radiotherapy alone. The advent of new IO agents with low toxicity and high systemic activity against bladder cancer promises to further improve the outcomes seen from the addition of chemotherapy to radiotherapy. The recent COVID-19 pandemic highlights the need for less-invasive ways of managing bladder cancer while preserving quality of life and bladder function – we may be on the verge of a major shift in the pattern of care for this long-neglected cancer.

External Beam Irradiation for Trimodality Therapy in Bladder Cancer

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Introduction

Radiation therapy is a fundamental component of trimodality therapy for bladder preservation along with aggressive transurethral surgery and radiosensitising systemic chemotherapy. This treatment strategy has evolved over the past >30 years with refinements in radiation techniques that have provided selected patients with an excellent chance for maintaining an intact bladder. Multiple series have suggested trimodality therapy has comparable, favourable results to radical cystectomy in selected patients [77–91] although the two have not been compared directly in a successfully completed randomized trial. The principles behind the radiation targets and fields are based on the delivery by conventional two-dimensional techniques, as almost all historical work in bladder-preservation utilized this technique. However, the evolution to three-dimensional conformal therapy has replaced this older approach, and newer technologies, such as intensity-modulated radiation therapy (IMRT) as well as daily image guidance, are now being more routinely used. These advanced technologies have allowed for more precise targeting of the bladder tumour and adjacent areas at risk while minimizing toxicity of therapy.

Radiotherapy Administration

Simulation

Patients are typically simulated supine with a pelvic/leg immobilizer. Arms are across the chest. IV contrast may be used to further delineate the pelvic vessels. Many institutions simulate and treat with the bladder empty, which is more reproducible and helps to minimize field size. Patients may also be simulated prone using a belly board to minimize small bowel in the field when it presents as a limiting factor. However, this is not standard and is dependent on institutional experience and patient tolerance.

Treatment Field Design, Targets, and Dose

Radiation Fields

There are multiple reasonable options based on trials/experiences to use certain doses, fields and frequency of radiotherapy (Table 22.3). Because of this, the recently activated SWOG/NRG 1806 trial (Clinicaltrials.gov NCT03775265) is very inclusive and radiation fields are per physician discretion. Hence, patients can be treated with a small pelvic radiation field, followed by (1) whole bladder boost followed by a bladder tumour boost, (2) whole bladder boost alone or (3) bladder tumour boost alone. Alternatively, patients can also be treated without a small pelvic field and receive only: (1) whole bladder radiation followed by a bladder tumour boost, (2) whole bladder radiation alone or (3) bladder tumour radiation alone. Any of the prior options are allowed on the protocol.

The small pelvic field includes the entire bladder, the prostatic urethra (in males) or proximal urethra (in females), as well as the lymph node basin in the pelvis (which include the external iliac, internal iliac and obturator lymph nodes). In general, the top border of this field is about the midsacroiliac joint (~S1/S2 or S2/S3). This limits the bowel volume, which is important in the case that bowel may be needed in the future for a possible urinary diversion. Quality-of-life (QOL) studies have also demonstrated that bowel irradiation resulted in side effects that contributed to effects on decreased QOL rather than toxicities from bladder irradiation [92, 93]. The inferior border is typically at the bottom of the obturator foramen, while the lateral field extends approximately 1.5 cm laterally from the pelvic brim. However, given that planning is now performed using CT simulation, these borders are deter-

Table 22.3 Major bladder organ-preservation chemoradiation trials

Study	N	Neoadjuvant chemotherapy	RT	Arms	Adjuvant chemotherapy	CR rate (%)	OS
RTOG 88–02 (12)	91	MCV	39.6 Gy	Cisplatin + RT	None	75	4 year: 62%
RTOG 89–03 (11)	Arm 1: 61 Arm 2: 62	MCV None	64.8 Gy	Cisplatin + RT Cisplatin + RT	None	59	5 year: 48% 5 year: 49%
RTOG 95–06 (7)	34	None	44 Gy BID	Cisplatin/5FU + BID RT	None	67	3 year: 83%
RTOG 97–06 (3)	47	None	64.8 Gy BID	Cisplatin/5FU + BID RT	MCV	74	3 year: 61%
RTOG 99–06 (8)	81	None	64.3 Gy BID	Cisplatin/paclitaxel + BID RT	Cisplatin/gemcitabine	81	5 year: 56%
RTOG 02–33 (43)	Arm 1: 46 Arm 2: 47	None None	64.3 Gy BID	Cisplatin/paclitaxel + BID RT Cisplatin/5FU + BID RT	Cisplatin/paclitaxel/ gemcitabine	87 79	5 year: 71% 5 year: 75%
Pooled results of above [10]	468		See above			69	5 year: 57% 10 year: 36%
BC 2001 [5]	Arm 1: 182 Arm 2: 178	Optional	64 Gy in 32 fx or 55 in 20 fx	5FU/MMC + RT RT alone	None None	67 66	5 year;: 48% 5 year: 35%
RTOG 07–12 (26)	Arm 1: 33 Arm 2: 33	None None	64.3 Gy daily RT versus 64 Gy BID	Cisplatin/5FU + BID RT Low-dose gemcitabine + daily RT	Cisplatin/gemcitabine	88 78	BI-DMFS3 year: 67% BI-DMFS3 year: 72%

Abbreviations: RT radiotherapy; BID twice daily; fx fractions; MCV methotrexate, cisplatin, vinblastine; FU fluorouracil; MMC mitomycin C; CR complete response; OS overall survival; BI-DMFS3 3-year bladder-intact distant metastasis-free survival

mined by contouring of the target organs and vessels. The external iliac vessels are contoured inferiorly to the top of the femoral heads, the internal iliac vessels are contoured inferiorly until they are no longer visible on the CT scan or they exit through the true pelvis via the greater sciatic notch. The obturator nodes are contoured superiorly where the internal/external iliac vessel contours stop and extend inferiorly to the top of the pubic symphysis. The small pelvis clinical target volume (CTV) should be trimmed to not extend outside the true pelvis.

The whole bladder target volume contains the entire bladder, including the outer wall. An expansion of either 1.0–1.5 cm for 3D conformal radiation therapy planning or 0.5–1.0 cm for IMRT constitutes the planning target volume (PTV) for this structure.

The bladder tumour target volume is defined as including any original bladder tumour as defined by transurethral resection of bladder tumour (TURBT), any imaging modality (i.e. CT, MRI, PET), intraoperative reports, cystoscopy or bimanual examination. The tumour boost can be difficult to define, given that the tumour has been fully resected, but close collaboration with urology is essential. The treating radiation oncologist should consult the urologist who performed the TURBT to confirm the area and size of the original tumour. Similar to the whole bladder target volume above, an expansion of either 1.0–1.5 cm for 3D conformal radiation therapy planning or 0.5–1.0 cm for IMRT constitutes the planning target volume (PTV) for this structure.

Radiation Dose

Radiation dose has been fairly standardized through multiple trials, typically in the 60–66 Gy range using standard fractionation of 1.8–2 Gy/fraction. However, moderate hypofractionation, in the form of 2.75 Gy/fraction to a total of 55 Gy, such as what was used in the BC2001 trial [81], is also an acceptable standard of care for radiation dose/schedule.

Radiation Frequency

Radiation can be delivered either daily or twice daily (BID). Some studies/centres have a built-in treatment break after approximately 40–45 Gy (induction course) for a restaging cystoscopy, repeat TURBT and biopsies. This is more often associated with the twice-daily radiation schedule, although it can also be built in with the daily radiation schedule as well. If the patient has a complete response or Ta/Tis residual disease on restaging cystoscopy, the patient can proceed with consolidation chemoradiation. If not, salvage cystectomy is recommended. Consolidation chemoradiation then typically consists of a boost to the entire bladder, followed by a tumour boost to a total dose of 64–65 Gy. Both the split-course RT (built-in break) versus the single-course RT schedules are very reasonable options, depending on institutional/physician/patient preference.

Considerations/Controversies

Including pelvic lymph nodes in the initial course of radiotherapy is an area of debate. The rationale for this treatment is due to the potential for occult lymph node metastases in these regions [94]. In addition, extensive lymphadenectomy at the time of surgery (radical cystectomy) was shown to improve survival in a study utilizing the National Cancer Database [95] – this is being evaluated formally in a randomized trial (SWOG S1011, Clinicaltrials.gov NCT01224665). However, there is a low rate of nodal failure when nodal fields are not included. In the BC2001 trial that compared radiation alone to chemoradiation, pelvic lymph nodes were not included in the radiation fields, and only 5.8% of patients developed pelvic relapses [81]. A single-institution study including patients treated with chemoradiation with weekly cisplatin randomized patients to either whole pelvic radiotherapy versus bladder only radiotherapy. There was no difference in 5-year disease-free survival, bladder preservation rates, nodal failures, nor overall survival observed [96]. Together, these data suggest that pelvic lymph node treatment may be omitted.

If pelvic radiotherapy is employed, the boost volume is another area of ongoing debate. Tumour-only boost can be employed, which may reduce the volume of bladder receiving the highest doses of radiation, thus potentially reducing long-term toxicities and preserving functionality.

However, it can be difficult to know exactly where the pre-TURBT tumour was located within the bladder, and accurate targeting can be tricky on a day-to-day basis. The bladder has been found to have significant inter- and intra-fraction movement based on bladder filling, changes to the rectum and variation of organ motion [97, 98]. Hence, some institutions employ whole-bladder boost volumes for the reasons stated above. The BC2001 trial [81] had a component of comparing radiation treatment volumes in its 2 × 2 design, evaluating whole-bladder radiation therapy compared to reduced high-dose volume radiation therapy (or partial bladder). It was found that the reduced high-dose volume did not result in a detriment to local disease control or survival, and there were no statistically significant differences in toxicity rates between the whole-bladder versus the reduced high-dose volume group [99].

The treatment break is another technique that is debated. On the one hand, it allows for early identification of patients who are responding poorly to therapy so that early salvage radical cystectomy can be performed in a timely manner, as well as allows for such surgery to occur after only 40–45 Gy of dose, rather than full-dose radiation. On the other hand, there are concerns regarding the radiobiological efficacy of such a split-course treatment [100, 101]. In addition, patients who have not yet responded after only 40–45 Gy may respond after higher doses; hence, they may be recommended for surgery prematurely and potentially unnecessarily.

Finally, radiation can be delivered once a day or twice a day, as discussed above. Most RTOG protocols utilized twice-daily treatment (Table 22.3), but this can be a logistical burden to patients and treating centres. RTOG 0712 [102] compared once-a-day radiation with gemcitabine to twice-a-day radiation using a cisplatin-based chemotherapy regimen, finding a rate of freedom from distant metastases of >75% with either regimen, suggesting that the two are comparable.

Normal Tissue Considerations

Careful attention must be paid to minimizing dose to normal organs, including the colon, rectum, small bowel and normal bladder (not in boost field). It is also important to minimize dose to the femoral heads. When treating the small pelvic field in women, it is prudent to minimize the amount of vulva in the field as this can limit the tolerance. Normal structure constraints as per the recent SWOG/NRG 1806 protocol (Clinicaltrials.gov NCT03775265) can be found in Table 22.4.

Table 22.4 Normal tissue constraints per the SWOG/NRG 1806 protocol

Organ-at-risk	Dosimetric parameter	Per protocol
Rectum	V30Gy[%] V55Gy[%]	≤50% ≤10%
Left femoral head Right femoral head	D0.03cc[Gy] V45Gy[%]	≤50Gy ≤50%
Small bowel	D0.03cc[Gy] V50Gy[cc] V45Gy[cc] V40Gy[cc] V40Gy[%] V30Gy[cc]	≤55Gy ≤15 cc ≤100 cc ≤130 cc ≤30% ≤150 cc

Novel Techniques

Advances in radiation technology and delivery include the utilization of IMRT, which results in improved conformality and reduced normal tissue exposure. IMRT has been reported to have excellent clinical outcomes with a noted reduction in toxicities in bladder cancer [103–107]. However, there is concern for marginal misses in regions with considerable target/organ motion; hence, advanced daily imaging techniques for accurate set-up is recommended when treating with IMRT.

Daily image guidance, particularly with cone beam CT, can greatly improve the accuracy of radiation targets, particularly when treating a smaller volume boost area with higher dose. Some institutions implant fiducial markers into the area where the bladder tumour was resected for further accuracy of targeting. Other targeting agents, such as injecting lipiodol or a radio-opaque hydrogel into the bladder wall, have been explored to further help with target delineation and daily image guidance throughout radiotherapy [108, 109].

Management of Toxicities

Acute Toxicities

Bladder radiotherapy is generally well tolerated for most patients. In a large, retrospective study of 487 patients treated with radiation to a mean total radiation dose of 65.5 Gy, the incidence of Radiation Therapy Oncology Group (RTOG) grade ≥3 acute bladder and bowel toxicity was 5% and 3%, respectively [110]. Concurrent chemotherapy may increase the risk for acute toxicities [111]; however, in the BC2001 trial comparing chemoradiation to radiation alone, there was not an increase of acute grade 3 or 4 adverse events in the chemoradiotherapy group compared to the radiotherapy group ($p = 0.07$). Events documented in this trial were mostly gastrointestinal (GI) toxicities [81].

Acute urinary toxicity can manifest as acute radiation cystitis. Depending on severity, this can usually be managed conservatively and/or with intravenous hydration, continuous bladder irrigation and uroprotective agents [112]. Severe cases can be referred for hyperbaric oxygen consideration. Phenazopyridine can be used for dysuria, oxybutynin can be an option for urinary urgency and tamsulosin may be useful for urinary irritation/obstructive symptoms in men as urinary bother may be from the prostate in the radiation field. Rectal toxicities include loose stools and/or diarrhoea, and other symptoms of radiation proctitis. These can be managed with low-residue diet, loperamide, sucralfate enemas, steroids and argon plasma coagulation. For severe, refractory cases, similar to the bladder, hyperbaric oxygen can be considered. Other acute toxicities include fatigue, nausea/vomiting (rare), possible skin reaction and decreased blood counts (particularly in combination with chemotherapy, as well as depending on size of pelvic field).

Late Toxicities

Per the retrospective study of 487 patients referenced above, the incidence of RTOG grade ≥3 late bowel/bladder toxicities, defined as toxicities that occurred or persisted after the third month from the end of radiation, was 12% and 3%, respectively [110]. Erectile dysfunction in men is a common late toxicity. This can be managed with phosphodiesterase type 5 inhibitors. Long-term chronic radiation proctitis and radiation cystitis is rare. These may be managed with medications for symptom amelioration, argon plasma coagulation/cauterization for persistent or more severe symptoms; hyperbaric oxygen is an option in the management of chronic, very severe refractory proctitis/cystitis.

In the BC2001 trial, there was not a significant increase in late toxicities between the chemoradiotherapy and radiotherapy group [81]. At 1 year, grade 3–4 RTOG adverse events (all genitourinary, GU) were reported in 3/92 patients (3.3%) in the chemoradiation group and 1/78 patients (1.3%) in the radiation alone group, $p = 0.34$.

In a pooled analysis of RTOG bladder-sparing protocols, overall late pelvic toxicity was low [113]. Median follow-up was 5.4 years (range 2.0–13.2), and 7 percent of patients experienced a late grade 3+ pelvic toxicity; of these, 5.7% was GU and 1.9% was GI. In only one of nine patients who experienced a grade 3+ GU toxicity did that toxicity persist. Most patients retained good long-term bladder and bowel function. A urodynamic assessment performed a median of 7 years after chemoradiation in 32 patients who underwent bladder preservation found normally functioning bladders in 24 patients [93], suggesting that the majority of patients retain adequate bladder function after chemoradiotherapy. In an analysis of a large, single-institution cohort of 475 patients treated with trimodality therapy with long-term follow-up [78], as well as the BC2001 [81] and RTOG 0712 [102] trials, the percent of cystectomies performed for late effects of radiotherapy on bladder function was <1% in all large experiences.

One study looked at long-term health-related quality of life (QOL) in muscle-invasive bladder cancer survivors who received trimodality therapy or radical cystectomy [114]. After a median follow-up of 5.6 years, patients who received trimodality therapy had improved general QOL compared to those who received a cystectomy (9.7 points, $p = 0.001$) and higher physical, social, emotional, role and cognitive function by

6.6–9.9 points, $p = 0.04$. Bowel function was also improved, as well as sexual function and body image. QOL needs to be prospectively evaluated in order to determine superiority with trimodality therapy as compared to radical cystectomy.

Given the limited randomised data comparing bladder-preservation therapy to radical cystectomy, one study compared effectiveness of trimodality therapy and radical cystectomy using decision-analytic modelling with the endpoint of quality-adjusted life years (QALYs), finding that trimodality therapy resulted in an incremental gain of 0.59 QALYs over cystectomy [115], which again supports the need for prospective validation of QOL endpoints in patients who receive bladder preservation therapy.

Oncologic Monitoring

Close observation post-chemoradiation for bladder preservation is key. The first cystoscopy is generally performed 8–10 weeks after the completion of treatment. The first two cystoscopies are recommended to be performed in the operating room with re-TURBT/biopsy of the original tumour site. If these are negative, the patient can then transition to office cystoscopies, along with urine cytology, every 3 months for two years, every 6 months years 2–5, and then yearly [116] for life.

Per NCCN guidelines, imaging consists of chest/abdominal/pelvic imaging along with upper tract evaluation every 3–6 months for 2 years, followed by chest/abdomen/pelvis imaging annually through year 5, and then as clinically indicated thereafter [116]. Per the recent SWOG/NRG 1806 protocol, imaging should consist of chest/abdomen/pelvis imaging (either CT or MRI) every 12 weeks for 2 years, followed by every 6 months for 2 years, followed by every 12 months for 2 years, then as clinically indicated thereafter.

Per NCCN guidelines, blood tests consist of the assessment of renal and liver function, as well as complete blood count/comprehensive metabolic panel every 3–6 months for year 1, and then as clinically indicated thereafter. Per RTOG 0712, blood tests should be performed every 3 months for year 1, every 4 months during year 2, every 6 months years 3–5, and then annually through year 10 of follow-up, and then as clinically indicated.

Long-term surveillance of patients treated with bladder-preservation chemoradiotherapy is essential, as 20% of de novo non-muscle-invasive bladder cancers can occur even after 10 years [117, 118]. It is critical to ensure that these patients are not lost to follow-up.

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Managing Urothelial Recurrences after Chemoradiation Therapy

23

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Overview

With appropriate patient selection, trimodal therapy (TMT, chemoradiation therapy) can have excellent outcomes for muscle-invasive bladder cancer (MIBC). In a 2018 meta-analysis of 57 studies containing 30,293 patients, Fahmy et al. found a complete response rate of 75.3% for TMT. In patients who achieved a complete response, which is an imperfect analysis, the 5-year survival rates were excellent with overall survival at 66.9%, disease-specific survival at 78.3%, and local recurrence-free survival at 46.8%. When compared to radical cystectomy (RC), 10-year overall survival was 30.9% for TMT and 35.1% for RC (p = 0.32) [1]. Since treatment selection biases exist for MIBC (i.e., younger healthier patients get cystectomy and older sicker patients get TMT), it is surmised from this analysis that outcomes between cystectomy and TMT are likely comparable. It is noteworthy that the complete response rate was higher (78.5%) in patients who received a split-dose protocol versus than those receiving continuous therapy (71.5%). However, there is selection bias with this analysis since non-responders identified after the first RT course are removed from split-dose protocols early and therefore excluded from long-term outcomes. Historically, split-dose RT was preferred by urologists due to their concerns regarding ineffective radiotherapy and concerns about performing salvage cystectomy in an irradiated field. Consequently, the early identification of non-responders was felt to be important. However, radio-biologically this may not make much sense since RT can take weeks to months to completely sterilize tumors and treatment delay may allow repair of RT-induced DNA damage. Currently, continuous dose RT is the most common regimen used.

The data above highlight that while disease-specific survival with TMT is high, a high proportion of patients that are initial complete responders to TMT will experience a local recurrence. Recurrence estimates range from approximately 25–50% in the various studies, and occur at a median time less than 2 years

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post-treatment [1, 2]. A recent analysis of prospective RTOG protocols showed 5-year rates of non-muscle invasive, muscle-invasive, regional nodal, and distant recurrences to be 26%, 16%, 12%, and 32%, respectively. Ten-year rates increased to 26%, 18%, 14%, and 35%, respectively [3]. Salvage cystectomy was performed in 29% by year 5 and 31% by year 10. This chapter will focus on the management of local (i.e., urothelial) recurrences of bladder cancer following TMT.

Non-muscle-Invasive Bladder Recurrences

In general, any suspicious bladder lesion identified during TMT follow-up, whether detected by imaging or cystoscopy, should be further investigated with transurethral resection of the bladder tumor (TURBT). TURBT has two main roles in this setting: (a) determine the severity of the suspected recurrence (stage, grade, presence of CIS, size, multi-focality, histology) and (b) provide complete surgical removal of the tumor(s) when feasible. All subsequent management decisions rely on accurate TURBT pathology, and urologists should strive for as complete a resection as possible, including the use of second-look repeat TURBT when indicated.

One of the earliest descriptions of the use of intravesical therapy after TMT was published by Shipley et al., who reported that 3 of 6 patients treated at Massachusetts General Hospital with TMT responded to intravesical therapy after NMIBC recurrence [4]. This early experience was updated in 2001 by Zietman et al. and again in 2018 by Sanchez et al., and represents to our knowledge the largest experience with NMIBC following TMT [5–8]. Of 85 post-TMT NMIBC recurrences, they were able to rescue 59 (69%) with TURBT +/− intravesical therapy, while 26 (31%) required either immediate or delayed cystectomy (after intravesical therapy failure). Similar results are reported by Weiss et al., who describe a series of 68 patients from Erlangen who experienced recurrent NMIBC after TMT [9]. Of these patients, 4 (6%) underwent immediate salvage cystectomy while 40 (59%) underwent TURBT alone, 9 (13%) TURBT + adjuvant intravesical chemotherapy, and 15 (22%) TURBT + BCG. Over a median follow-up of 55 months, 31 (48%) of those patients managed with TURBT (+/− adjuvant intravesical therapy) were disease-free, 21 (33%) developed additional NMIBC recurrences, and 12 (19%) progressed to muscle-invasive disease. These and other smaller series are summarized in Table 23.1 [10–13].

The toxicity of intravesical therapy appears to be somewhat worse following TMT than in non-irradiated bladders [5–8]. In particular, there is an increased risk of bladder contracture (up to 10%) and an increased risk of being unable to tolerate normal 2-hour dwell times and maintenance, presumably due to bladder shrinkage. That being said, these side effects are of lesser impact than those associated with salvage post-TMT radical cystectomy, which must be considered in treatment decision-making [5].

Muscle-Invasive Bladder Recurrences

The risk of metastatic spread increases with muscle invasion; therefore, if TURBT pathology reveals a muscle-invasive recurrence, the standard of care is salvage radical cystectomy, assuming the patient is a surgical candidate. The assessment of candidacy for surgery should be conducted by the urologist in cooperation with the anesthesiology team and other relevant specialists (e.g., cardiology, pulmonology). Without salvage cystectomy (whether due to patient preference or not candidates for surgery), median survival is 9.7 months [13].

Although cystectomy rates following TMT were reported by Shipley et al. in 1998, these rates were for cystectomy for incomplete response to induction therapy during a split-course radiation regimen, rather than treatment failure and MIBC recurrence, and therefore underestimate the actual cystectomy rate. Care should be taken when analyzing early reports of outcomes from recurrent management because they are often reported without stratification

Table 23.1 Non-muscle-invasive bladder cancer recurrences following TMT

Study	Institution	TMT cases		NMIBC recurrences			NMIBC management		
		N	F/U	N	Median time	Survival	Immediate cystectomy	TURBT → cystectomy	TURBT +/− adjuvant IVT
Shipley 1990* [4]	MGH, Boston, USA	–	–	6	–	–	–	N = 3	3
Pisters 1991 [6]	Univ. of Florida, Gainesville, USA	–	–	20	11.1 Mos	–	–	N = 5	N = 15
Weiss 2008 [9]	University of Erlangen, Erlangen, Germany	531	55 Mos	68	15.4 Mos	D = 15 DFS5y = 87% DFS10y = 72%	N = 4 D = 1 (25%)	N = 14 D = 7 (50%)	N = 50 D = 7 (14%)
Buchser 2019 [10]	Hosp. Univ. La Princesa, Madrid, Spain	71	94 Mos	15	–	–	N = 4 D =?	–	N = 11 D = 2
Mitin 2016 [11]	Multi-institutional, USA	119	5.9 yrs	23	–	–	–	–	–
Onozawa 2012 [12]	Univ. of Tsukuba, Tsukuba, Japan	77	39 Mos	14	14.1 Mos	–	N = 3	N = 4	N = 7
Sanchez 2018* [7]	MGH, Boston, USA	342	5.3 yrs	85	1.8 yrs	–	N = 8 D = 2	N = 18	N = 59
Zietman 2001* [8]	MGH, Boston, USA	190	6.7 yrs	32	2.1 yrs	–	N = 3	N = 7	N = 21
Rödel 2002 [13]	University of Erlangen, Erlangen, Germany	415	36 Mos	41	–	DFS5y = 76% DFS10y = 52%	–	–	N = 41

D dead of bladder cancer; *IVT* intravesical therapy; * These studies are from the same center and represent early and updated series

based on reason for salvage cystectomy. In 2002, Rödel et al. published both salvage cystectomy rates and long-term outcomes for 415 patients from 1982–2000, noting 51 invasive or presumed invasive recurrences, with a 15% salvage cystectomy rate, and 5- and 10-year DSS was 50% and 45%, respectively [13].

Similar results were seen in one of the largest and longest followed cohorts of TMT patients from Massachusetts General Hospital (MGH). Outcomes from this group were first published by Shipley et al. in 2002, reporting an invasive recurrence rate of 16% (30 of 190 patients), and in that group, salvage cystectomy was performed in 83% (25 of 30 patients) [14]. An updated analysis from this institution was published in 2012 by Eswara et al., specifically reporting salvage cystectomy outcomes for 42 of 348 patients. Salvage cystectomy had improved 10-year DSS compared to immediate, cystectomy, 61% vs 38%, but no difference in 10-year OS [15]. Results from a pooled cohort of RTOG protocols were published by Mak et al. in 2014, which analyzed across both University of Erlangen and MGH. They reported MIBC recurrences in 56 patients (13%), of which 36 underwent salvage cystectomy, DSS was not stratified for incomplete response and recurrence, but overall cystectomy 5-yr and 10-yr DSS was 60% and 47%, respectively [16]. Most recent analysis for these patients by Giacolone et al. in 2017 reported a 13.5% salvage cystectomy rate (64 of 475 patients), with 5, 10, and 15 year DSS of 58%, 44%, and 44%, respectively. These and other smaller series are summarized in Table 23.2 [17–19].

Table 23.2 Muscle-invasive bladder cancer recurrences following TMT

Study	Institution	TMT cases		MIBC recurrences		Incomplete responses	Salvage cystectomy rate			
		N	F/U	N	Median time	N	For non or incomplete response	Survival	For MIBC recurrence	Survival
Rödel 2002 [13]	University of Erlangen, Erlangen, Germany	415	36 Mos	51	–	110	N = 41 (10%)	DFS5y = 21% DFS10y = 18%	N = 42 (10%)	DFS5y = 50% DFS10y = 45%
Shipley 2002* [14]	MGH, Boston, USA	190	6.7 yrs	25	–	41	N = 41 (22%)	**	N = 25 (13%)	DFS5y = 48% DFS10y = 41%
Eswara 2012* [15]	MGH, Boston, USA	348	12 yrs	–	–	–	N = 50 (14%)	DFS10y = 38% OS10y = 25%	N = 41 (12%)	DFS10y = 61% OS10y = 25%
Efstathiou 2012* [34]	MGH, Boston, USA	348	7.7 yrs	–	–	–	N = 60 (17%)	**	N = 42 (12%)	DFS10y = 44%
Giacolone 2017* [3]	MGH, Boston, USA	475	4.5 yrs	–	–	111	N = 65 (14%)	DFS5y = 51% DFS10y = 32%	N = 64 (13%)	DFS5y = 64% DFS10y = 55%
Lee 2014 [18]	Shin Kong Wu Ho-Su Memorial Hospital, Taipei City, Taiwan	70	24 Mos	7	–	20	N = 0	–	N = 1 (14%)	–
George 2004 [17]	Hopital Salvator, Marseille, France	60	48.5 Mos	5	–	14	N = 6 (43%)	D = 5	N = 5 (100%)	D = 2
Onozawa 2012 [12]	Univ. of Tsukuba, Tsukuba, Japan	77	38.5 Mos	3	29.7 Mos	–	–	–	N = 3 (100%)	–
Takoaka 2016 [19]	Univ. of Tsukuba, Tsukuba, Japan	70	3.4 yrs	4	–	Excluded from analysis	–	–	N = 2 (50%)	–
Mak 2014 [16]	Erlangen and MGH	486	4.3 yrs	56	–	151	62	**	36	DFS5y = 60% DFS10y = 47%

D dead from bladder cancer; * These studies are from the same center and represent early and updated series; ** DFS not stratified by cystectomy for incomplete response versus recurrent invasive disease

Historically, urologists raised safety concerns regarding operating in a previously irradiated pelvis, as radiation fibrosis begins to occur 3 months after radiation. However, published 90-day mortality rates are generally <5% for salvage cystectomy and similar to mortality rates for standard radical cystectomy [15, 20]. Cystectomy for incomplete response during split-course radiation is at a higher risk of significant 90-day cardiovascular/hematological complications (e.g., pulmonary embolism, myocardial infarction, deep vein thrombosis, transfusion), whereas salvage cystectomy for recurrent disease is at higher risk for tissue healing complications (e.g., fascial dehiscence, wound infection, ureteral stricture, anastomotic stricture, stoma/loop revisions) [15]. Practice at many institutions is to utilize the ileal or transverse colon conduit rather than a neobladder in most salvage cystectomies because neobladders in the irradiated pelvis seem to carry a higher risk of functional complications. This is similar to the situation for salvage prostatectomy.

The Role of Additional Radiation Therapy

In general, further pelvic radiation therapy is not recommended after TMT due to the risk of significant toxicity from cumulative radiation dose to the pelvic viscera and bones. Once the bladder has been irradiated during TMT, further radiation significantly increases the risk of developing a contracted, non-functioning bladder as well as injury to bowel, blood vessels, pelvic nerves, and pelvic bones (e.g., femoral heads).

However, palliative radiation has been shown to be beneficial with intractable hematuria or pelvic pain. Lower doses and shorter patient survival make palliative radiation more feasible. Lacarrière et al. reported on 32 patients who underwent 20–30 Gy palliative radiotherapy for intractable hematuria, noting 69% of patients hematuria free at 2 weeks, but unfortunately, 69% of all patients developed recurrent hematuria after 6 months, indicating that this is not a permanent fix for most patients [21]. However, Dirix et al. reported their experience with a more protracted dose regimen for 44 patients, finding a mean hematuria-free survival of 13 months, with severe (≥grade 3) acute and late urinary toxicity rates of 9% and 19%, respectively [22].

Furthermore, Yi et al. reported their experience with palliative radiation for a patient with recurrent bladder cancer and pelvic pain refractory to oral and parenteral analgesics, but had complete resolution of pain following 50 Gy in 5 weeks [23]. Palliative radiation should be considered as needed for symptoms.

Upper Urinary Tract (Ureter, Renal Pelvis) Recurrences

Following radical cystectomy, approximately 5–10% of patients will experience an upper urinary tract recurrence, and this probability increases with the duration of follow-up [24–29]. In a meta-analysis of 13,185 patients who underwent radical cystectomy, those who had NMIBC were twice as likely to develop an upper tract recurrence when compared to those with muscle-invasive disease [27]. There are few published data regarding the occurrence of upper tract or urethral cancer recurrences after TMT. This is an area in which data are sparse and studies are needed to show recurrence rates in these patients, as we currently mainly have studies reporting recurrence rates following radical cystectomy. In a systematic review, Gakis et al. found that upper tract recurrences were only detected by cytology alone ~7% of the time, while imaging increased detection to ~30% [30]. Urine cytology from the irradiated urothelium is notoriously unreliable and our practice has been to avoid this test in most irradiated bladders. Management of upper tract urothelial carcinoma in patients with irradiated bladders can be managed similarly to those occurring otherwise.

Urethral Recurrences

After radical cystectomy, approximately 4–5% of patients will experience a urethral recurrence, and similar to the upper urinary tract, this probability increases with prolonged follow-up [31–33]. If a urethral recurrence is found, attention should be paid to additional sites of recurrence. Gakis et al. found that 33% of patients had other recurrences in addition to the urethra: urethra and distant disease (21%), urethra and pelvis (8%), and urethra and distant disease and pelvis (4%) [30]. Like upper tract tumors, like is known about urethral cancer following bladder radiation. Urethral cancer (primary or secondary) are uncommon tumors and clinicians may follow current guidelines regarding its management.

Distant Recurrence

As noted above, the 10-year metastasis rates after TMT are roughly 30%–35% [3, 34]. In Rödel's study, 5-year metastasis-free survival was 79% if patient demonstrated a complete response to therapy, but only 52% if they failed to respond [13].

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24 Cytotoxic Chemotherapy for Advanced Bladder and Upper Tract Cancer

Rosa Nadal and Joaquim Bellmunt

Chemotherapy

Indications

First-Line Setting

In general, a decision regarding treatment should take into account the patient's performance status and the clinician's medical judgment as to the patient's ability to tolerate chemotherapy:

- A cisplatin-based combination chemotherapy regimen is the preferred initial therapy for patients with advanced bladder and upper tract cancer who are fit candidates for cisplatin. It is worth it to note that a small subset of patients with nodal or lung metastases may be cured by combination chemotherapy.
- As described further, cisplatin-based combination chemotherapy results in superior survival when compared with single-agent cisplatin. However, cisplatin-related toxicity is a concern for many patients. In addition, not all patients with urothelial cancer are appropriate candidates for cisplatin therapy.
- For patients considered unfit for cisplatin-based chemotherapy with a good performance status (i.e., ECOG performance status <2) who are otherwise candidates for platinum-based combination chemotherapy, we suggest a carboplatin-based regimen (e.g., carboplatin and gemcitabine). However, a non-platinum-based combination (e.g., paclitaxel plus gemcitabine) would be a reasonable alternative.
- For patients who are not eligible for cisplatin-containing chemotherapy and whose tumors have high expression of PD-L1, two immune-checkpoint inhibitors (e.g., pembrolizumab or atezolizumab) have been approved by the FDA. The choice of a specific treatment is based on patient and provider preference.
- For patients with a poor performance status who are not candidates for platinum-containing chemotherapy, we suggest an immune-checkpoint inhibitor (e.g., pembrolizumab or atezolizumab). Single-agent chemotherapy are reasonable options (e.g., taxanes or gemcitabine). The choice of a specific treatment is based on patient and provider preference.

Second-Line Setting

- Although a significant number of patients have an objective response to first-line therapy, most eventually progress. Second-line chemotherapy may be indicated for those who are not candidates for immunotherapy

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and for those who progress during or after immunotherapy.

- Vinflunine is approved in Europe for second-line treatment of urothelial cancer based upon one trial that showed a benefit to treatment when compared with best supportive care. However, vinflunine is not approved in the United States.

Table 24.1 Consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy

Patients meeting at least one of the following are unfit for cisplatin-based chemotherapy
WHO or ECOG performance status 2, or Karnofsky performance status of 60–70%.
Creatinine clearance (calculated or measured) less than 60 ml/min/1.73m^2.
CTCAE grade 2 or above audiometric hearing loss.
CTCAE grade 2 or above peripheral neuropathy.
NYHA class III heart failure.

Patient Preparation

Patients who have metastatic disease are generally treated with systemic therapy. A complete history and physical examination should be undertaken, together with laboratory tests evaluating full blood counts and renal function.

Imaging studies should include a chest radiograph and computed tomography of the chest, abdomen, and pelvis (with intravenous contrast if possible). For those patients with clearance of creatinine less than 60–50 ml/min/1.73m^2, non-contrast CT scan of the chest and MRI of the abdomen and pelvis with intravenous gadolinium is recommended. The need of additional imaging studies, including bone scan and positron emission tomography (PET) scanning, depends on the clinical presentation, laboratory results, and sites of disease. Central nervous system imaging should be considered if clinically indicated.

Cisplatin-based combination chemotherapy is the first-line standard of care for patients with metastatic urothelial carcinoma. However, approximately half of patients are cisplatin-ineligible owing to comorbidities or impaired functional status [1]. In preparation to start systemic chemotherapy, determine fitness for cisplatin is crucial.

This discrepancy between the median age at the time of death from advancer bladder cancer (78 years) [2] and the median age for patients enrolled in phase 3 trials that assess cisplatin-based chemotherapy regimens (64 years) [3] and the associated high rate of renal insufficiency and impaired functional status with advancing age [4] has resulted in a disconnect between treatment efficacy and treatment effectiveness when applied to the general population of patients with advanced bladder cancer. Investigators have long appreciated this disconnect and have designed trials specifically for patients who are unfit for cisplatin-based chemotherapy [5]; however, variability in the eligibility criteria defining unfit patients has created difficulty in interpretation of the results.

In 1997, the European Organization for Research and Treatment of Cancer (EORTC) conducted a survey of genitourinary oncologists to try to determine cisplatin ineligibility [6]. The majority of respondents considered preserved renal function, defined as creatinine clearance (CrCl) ≥60 mL/min, and World Health Organization (WHO) performance status (PS) 0 or 1 as requirements for cisplatin treatment.

Subsequently, Galsky and colleagues conducted a review of criteria used to define eligibility for cisplatin in clinical trials [1, 7]. The use of criteria published by a consensus working group that defined medically unfit patients is widely accepted by the oncology community. (Table 24.1).

In view of the direct relation between age and creatinine clearance, a common misconception is that elderly patients are cisplatin-ineligible and cannot receive platinum-based treatment. Age was not a prognostic factor for survival in patients with advanced urothelial carcinoma who had been treated with cisplatin-based chemotherapy [8]. Thus, the available data suggest that age alone should not be used as an eligibility criterion for clinical trials of unfit patients. However, the effect of age, together with urinary-tract obstruction related to bladder cancer, and smoking-related vascular disease, leads to a

very high rate of renal impairment in patients with bladder cancer [4].

The use of cisplatin is mainly limited by nephrotoxic, neurotoxic, and ototoxic effects. Because cisplatin is potentially nephrotoxic, pre-existing renal impairment is a risk factor for nephrotoxic effects. Cisplatin is routinely avoided in patients with renal impairment. Although there are no definitive studies to help guide the threshold level of renal function that should preclude cisplatin, a review of cisplatin-based chemotherapy trials confirms the standard threshold of a creatinine clearance of more than or equal to 60 mL/min as the most commonly used inclusion criterion.

Cisplatin use in patients with a solitary kidney has been controversial and is perhaps most relevant to patients with metastatic upper tract urothelial carcinoma who have undergone nephroureterectomy. Importantly, a study evaluated the renal safety of cisplatin-based chemotherapy in 60 patients with metastatic urothelial carcinoma and a solitary kidney and demonstrated a significant decline in estimated glomerular filtration rate after 3 cycles of treatment [9]. However, this decline correlated with baseline renal insufficiency and led to clinically significant renal toxic effects in only three patients. Therefore, with no impaired renal function, patients with a solitary kidney need not be uniformly considered as cisplatin-ineligible. Clearly, extra care with vigorous hydration is warranted in this setting to optimally preserve renal function.

Poor functional status has been associated with increased toxic effects and decreased efficacy in patients with metastatic urothelial carcinoma who are treated with cisplatin-based chemotherapy [8]. In the absence of definitive prospective studies showing the safety of chemotherapy in patients with advanced bladder cancer and a performance status of 3, the working group favored an ECOG performance status of 2 as an eligibility criterion for clinical trials of unfit patients.

Similarly, the association between comorbidities, treatment efficacy, and treatment-related toxic effects is complex and has not been adequately explored in patients with advanced bladder cancer. Congestive heart failure was viewed by consensus working group and New York Heart Association class III–IV heart failure is often an exclusion criterion for cisplatin-based trials. However, left ventricular ejection fraction (LVEF) screening is routinely measured to assess left ventricular dysfunction only prior to chemotherapy with doxorubicin or if clinically indicated.

Individual susceptibility to hearing loss due to cisplatin includes renal impairment, older age, and pre-existing hearing loss. Hearing loss after cisplatin occurs mainly at high frequencies and at cisplatin dosages greater than 60 mg/m^2 [10]. The Common Terminology Criteria for Adverse Events version 4 (CTCAE) defines grade 2 auditory loss as decibel losses of 25 dB at two contiguous frequencies. Because cisplatin can induce hearing loss of 19–20 dB, the use of cisplatin in patients with pre-existing hearing loss is likely to induce additional damage. Therefore, the working group recommended baseline audiometric hearing loss that is equal to and greater than grade 2 to define the unfit population. The risk of cisplatin-induced peripheral neuropathy is also increased in patients with pre-existing neuropathy. In view of the effect of severe neuropathy on ambulation and quality of life, the working group recommended inclusion of a CTCAE grade 2 and above peripheral neuropathy to determine cisplatin ineligibility. In summary, host-related factors, such as renal function, performance status, comorbidities, should be considered when choosing treatment strategy.

Prognostic

A number of pre-treatment patient-related factors and tumor molecular characteristics are correlated with survival in advanced bladder cancer treated with chemotherapy. An understanding of these prognostic factors is important for risk stratification and the interpretation of clinical trial results, as well as for determining which patients may benefit from therapy.

The presence of visceral (i.e., pulmonary, liver, bone) metastases and a poor performance status correlate with poor survival in chemotherapy clinical trials. This was demonstrated by an intergroup trial that compared

single-agent cisplatin with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) in the metastatic setting [11, 12]. A poor performance status and the presence of bone or liver metastases were the best discriminators of poor outcomes. The presence of these unfavorable characteristics was associated with a median survival of 4 months, compared with 18 months in those patients without these features [11]. No patients with bone or liver metastases, and only one patient with a Karnofsky Performance Status less than 80 percent survived past 6 years. [12]

Several subsequent reports have confirmed the association between decreased survival and the presence of visceral metastases and poor performance status [8, 13–16]. For first-line therapy, Karnofsky PS of 80% or less and the presence of visceral metastases are independent poor prognostic factors for survival [8]. Bellmunt et al. also proposed a three-factor prognostic model consisting of the Eastern Cooperative Oncology Group performance status (ECOG) performance status, hemoglobin level, and liver metastasis [14]. Thereafter, a duration from prior chemotherapy of shorter than 3 months and an albumin level below the lower limit of normal were also reported as adverse prognostic indicators [17, 18]. For second-line therapy, independent, adverse prognostic factors for survival (PS >0, hemoglobin level <10 g/dl, and the presence of liver metastasis) for patients failing platinum-based chemotherapy have also been defined and validated [14].

Molecular abnormalities have been studied as prognostic and predictive factors in an attempt of using the molecular characteristics of an individual tumor to guide treatment selection and predict outcome. However, none of these factors has been validated, and routine molecular testing is not recommended to make clinical decisions. The role of mutations in the p53 gene has been extensively studied with inconclusive results. Multiple studies have suggested that such mutations are associated with resistance to MVAC chemotherapy and a poor prognosis [19–22] In contrast, the presence of p53 mutations was neither predictive nor prognostic in an analysis of another trial [23].

The excision repair cross-complementing group 1 (*ERCC1*) gene is involved in the nucleotide excision repair pathway and may mediate resistance to alkylating-agent chemotherapy. In a Spanish Oncology Genitourinary Group (SOGUG) study of 57 patients with advanced bladder cancer who were treated with a cisplatin-based regimen, the median survival was significantly longer in patients with low ERCC1 levels (25 versus 15 months in those with high ERCC1 expression) [24]. Other potential markers of chemotherapy resistance include the multidrug resistance p-glycoprotein, multidrug resistance-associated protein, glutathione, and metallothioneins [25–28].

Selection of Agent

The last three decades, several randomized trials investigating the use of systemic chemotherapy in patients with advanced bladder cancer were published. Table 24.2 summarizes selected phase III trials on metastatic urothelial carcinoma.

Cisplatin-Based Regimens

Historically, cisplatin has been the cornerstone of chemotherapy regimens for urothelial carcinoma [11]. Cisplatin was approved in the United States in 1993, based on a total of 45 patients treated with single-agent cisplatin showing a response rate of 16% [29]. However, a combination of cisplatin with other cytotoxic agents was shown to be more effective than cisplatin monotherapy. Cisplatin-based combination chemotherapy such as dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), or gemcitabine-cisplatin is the standard of care for patients with advanced bladder cancer and upper tract cancer, as supported by level 1 evidence for cisplatin-eligible patients [30].

The efficacy of MVAC was first reported in a single-arm study [31] and subsequently compared to single-agent cisplatin in a multicenter phase III trial. In this randomized study, MVAC was shown to provide a survival advantage over cisplatin alone (median survival: 12.5 vs 8.2 months, respectively) [11]. In another randomized study, MVAC resulted in higher response rates and longer survival than a combination of cisplatin, cyclophosphamide, and doxo-

Table 24.2 Selected phase III trials on metastatic urothelial carcinoma

First line						
Study arm	Control arm	Number of patients	Overall response rate (%)	Median PFS (months)	Median OS (months)	Reference
Methotrexate, vinblastine, doxorubicin, cisplatin (MVAC)	Cisplatin	202	45.7	8.3	15.2	11
Dose-dense MVAC	MVAC	134	62.0	9.1	15.5	39
Gemcitabine, cisplatin	MVAC	203	49.4	7.7	14.0	3
Paclitaxel, gemcitabine, cisplatin	Gemcitabine, cisplatin	312	55	8.3	15.8	42
Cisplatin-larotaxel	Gemcitabine, cisplatin	166	57	5.6	13.7	38
Dose-dense gemcitabine	Dose-dense MVAC	64	60.3	7.8	18	41
Bevacizumab, gemcitabine, cisplatin	Gemcitabine, cisplatin	252	40.4	7.7	14.5	43
Second line						
Study regimen	Comparator arm	Number of patients	Overall response rate (%)	Median PFS (months)	Median OS (months)	Reference
Vinflunine	Best-supportive care	253	8.6	3.0	6.9	77
Ramucirumab, docetaxel	Docetaxel	263	24.5	4.07	9.4	68

Results are of study arm

rubicin (median survival: 48 versus 40 weeks, respectively) [32].

Despite superior outcomes with MVAC, its use has been severely limited by substantial toxicities, including neutropenia, mucositis, cardiac and neurologic toxicities, and a significant 3–4% death rate [11, 31]. In an attempt to improve tolerability, other regimens have been investigated.

The combination of gemcitabine-cisplatin was studied in a random comparison with MVAC in the same patient population. In three phase II trials, gemcitabine-cisplatin had similar anti-tumor activity than MVAC with a better toxicity profile [33, 34]. Soon after, a randomized trial designed to demonstrate superior efficacy of gemcitabine-cisplatin over MVAC showed no significant differences in clinical activity between regimens [3]. The overall response rates in the gemcitabine-cisplatin and MVAC arms were 49.4 percent and 45.7 percent, respectively, with median overall survival of 13.8 and 14.8 months. The MVAC arm consistently reported higher incidences of neutropenic sepsis, significant mucositis, and alopecia than the gemcitabine-cisplatin arm. Long-term follow-up also confirmed no difference in five-year survival (gemcitabine-cisplatin 13% and MVAC 15.3%) [13]. Because of the results, the combination of gemcitabine-cisplatin emerged as a preferred regimen for many oncologists given favorable tolerability and similar efficacy compared to MVAC [3, 13, 35].

A potential improvement over the existing standards has been suggested by the use of alternative cisplatin-based combinations. For example, cisplatin–taxane regimens have also yielded favorable activity against advanced urothelial carcinoma, with median overall survival of 10.6–13.6 months and overall response rate ranging from 50% to 60% [36, 37]. In the same clinical setting, a randomized phase III trial showed that the combination of larotaxel (a novel semisynthetic taxoid) and cisplatin for locally advanced upper tract or bladder cancer had inferior outcomes compared to the standard combination of gemcitabine and cisplatin. This trial was also terminated prematurely following

the sponsor's decision to stop clinical development of larotaxel [38].

The practice of dose intensification or the addition of new agents have also been studied with the hope of improvement in clinical outcomes. Traditional MVAC was compared to dose-dense MVAC in the phase III trial. In this study, a 14-day cycle of MVAC with G-CSF was used. Investigators demonstrated that dose-dense MVAC led to significantly greater complete responses (21% vs 9%) with equivalent overall and progression free survival [39]. With longer-term follow-up, however, the survival curves separated, and 5-year overall survival was 21.8% in the dose-dense group compared with 13.5% in the traditional group [40]. Dose-dense MVAC appeared to have superior clinical activity and more favorable toxicity profile compared to standard-dose MVAC. Based on this data, dose-dense MVAC is preferred over standard MVAC based on category 1 evidence for metastatic disease and traditional MVAC is no longer recommended [30]. Similarly, a phase III randomized study assessing dose-dense gemcitabine-cisplatin as a new option comparing dose-dense MVAC compared to dose-dense gemcitabine-cisplatin as first-line therapy in 174 patients with advanced bladder cancer did not result in an improved median overall survival [41].

The addition of paclitaxel to gemcitabine-cisplatin is a triplet option for metastatic urothelial carcinoma. This was demonstrated in EORTC study 30,987, which enrolled 626 patients with advanced urothelial carcinoma (81 percent with primary bladder cancer) and randomly assigned them to treatment with gemcitabine-cisplatin or paclitaxel-gemcitabine-cisplatin for a maximum of 6 cycles [42]. With a median follow-up of 4.6 years, the 3-drug regimen resulted in an increase in the overall response rate compared with gemcitabine-cisplatin (56 versus 44 percent, $p = 0.003$), a trend toward an improvement in progression-free survival (median 8.3 versus 7.6 months) and a trend toward longer overall survival. When the analysis was restricted to patients who met all eligibility criteria (92 percent of the randomized population), paclitaxel-gemcitabine-cisplatin was associated with a significant increase in overall survival (median 16 versus 13 months). A non-intention-to-treat analysis showed that paclitaxel-gemcitabine-cisplatin was associated with a significant improvement in overall survival among patients with primary bladder cancer [42]. An increased incidence of serious (grade 3/4) toxicity, including neutropenia (65 versus 51 percent), fatigue (15 versus 11 percent), and infections (18 versus 14 percent), but a lower incidence of serious (grade 3/4) thrombocytopenia (35 versus 52 percent). The addition of a paclitaxel to gemcitabine-cisplatin has been shown to be of some benefit in a subset of patients having the bladder as the primary origin of the disease and may be considered as an option in highly selected patients [42].

Results of a phase III (CALGB 90601 study) randomized control trial comparing gemcitabine and cisplatin with bevacizumab, a VEGF-targeted tyrosine kinase, or placebo in patients with metastatic urothelial carcinoma have also been recently reported. Patient characteristics of patients enrolled in this study included no prior chemotherapy for metastatic disease and >12 months from prior (neo)adjuvant chemotherapy and ECOG PS 0–1. The addition of bevacizumab to gemcitabine and cisplatin chemotherapy did not improve overall survival and only 1-month improvement in progression-free survival as first-line therapy for metastatic urothelial carcinoma Toxicity of the bevacizumab-gemcitabine and cisplatin combination was comparable to historical data [43].

Carboplatin-Based Regimens

Carboplatin is a platinum compound that is often considered an alternative to cisplatin in treatment regimens for patients who are unfit for cisplatin. Carboplatin has reduced nonhematologic toxicities including nephrotoxicity and the dose is administered based on the glomerular filtration rate. These are important factors that present carboplatin as a therapeutic option for advanced bladder cancer patients with poor renal function [44, 45]. However, carboplatin seems not to be as active as cisplatin, although randomized phase 3 data are unavailable and real-world data are limited in cisplatin-ineligible patients [46].

In cisplatin-eligible patients, results of a randomized phase 2 trial compared MVAC to MCAVI (methotrexate, carboplatin, and vinblastine) have been reported. Overall response rates were 52.0% and 39.0% in the MVAC and MCAVI groups, respectively. Median overall survival was 16.0 months in the MVAC group, compared with 9.0 months in the MCAVI group. Not surprising, MCAVI resulted in an improved toxicity profile with fewer adverse events than MVAC [47]. In the same patient population, gemcitabine and carboplatin were also inferior to gemcitabine and cisplatin [48],. and carboplatin and paclitaxel were inferior to standard MVAC [49].

Several lines of evidence indicate that the combination of gemcitabine and carboplatin is effective, with a better toxicity profile than cisplatin-based chemotherapy, and support its use in patients with impaired renal function or a poor performance status (ECOG ≥2) who are otherwise candidates for combination chemotherapy. A phase 2 trial conducted by Linardou and colleagues evaluated the gemcitabine–carboplatin treatment regimen in 56 untreated patients who were elderly or otherwise deemed unfit for cisplatin-based chemotherapy [50]. Participants in the study had an ECOG performance status of 2–3 (46%), and/or a GFR of 50 mL/min or less (68%), and/or were o ≥75 years (range 54–86). Gemcitabine and carboplatin treatment resulted in an overall response rate of 36.0%, a median progression-free survival of 4.8 months, and a median overall survival of 7.2 months [50]. In another study, 17 patients with impaired renal function with a mean creatinine clearance of 45.4 mL/min received gemcitabine plus carboplatin. The overall response rate was 56.0%, with a median overall survival of 10.0 months [51]. Bellmunt and colleagues administered the gemcitabine–carboplatin combination to 16 patients considered unfit for cisplatin-based therapy because of low creatinine clearance (≤60 mL/min/1.73m^2). The overall response rate was 44.0%. The median overall survival was not reported [52]. Based on these results, the European Organization for Research and Treatment of Cancer (EORTC) conducted a phase 2/3 trial (EORTC 30986 study) in 238 chemotherapy-naïve patients with impaired renal function (glomerular filtration rate <60 but >30 mL/min/1.73m^2) and/or a poor performance status (ECOG ≥2) comparing the gemcitabine–carboplatin regimen to MCAVI in patients who were not candidates for cisplatin-based chemotherapy [53]. This study reported no significant differences in efficacy between the two treatment groups. The incidence of severe acute toxicities was higher for those receiving M-CAVI, including neutropenia (52 versus 63 percent) and febrile neutropenia (5 versus 15 percent) [54]. The final results of this trial suggest that the clinical activity of the combination of gemcitabine and carboplatin was comparable to MCAVI, with a better toxicity profile, and support its use in patients with impaired renal function or a poor performance status (ECOG ≥2) who are otherwise candidates for combination chemotherapy.

Microtubule inhibitors such as the taxanes are non-nephrotoxic, with relatively low renal excretion, and have been evaluated alone or in combination for use in patients that cannot tolerate cisplatin. For example, an ECOG phase 2 trial (E2896) evaluated the activity of a paclitaxel–carboplatin regimen in 37 untreated patients with metastatic urothelial carcinoma and renal dysfunction [median serum creatinine of 1.7 mg/dL (range1.5–3.0]. The paclitaxel–carboplatin treatment regimen showed an overall response rate of 24.3%, with a median progression-free survival of 3.0 months, and a median overall survival of 7.1 months [55]. The addition of gemcitabine to the paclitaxel–carboplatin regimen led to a higher overall response rate of 68.0% and a median overall survival of 14.7 months [56].

Human epidermal growth factor receptor-2 (HER2) genomic alterations are commonly described in urothelial cancer. The efficacy of HER2-targeted agent trastuzumab co-administered with gemcitabine, paclitaxel, and carboplatin to patients with HER2-positive chemo-naïve advanced urothelial carcinoma was assessed in a phase 2 trial. This study enrolled patients with serum creatinine of 2 mg/dL or lower and adequate cardiac function. The overall

response rate was 70 percent and the median overall survival was 14.1 months. Cardiac toxicity rates were higher than projected, but low-moderate grade [57].

Alternative potential approach to multiagent therapy for advanced bladder cancer is dose-dense chemotherapy, in which treatment is administered more frequently. It is postulated that dose dense chemotherapy will minimize tumor regrowth between cycles. Galsky et al. evaluated a dose-dense, sequential regimen in 25 chemo-naive, cisplatin-ineligible patients in a single-arm phase 2 trial [58]. Twenty-five chemo-naive, cisplatin-ineligible patients were enrolled who had creatinine clearance of 30–60 mL/min and/or had prior nephrectomy. Patients received doxorubicin and gemcitabine once every 2 weeks for 5 cycles, followed by paclitaxel and carboplatin once a week for 12 cycles. The overall response rate was 56 percent, with a median overall survival of 15.0 months.

In summary, the available phase 2 data suggest that carboplatin is not as active as cisplatin in advanced bladder cancer. The EORTC 30986 study comparing gemcitabine–carboplatin with MCAVI in cisplatin-ineligible patients demonstrated that gemcitabine–carboplatin is as effective and better tolerated than MCAVI. Until very recently, gemcitabine–carboplatin combination was the preferred course for first-line therapy for cisplatin-ineligible advanced bladder cancer due to the ease of this regimen and its lower toxicity profile relative to the cisplatin-based regimen. Recently, two studies have been undertaken to explore the role of immune-checkpoint inhibitors – atezolizumab and pembrolizumab – in the first-line setting for patients with cisplatin-ineligible advanced bladder cancer whose tumors are positive for PD-L1 expression.

Finally, it should not be assumed that carboplatin can be substituted for cisplatin in most patients without compromising efficacy. It is crucial to ascertain the basis for renal dysfunction prior to selecting a regimen. When reversible causes, such as urinary obstruction by a primary tumor, are the basis for reduced renal function, they should be corrected first; this may allow the use of standard MVAC or gemcitabine-cisplatin regimens.

Non-Platinum-Based Therapy

Regimens that combine gemcitabine with a taxane compound (either paclitaxel or docetaxel) rather than platinum have been evaluated with promising results. Paclitaxel plus gemcitabine appears to be more active than docetaxel plus gemcitabine in patients with advanced bladder cancer. The combination of paclitaxel plus gemcitabine results in objective response rates of 54 to 70 percent and median survival of 13 to 16 months [59–62]. Toxicity with this combination is primarily hematologic, although severe pulmonary toxicity was reported in five patients treated with paclitaxel on a weekly schedule in one series [61]. Based on these results, the weekly gemcitabine–paclitaxel regimen was not recommended for further investigation for patients with advanced bladder cancer. Two phase II trials reported outcomes using the combination of docetaxel plus gemcitabine with objective response rates of 33 and 52 percent and median OS of 13 and 15 months [63, 64]. Interestingly, a systematic review and meta-analysis of standard gemcitabine and carboplatin versus gemcitabine plus taxanes demonstrated median response rates, progression-free survival, and overall survival that were very similar between the two strategies across 27 included studies [65]. As expected, there were differences in toxicity, with more myelosuppression associated with carboplatin and more neuropathy associated with taxanes.

The reduced renal toxicity of epirubicin supported the investigation of its activity and tolerability in a treatment regimen for cisplatin-ineligible patients [66]. A phase 2 study was conducted to evaluate the efficacy of a gemcitabine–epirubicin combination regimen in 38 untreated patients with advanced bladder cancer, who could not receive cisplatin-based treatment because of poor performance status or renal dysfunction [66]. Study participants were 75 years or older, or had ECOG performance status ≥2, or creatinine clearance of 60 mL/min/1.73 m^2 or less. The overall response rate was 39.5 percent, with a median progression-free survival of 4.8 months, and a median overall survival of 8.0 months.

In the same line, this JASINT study investigated the safety and efficacy of vinflunine-

gemcitabine versus vinflunine-carboplatin chemotherapy in 69 cisplatin-ineligible patients with good performance status but impaired renal function as first-line treatment for metastatic urothelial carcinoma. The majority of patients had undergone major surgery before chemotherapy (approx. 80% in both arms), and 55% of patients in the vinflunine-gemcitabine arm and 43% in the vinflunine-carboplatin arm had upper tract urothelial carcinoma. The rates of grade 3–4 hematological adverse events were significantly lower for patients treated with vinflunine-gemcitabine compared to vinflunine-carboplatin (neutropenia 38% versus 68%; febrile neutropenia 3% versus 14%). The disease control rate (defined as complete response plus partial response plus stable disease) was 77 percent for both groups and overall survival ranged between 13 and 14 months. This data showed that the two vinflunine doublets have acceptable clinical activity in these patients.

Given the lack of data on alternative chemotherapeutic regimens for patients with recurrence after radical nephroureterectomy for upper tract urothelial carcinoma, as most of them will suffer from impaired renal function postoperatively [67], vinflunine doublets may become clinically relevant for patients with recurrence after radical treatment for upper tract urothelial carcinoma since this population accounted for approximately half of the patients in this study.

Ramucirumab is an antibody that binds the vascular endothelial growth factor (VEGF) receptor-2 (VEGFR-2), blocking all VEGF ligands from binding to VEGFR-2 and leading to more complete target inhibition of the VEGF pathway. In the phase III RANGE trial, patients with advanced or metastatic urothelial carcinoma were randomly assigned to docetacel plus ramucirumab or docetaxel plus placebo [68]. All patients had progression during or after platinum-based therapy. Progression-free survival with the combination was modestly prolonged compared with docetaxel alone (median 4.1 versus 2.8 months), while the objective response rate was increased with the combination (24.5 versus 14.0 percent). An assessment of the role of ramucirumab in combination with docetaxel will require longer follow-up and an analysis of overall survival, as well as information on its activity in patients who have received checkpoint inhibitor immunotherapy. Ramucirumab is not currently approved for patients with advanced urothelial carcinoma.

Monotherapy

A number of chemotherapy drugs have single-agent activity in patients with metastatic urothelial carcinoma, either in the first-line setting or in previously treated patients. These include platinum compounds (cisplatin, carboplatin), gemcitabine, vinca alkaloids (vinblastine, vinflunine), anthracycline (doxorubicin, epirrubicin), methrotrexate, taxanes (paclitaxel, docetaxel), premetrexed, and ifosfamide.

For first-line therapy, single agent paclitaxel has led to overall response rates of 30.8–42 percent, and median overall survival of 8.4–9.0 months [69, 70] and docetaxel has demonstrated overall response rates of 31.0–45.5%, and median overall survival of 11.0 months [71, 72]. Nanoparticle, albumin-bound paclitaxel (nabpaclitaxel) has demonstrated significant activity as a second-line therapy in patients with metastatic urothelial cancer. As an example, in a phase II study of nabpaclitaxel involving 48 patients, the overall response rate was 28 percent [73].

Gemcitabine was evaluated in a single-arm phase 2 study involving 35 patients that had received at least one previous cisplatin-based chemotherapy. The overall response rate was 22.5 percent, with a median progression-free survival of 3.8 months, and a median overall survival of 5.0 months [74]. The single-agent activity and toxicity profiles of these agents encouraged their incorporation into various treatment regimens.

Pemetrexed is an anti-folate that targets key enzymes in the purine and pyrimidine biosynthetic pathways. Pemetrexed has demonstrated activity in several malignancies including urothelial carcinoma. In a phase 2 study, Sweeney et al. administered pemetrexed to 47 previously treated patients, resulting in an overall response rate of 27.7 percent. The median progression-free survival was 2.7 months, and the median overall survival was 9.6 months [75]. In another study, pemetrexed was administered to 13 patients with advanced bladder

cancer that had received previous chemotherapy. The overall response rate of 8.0 percent did not warrant expansion of the trial as defined by the two-stage Simon design, and the trial was terminated [76]. Note that the use of pemetrexed in patients with significant renal insufficiency (creatinine clearance <40 mL/min) is not warranted.

As a single agent, only vinflunine has been assessed in a randomized phase III trial designed to compare overall survival between patients receiving this agent versus and best supportive care versus best supportive care alone [77]. Although in the intention-to-treat population no benefit in survival was observed, the pre-planned final analysis in the eligible population demonstrated a median overall survival of 6.9 months for the vinflunine arm as compared to 4.3 months for the best supportive care alone arm, with an estimated 22% reduction in the risk of death ($P = 0.0227$). Overall response rate, disease control, and PFS were also statistically significant in favor of the study drug. Vinflunine is approved by the European Medicines Agency and recommended in European guidelines for the treatment of advanced or metastatic bladder cancer after failure of platinum-based therapy.

Administration

Cytotoxic chemotherapy is an essential component of the therapeutic arsenal for metastatic urothelial cancers. The conventional schedule of most common chemotherapy regimens used in the treatment of metastatic bladder cancer and upper tract cancer is described in Fig. 24.1.

Management of Toxicity

Cytotoxic chemotherapy is associated with a unique spectrum of specific adverse events including infusion reaction, nausea and vomiting, alopecia, myelotoxicity, nephrotoxicity, and neurotoxicity among others. These adverse effects are typically transient however, some can be severe or life-threatening. Health-care team must be trained to prevent and recognize these adverse events to ensure optimal safety outcomes. Figure 24.2 summarizes most common adverse events of cytotoxic agents used in bladder and upper tract cancer and management recommendations.

Oncologic Monitoring

There is no a generally accepted follow-up protocol. Tumor response evaluation every 2 to 3 cycles of chemotherapy using the baseline imaging tests performed prior to chemotherapy is commonly used in routine practice. During follow-up, monitoring of long-term treatment toxicities such as peripheral neuropathy or cardiotoxicity per above-mentioned treatments and potential recurrences of secondary tumors should be carried out.

Cisplatin-Based Regimen	
Dose-dense MVAC	Methotrexate (30mg/m² on days 1), vinblastine (3 mg/m² on days 2), doxorubicin (30 mg/m² on day 2), and cisplatin (70 mg/m² on day 2), repeated every 14 days for six cycles
GC	Gemcitabine (1000 mg/m² on days 1, 8, 15) plus cisplatin (70 mg/m² on day 1 or day 2), repeated every 28 days for a maximum of six cycles OR Gemcitabine (1000 mg/m² on days 1, 8) plus cisplatin (70 mg/m² on day 1 or day 2), repeated every 21 days for a maximum of six cycles
Carboplatin-Based Regimen	
Gemcitabine-Carboplatin	Gemcitabine (1000 mg/m² on days 1, 8) plus carboplatin(AUC 5-6 on day 1), repeated every 21days for a maximum of six cycles
Monotherapy	
Vinflunine	Vinflunine 320 mg/m² every 21 days for patients with an ECOG PS of 0 and without previous irradiation of the pelvic area Vinflunine 280 mg/m² at the first cycle for patients with dose escalating to vinflunine 320 mg/m² every 21 days for patients with ECOG performance status of 1 and patients with ECOG performance status of 0 with previous irradiation of the pelvis area

Fig. 24.1 Most common chemotherapy regimens used in the treatment of metastatic bladder cancer and upper tract cancer

Dose - dense MVAC	
Supportive Care	
Hydration	Hydration is required with supplemental electrolytes pre- and post-administration of cisplatin **Example of recommended hydration:** Sodium chloride 0.9% with KCl 20 mEq per liter and magnesium sulfate 8 mEq (1 gram) per liter infused IV at a rate of 250 – 500 mL/hour pre- and post-Cisplatin administration for a total of 1000 – 3000 mL to be infused
Emesis Risk	Day 1 minimal emetic risk Day 2 high emetic risk Scheduled prophylactic antiemetic regimen should be given for prevention of acute and delayed nausea and vomiting based on the emetic risk. All patients should be provided with at least one medication for breakthrough emesis.
Prophylaxis for infusion reactions	Febrile neutropenia risk is high for this regimen. Filgrastim (or clinically appropriate G-CSF agent) 5 mcg/kg subcutaneously daily is recommended to start the day following or up to 3 – 4 days after completion of chemotherapy and to continue until post-nadir ANC recovery to normal or near-normal levels by laboratory standards. OR Pegfilgrastim (or clinically appropriate biosimilar) 6 mg subcutaneously once, recommended to be given the day following or up to 3 – 4 days after completion of chemotherapy. There are insufficient data to support use of pegfilgrastim for cytotoxic chemotherapy regimens administered less frequently than every 2 weeks. Same-day administration is not recommended.
Vesicant Irritant properties	**Vinblastine** is a vesicant. This agent is for IV use only. Vinblastine should be administered via a minibag (eg, 25 mL – 50 mL). Central venous access is recommended for administration of this agent. **Doxorubicin** is a vesicant This agent is administered IV push. The preferred IV push method for a vesicant is administration through the side port of a freely flowing IV; alternatively, the drug can be administered via direct IV push. Central venous access is recommended for administration of this agent. **Cisplatin** is an irritant.
Infection	Primary prophylaxis with granulocyte colony stimulant factors is not justified. The estimated risk of febrile neutropenia is < 20%
Dose adjustments for pre-existing baseline liver or renal dysfunction	**Methotrexate**. A lower starting dose of methotrexate may be needed for patients with liver or renal impairment, and in those with third-space fluid collections (ascites, pleural effusion, etc).Methotrexate should not be administered in the setting of severe liver impairment (total bilirubin >4 x ULN). Adjustment of initial vinblastine and doxorubicin doses may be needed for preexisting liver dysfunction. Adjustment of cisplatin doses may be needed for preexisting renal dysfunction. **Cisplatin** is recommended for patients with a clearance of creatinine > 60 ml/min/1.73m^2. For patients with borderline renal function or minimal dysfunction, a split-dose administration of A lower starting dose of gemcitabine may be needed for patients with liver impairment.
Safety parameters and special Instructions	**Methotrexate** has multiple potential drug interactions including, but not limited to, the following: sulfonamides, salicylates, NSAIDs, penicillins, proton pump inhibitors, and probenecid. The chronic use of these agents during methotrexate therapy should be monitored as they may impact methotrexate clearance. Secondary malignancies have been associated with this drug. **Doxorrubicin** is associated with cardiomyopathy, the incidence of which is related to cumulative dose. Assess LVEF before and regularly during and after treatment with doxorubicin. Doxorubicin is contraindicated for patients with recent myocardial infarction, severe myocardial dysfunction, severe arrhythmia, or previous therapy with high cumulative doses of doxorubicin or any other anthracyclines. Secondary malignancies have been associated with this drug. **Vinblastine**. This agent may cause constipation. Evaluate risk prior to initiation of therapy, then monitor for symptoms as clinically indicated for potential dose modification or discontinuation. Patients often require prophylaxis with a bowel regimen to maintain normal bowel function.
Monitoring	
CBC and differential and platelet count prior to each treatmentand as clinically indicated	
Assess electrolytes, renal and liver function prior to each treatment and as clinically indicated	
Asses changes in neurologic function prior to each cycle	

Fig. 24.2 Prophylaxis and Management of Toxicities Related to Dose-dense MVAC and Cisplatin-Gemcitabine

Assess left ventricular ejection fraction prior to treatment initiation and as clinically indicated during therapy
Evaluate for third-space fluid collections as clinically indicated
Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated
For methotrexate: • Renal function should be monitored prior to each cycle and as clinically indicated for potential dose modification or discontinuation. • Liver function should be monitored prior to each cycle and as clinically indicated for potential dose modification or discontinuation. • This agent may cause dermatologic toxicities. Evaluate risk of dermatologic toxicity prior to initiation of therapy, then monitor for signs and symptoms as clinically indicated for potential dose modification or discontinuation.
For vinblastine: • Signs and symptoms of neurotoxicity should be monitored prior to each cycle for potential dose modification or discontinuation. This agent may cause peripheral neuropathy. Monitor patients as clinically indicated for persistent issues with altered sensation including pain or discomfort and/or regional motor weakness that may interfere with activities of daily living. Dose modification or discontinuation of therapy may be warranted. • Liver function should be monitored prior to each cycle for potential dose modification or discontinuation.
For Doxorubicin: • This agent is an anthracycline. Cumulative anthracycline dosage should be monitored. Ejection fraction should be monitored prior to initiation of treatment and as clinically indicated. • Liver function should be monitored prior to each cycle and as clinically indicated for potential dose modification or discontinuation.
For Cisplatin: • Hypersensitivity reaction may occur with cumulative infusions. Monitor for and treat hypersensitivity reactions institutionalstandard. Based on severity of reaction, adjustment of pre-medications and infusion rates, implementation of a desensitization protocol or referral to a specialist, or discontinuation of therapy may be warranted. • Ototoxicity manifested by tinnitus and/or loss of high-frequency hearing may occur with therapy. Ototoxicity is cumulative and audiometric testing should be considered prior to initiation and as clinically indicated based on clinical exam. • Cisplatin may cause peripheral neuropathy. Monitor patients as clinically indicated for persistent issues with altered sensation including pain or discomfort and/or regional motor weakness that may interfere with activities of daily living. Dose modification or discontinuation of therapy may be warranted.

Recommendations for dose modifications for toxicity and hold parameters	
Myelotoxicity	Delay treatment cycle until the WBC count is >3000/mm^3 and platelet count is >90,000 mm^3 Methotrexate and doxorubicin doses should be reduced by 33% in patients who have a nadir WBC <2000/mm^3.
Neurologic Toxicity	Cisplatin therapy should be discontinued when neurologic symptoms are first observed. The manufacturer recommends a dose reduction of vinblastine by 1 mg/m^2 in patients with severe neurotoxicity.
Mucositis	Doses of methotrexate should be reduced by 33% in patients who develop grade 3 or grade 4 mucositis.
Cardiotoxicity	Discontinue doxorubicin in patients who develop signs/symptoms of cardiomyopathy.
Dose adjustment for renal dysfunction	Hold cisplatin until serum creatinine <1.5 mg/dL and/or blood urea nitrogen <25 mg/dL.
Dose adjustment for liver dysfunction	Reduce the dose of vinblastine by 50% for patients with a direct serum bilirubin >3 mg/dL. [6]Dose reductions for doxorubicin are recommended for total bilirubin >1.2 mg/dL and doxorubicin is contraindicated in patients with total bilirubin >5 mg/dL

Cisplatin-gemcitabine	
Supportive Care	
Hydration	Hydration is required with supplemental electrolytes pre-and post-administration of cisplatin **Example of recommended hydration:** Sodium chloride 0.9% with KCl 20 mEq per liter and magnesium sulfate 8 mEq (1 gram) per liter infused IV at a rate of 250 –500 mL/hour pre-and post-Cisplatin administration for a total of 1000 –3000 mL to be infused
Emesis Risk	**Day 1** High-If cisplatin given on Day 1

Fig. 24.2 (continued)

	Day 2 High-If cisplatin given on Day 2 Days of Gemcitabine are low risk of emesis Scheduled prophylactic antiemetic regimen should be given for prevention of acute and delayed nausea and vomiting based on the emetic risk. All patients should be provided with at least one medication for breakthrough emesis.
Prophylaxis for infusion reactions	Routine prophylaxis is not indicated
Vesicant Irritant properties	Gemcitabine is an irritant Cisplatin is an irritant
Infection	Primary prophylaxis with granulocyte colony stimulant factors is not justified. The estimated risk of febrile neutropenia is < 20%
Dose adjustments for pre-existing baseline liver or renal dysfunction	Cisplatin is recommended for patients with a clearance of creatinine > 60 ml/min/1.73m^2. For patients with borderline renal function or minimal dysfunction, a split-dose administration of Cisplatin may be considered (such as 35 mg/m^2 on Days 1 and 2 or Days 1 and 8). While safer, the relative efficacy of the Cisplatin-containing combination administered with such modifications remains undefined. A lower starting dose of gemcitabine may be needed for patients with liver impairment.
Monitoring	
CBC and differential and platelet count weekly during treatment	
Assess electrolytes, renal and liver function weekly during treatment	
For Cisplatin: • Hypersensitivity reaction may occur with cumulative infusions. Monitor for and treat hypersensitivity reactions institutional standard. Based on severity of reaction, adjustment of pre-medications and infusion rates, implementation of a desensitization protocol or referral to a specialist, or discontinuation of therapy may be warranted. • Ototoxicity manifested by tinnitus and/or loss of high-frequency hearing may occur with therapy. Ototoxicity is cumulative and audiometric testing should be considered prior to initiation and as clinically indicated based on clinical exam. • Cisplatin may cause peripheral neuropathy. Monitor patients as clinically indicated for persistent issues with altered sensation including pain or discomfort and/or regional motor weakness that may interfere with activities of daily living. Dose modification or discontinuation of therapy may be warranted	
Recommendations for dose modifications for toxicity	
Myelotoxicity	Each cycle should not begin until the WBC is ≥3000/microL and platelet count is ≥100,000/microL. Gemcitabine should be withheld on day 8 and/or day 15 of the scheduled treatment if the WBC is <2000/microL or the platelet count is <50,000/microL. If the day 8 or 15 dose of gemcitabine is omitted, the treatment cycle may be shortened to 21 days.
Neurologic Toxicity	Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m^2, although there is marked interindividual variation. Patients with mild neuropathy can continue to receive full cisplatin doses. However, if the neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment.
Pulmonary Toxicity	A variety of manifestations of pulmonary toxicity have been reported. Discontinue gemcitabine immediately and permanently.
Hepatotoxicity	Gemcitabine is commonly associated with a transient rise in serum transaminases, but these are seldom of clinical significance. There is insufficient information from clinical studies to allow clear dose recommendations in these patients.
Nephrotoxicity	Hold cisplatin until serum creatinine <1.5 mg/dL and/or blood urea nitrogen <25 mg/dL. For grade 2 nephrotoxicity during treatment (creatinine >1.5 times normal value despite adequate hydration), creatinine clearance should be determined prior to next cycle, and cisplatin dose reduced if <60 mL/min/1.73m^2
Thrombotic microangiopathy	Thrombotic microangiopathy has been associated with gemcitabine, in individuals who have received a large or small cumulative dose. Consider the possibility of thrombotic microangiopathy if the patient develops Coombs-negative hemolysis, thrombocytopenia, renal failure, and/or neurologic findings. Management consists of drug discontinuation and supportive care, without plasma exchange, as long as there is high confidence in a drug-induced etiology.

Fig. 24.2 (continued)

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Immunotherapy for Metastatic Urothelial Carcinoma

25

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Introduction

Immune checkpoint inhibitors have transformed the landscape of cancer therapy over the last decade and have become part of the standard of care for multiple cancer types. Prior to the advent of immunotherapy, urothelial carcinoma (UC) had been without significant advances in life prolonging therapy for over the last 30 years. For patients with locally advanced or metastatic disease the preferred first-line therapy consists of cisplatin-based chemotherapy which is the only treatment shown to prolong overall survival (OS) in the first line setting. As previously discussed, treatment typically consist of gemcitabine in combination with cisplatin or dose dense M-VAC. These chemotherapy combinations are associated with a response rate in the range of 50–60% and median survival of 12–15 months [1].

However, bladder cancer patients are usually older patients, many of them former or current tobacco smokers with multiple other comorbidities and thus many are not eligible for cisplatin-based therapy [2]. Patients not eligible for cisplatin-based therapy are those with Eastern Cooperative Oncology Group (ECOG) performance status ≥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 or higher [2]. For these patients, treatment options typically included carboplatin-based regimens, single-agent chemotherapy, or best supportive care alone. Carboplatin-based regimens are associated with a shorter OS of approximately 9 months when compared to cisplatin-based therapy [3]. Up to 50% of patients may not be candidates for any type of systemic chemotherapy and thus are offered supportive care alone [4].

Urothelial carcinoma has been known to be an immune responsive tumor since the 1970s when BCG was first studied for the treatment of non-muscle invasive bladder cancer (NMIBC). The US Food and Drug administration (FDA) approved BCG in 1990 and remains the most effective local therapy for the management of high grade NMIBC [5]. Modern immunotherapy, however, has focused on the development of checkpoint inhibitors to enhance the systemic activity of the immune system. The PD-1 receptor is overexpressed on activated effector T-cells and is a negative regulator of T-cell function. Tumor cells and suppressive immune cells in the tumor microenvironment express the ligand for PD-1 (PD-L1) and activate the PD-1 receptor, leading to suppression of T-cell function. PD-L1 is frequently overexpressed in

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urothelial cancer and antibodies have been developed that block this interaction in order to re-activate exhausted T cells leading to an anti-tumor immune response [6].

Indications

Currently five blocking antibodies targeting the PD-1 pathway have been approved for patients with metastatic urothelial carcinoma. All of these agents are currently approved in the second-line setting after the failure of platinum-based chemotherapy [7]. Two of these agents target the PD-1 receptor (nivolumab and pembrolizumab) and three other agents target PD-L1 (atezolizumab, avelumab, and durvalumab).

Atezolizumab and pembrolizumab are now also approved in the first-line setting for cisplatin ineligible patients. Initially the indication was for all cisplatin-ineligible patients, however, more recently in August 2018, the FDA restricted their use to PD-L1 positive patients or patients who are not eligible for any platinum-containing chemotherapy [8]. This occurred after the data monitoring committee for two ongoing randomized phase 3 trials, IMvigor 130 and KEYNOTE-361, found that patients with low PD-L1 expression treated with atezolizumab or pembrolizumab monotherapy had decreased survival compared to those receiving chemotherapy. This decrease in response rate was seen in patients treated with atezolizumab or pembrolizumab as first-line therapy who also had PD-L1 low or negative tumors based on Ventana PD-L1 (SP142) assay or the Agilent PD-L1 IHC 22C3 pharmDx assay, respectively.

Lastly, avelumab has now been approved by the FDA for use as maintenance therapy for patients with advanced urothelial cancer whose disease has not progressed after first-line platinum-based chemotherapy. This approval came after the phase III Javelin Bladder 100 demonstrated improved OS in this patient population [9].

The success of immunotherapy in the metastatic setting has led to research of the utility of these agents in earlier stages of disease. KEYNOTE-057 was a phase 2 study of the efficacy and safety of pembrolizumab 200 mg every 3 weeks for 24 months for patients with BCG unresponsive NMIBC. For these patients radical cystectomy (RC) is the only standard option; patients unwilling or unable to undergo RC were included in this study. Preliminary data from cohort A, which included patients with carcinoma in situ (CIS) with or without papillary tumor, showed a complete response (CR) rate of 40% at 3 months [10]. In the neoadjuvant setting two studies have recently tested immunotherapy for MIBC. PURE-01 was a small study of 27 patients that studied 3 cycles of pembrolizumab 200 mg every 3 weeks prior to cystectomy. Pembrolizumab achieved tumor downstaging in 54% of patients and a CR rate of 42% [11]. Similarly, ABACUS studied 2 cycles of atezolizumab 1200 mg every 3 weeks prior to RC. In this study 39% of patients had tumor downstaging at RC and 29% achieved a CR [12]. These are promising data suggestive of efficacy in localized bladder cancer and warrant further testing in larger randomized trials which may lead to new standards of care in the future.

Patient Preparation

Immunotherapy is fairly well tolerated and associated with improved quality of life when compared to chemotherapy in randomized trials [13, 14]. No significant preparation is required prior to starting therapy. As per NCCN guidelines patients should undergo an assessment of their disease burden with body imaging prior to starting treatment [15]. Baseline laboratory data, including complete blood count (CBC), comprehensive metabolic panel (CMP), and thyroid-stimulating hormone (TSH), are also obtained to monitor for toxicity.

The patient's medical history should be explored for the history of autoimmune disease as there is concern that checkpoint inhibitor therapy could lead to exacerbation or unmasking of autoimmune conditions. Although trials with immunotherapy typically excluded patients with

the history of autoimmune disease, the limited options for patients with metastatic urothelial carcinoma may require consideration of these agents. There is a limited amount of data on the safety of immunotherapy in these patients. However, the results from SAUL, a multinational single-arm safety study of atezoluzimab in patients with advanced UC, suggest that this approach may be safe and effective. The purpose of this trial was to determine the safety of atezolizumab in a real-world setting and thus it included patients otherwise ineligible for the pivotal IMvigor 211. In this study 35 patients with stable and controlled autoimmune disease were included. ORR in this subgroup of patients was 11% with Grade ≥3 or higher treatment related AE's occurring in 9 (26%) patients with 3 (9%) requiring treatment discontinuation.

Additional data from a retrospective study in patients with melanoma has also suggested that anti PD-1 agents pembrolizumab or nivolumab can be given safely in some patients with pre-existing autoimmune disorder; however, this should be only pursued in consultation with a specialist in the immune disorder and after a thorough discussion of the potential risks and benefits of treatment [16]. Clinicians should also closely monitor for immune related adverse events (irAEs).

Not all patients will benefit from immunotherapy and the development of biomarkers that may predict response is an active area of ongoing research [17]. PD-L1 expression on either tumor cells or infiltration immune cells has been shown to correlate with response probability to PD-1 targeting agents. In both IMvigor 210 and Checkmate 275 studies, PD-L1 expression on immune and tumor cells respectively was associated with a response [18, 19]. However, low expression or absence of PD-L1 did not preclude responses. Other markers considered to predict response include tumor mutational burden (TMB) and The Cancer Genome Atlas (TCGA) bladder cancer subtype. Although studied biomarkers have correlated with response rates, they have failed to identify patients who would not benefit from immunotherapy.

Selection of Agent

Response rates and survival observed with the 5 approved agents targeting the PD-1 pathway have been comparable across the individual phase I, II, and III studies that have supported their approval. As no comparative trials have been conducted to formally assess differences in safety or efficacy between these agents, the choice of which agent will be largely driven by patient and physician preference, schedule of administration, and insurance/formulary restrictions.

Atezolizumab

Atezolizumab, a PD-L1 inhibitor, was the first immunotherapy agent approved for urothelial carcinoma on the basis of IMvigor 210, a phase 2 study that enrolled two cohorts of patients. Results of patients in cohort 2 led to the accelerated approval of this agent in the second-line setting [18]. 310 patients with platinum-pretreated metastatic urothelial carcinoma were treated with atezolizumab 1200 mg IV every 3 weeks. This cohort consisted of a heavily pretreated patient population with about 40% of patients having received more than two previous regimens. The objective response rate (ORR) with atezolizumab was 15% which improved on the historical response rate of 10% associated with single-agent chemotherapy, the previous standard. Responses were enriched in the subset of patients with higher levels of PD-L1 as measured by the SP142 assay. However durable responses were also seen in patients with low levels of PD-L1.

Cohort 1 enrolled 119 patients who were considered cisplatin-ineligible to receive atezolizumab every 3 weeks until RECIST progression [20]. The ORR for the entire study was 23% which included 9% of patients who achieved a complete response (CR). Responses were durable and OS for this cohort was 16 months. Based on these results, atezolizumab was granted approval by FDA in April 2017 for patients not candidates for cisplatin-based therapy.

IMvigor 211 was to be the confirmatory phase 3 trial for atezolizumab. The study's primary endpoint was not met as it failed to show improvement of OS in the PD-L1 positive population [14]. In the subset of patients with ≥5% expression of PD-L1 on tumor infiltrating immune cells median OS was 11.1 months with atezolizumab when compared to 10.6 months with investigator's choice chemotherapy (vinflunine, paclitaxel or docetaxel). In this study the PD-L1 positive subgroup benefitted similarly from chemotherapy with ORR of 23% with atezolizumab vs 22% with chemotherapy. However, the duration of response was significantly longer with atezolizumab compared with chemotherapy (15.9 vs 8.3 months). An exploratory analysis of the intent to treat population revealed no difference in ORR, but the duration of response was again longer with atezolizumab (21.7 vs 7.4 months). A benefit for survival with a hazard ratio of 0.85 was also observed in the intent-to-treat population, further supporting atezolizumab's approval based on the prior results from IMvigor 210.

Adverse events to atezolizumab were very similar across these studies. The majority of AEs were mild to moderate in severity with fatigue, nausea, decreased appetite, and pruritus as the most commonly reported. Rates of grade 3 and 4 adverse ranged between 15 and 20% which is significantly lower to that seen with chemotherapy.

Pembrolizumab

Pembrolizumab was the last agent to be approved in the second-line setting for patients with metastatic urothelial carcinoma. KEYNOTE-045 was a randomized phase III clinical trial that compared pembrolizumab 200 mg every 3 weeks to investigator's choice chemotherapy [13]. Chemotherapy options included either paclitaxel or docetaxel for patients in the United States; vinflunine was also an option for patients enrolled in the European Union. A total of 542 patients who had progressed after platinum-based therapy were enrolled to this trial. Pembrolizumab was associated to a significantly higher median OS of 10.3 months versus 7.4 months with chemotherapy. Pembrolizumab was also associated to an improved response rate when compared to chemotherapy (21% vs 11%, respectively). Interestingly, PD-L1 positivity as measured by the 223C assay did not predict response in this study. Response rates to pembrolizumab were the same regardless of PD-L1 expression, however associated with a worse prognosis in patients treated with chemotherapy.

Pembrolizumab was also studied in the first-line setting for cisplatin-ineligible patients in the KEYNOTE-052 trial [21]. In this study 370 patients were treated with pembrolizumab 200 mg every 3 weeks. Patients in this study had a median age of 74 years, 85% of them had visceral disease, and 21% had liver metastases. The ORR which was the primary endpoint for the study was 29% for the entire cohort. 7% of patients had achieved a CR. Again, responses were durable with duration of response (DoR) not reached at the time of analysis. An updated long-term follow-up analysis revealed a median OS of 11.5 moths for the entire cohort. However, in patients with a PD-L1 expression combined positive score (CPS) of ≥10 ORR was 47.3% and median OS was 18.5 months [22].

Adverse events to pembrolizumab were similar to those seen when used for other malignancies. In general, severe adverse events were less frequently observed with pembrolizumab relative to chemotherapy in the KEYNOTE-045 study. The most common adverse events were pruritus, fatigue, and nausea [13]. Grade ≥3 treatment-related events were observed in 15% of patients treated with pembrolizumab versus 49% of those treated with chemotherapy. A similar side effect profile was seen in KEYNOTE-052 with a reported irAEs of 17%. These results suggest that pembrolizumab is a tolerable agent even for patients with poor functional status.

Nivolumab

Nivolumab is a PD-1 inhibitor which was tested in CheckMate-275, a single arm phase II study of previously treated metastatic bladder cancer

patients [19]. A total of 270 patients were enrolled and treated with nivolumab 3 mg/kg every 2 weeks. The ORR was 19.6% for the entire cohort, although patients with higher levels of PD-L1 expression had longer OS, responses were also seen in those with low levels PD-L1. Safety profile with nivolumab is similar to other immunotherapy agents. Grade ≥3 treatment-related adverse events occurred in about 20% of patients. Most common adverse events included fatigue and diarrhea. Three deaths attributed to the treatment occurred in this trial one each with pneumonitis, acute respiratory failure, and cardiovascular failure. For this reason, it is paramount to be vigilant about irAEs as early recognition can prevent higher grade and potentially fatal toxicity.

Avelumab

Avelumab is a fully humanized anti-PD-L1 antibody. This agent was first tested as part of the JAVELIN trial, which was a multi-arm, multicohort phase 1 study of avelumab in a number of diseases [23]. Patients in the bladder cancer cohort were treated with avelumab 10 mg/kg every 2 weeks after they had progressed on platinum-based therapy. Avelumab achieved an ORR of 18%, similar to other agents in this class. Rates of irAEs were also similar in this group. Grade ≥3 adverse events were seen in about 8% of the patients treated. The most common adverse events included fatigue and infusion-related reactions which are unique to this agent and likely relate to the fact that it is a fully humanized antibody. With these results avelumab was approved by the FDA in 2017 for patients with metastatic urothelial carcinoma in the second-line setting.

More recently avelumab was also shown to improve outcomes when used as switch maintenance in the JAVELIN Bladder 100 phase III trial [9]. In this study 668 patients with advanced urothelial carcinoma were treated with standard platinum-based first-line chemotherapy for 4–6 cycles. Patients with responding or stable disease were then randomized to receive either avelumab 10 mg/kg IV every 2 weeks or best supportive care (BSC) alone. Maintenance avelumab was associated to an OS of 21.4 months when compared to 14.3 months with BSC alone. Based on this data the FDA-approved avelumab for maintenance therapy in June 2020.

Durvalumab

Durvalumab is a PD-L1 inhibitor that was tested as part of a multi-cohort phase 1 study in 17 different tumor types. Patients with metastatic urothelial carcinoma who had progressed on platinum-based therapy were treated with durvalumab 10 mg/kg every 2 weeks. In the expanded cohort of this phase I/II study, a total of 191 patients with urothelial carcinoma were treated with durvalumab. Confirmed objective responses were seen in 17.8% of patients with 7 patients achieving a CR [24]. Responses were higher in those patients with high PD-L1 expression as assessed by the companion diagnostic SP263. Although response rates were lower in those with low PD-L1 expression it did not preclude responses. Based on these results, the FDA-approved durvalumab for patients with UC in the second-line setting in 2017. Safety with this agent was similar to that reported with other immunotherapy drugs. Grade 3 and 4 adverse events were seen in 7% of patients. Two grade 5 irAEs occurred – one with autoimmune hepatitis and another with pneumonitis.

Administration

All above immunotherapy agents are administered intravenously at their pre-specified doses and schedules. Avelumab is the only agent that requires premedication with diphenhydramine and acetaminophen prior to the first infusion in order to prevent infusion reactions. The remaining agents do not require any additional premedication:

- Atezolizumab: 1200 mg every 3 weeks [18, 20].
- Pembrolizumab: 200 mg every three weeks [13, 21] or 400 mg every 6 weeks.

- Nivolumab: 3 mg/kg every 2 weeks [19]. However, this agent has moved toward flat dosing of 240 mg every 2 weeks or 480 mg every 4 weeks.
- Avelumab: 10 mg/kg every 2 weeks [23].
- Durvalumab: 10 mg/kg every 2 weeks [24].

Management of Toxicity

Immunotherapy has led to the development of a new class of side effects termed irAEs [25]. As essentially any organ system can be affected by the immune system, a broad knowledge base of both common and uncommon immune-related toxicities is critical for the safe administration of these agents. The most significant irAEs are typically respiratory and gastrointestinal toxicities. However, other severe yet rare toxicities such as cardiac or neurologic toxicity can also occur. Given that fatal toxicities can occur, prompt recognition and initiation of therapy are of paramount importance. The American Society of Clinical Oncology (ASCO) has proposed general guidelines for the management of irAEs associated to immunotherapy [26].

Unlike toxicity with chemotherapy which tends to be cumulative over time, timing of irAEs is highly unpredictable and can happen at any time, although they are most common during the first 6 months of therapy. Additionally, late occurring toxicity has been reported several months after treatment discontinuation which highlights the importance of continued monitoring [27].

The algorithm for managing irAEs depends on the severity of the observed toxicity; however, corticosteroids are a mainstay of management. Patients with grade 1 toxicity can generally be observed and monitored for worsening side effects. For those patients with grade 2 toxicity treatment should be held, corticosteroids initiated (usually at a dose of 1 to 2 mg/kg daily prednisone or equivalent), and not resumed until symptoms improve to grade 1 or less and steroids tapered to 10 mg prednisone daily or less. Even with higher grade irAEs, symptoms usually resolve within 1–2 days from initiation of corticosteroids, which should usually be tapered over a minimum of 4 weeks.

For patients presenting with severe or life threatening irAEs (grade ≥3 toxicity) treatment with checkpoint inhibitors should be permanently discontinued and high doses of corticosteroids should be promptly initiated. Corticosteroids should be continued until symptoms improve to grade 1 toxicity or less, and then these should be gradually tapered over 4–6 weeks. In the event that symptoms do not improve after 3 days of high-dose intravenous steroids, infliximab at a dose of 5 mg/kg should be considered as it has been shown to be effective in managing certain irAEs which are unresponsive to steroids.

Fatigue is among the most common side effects and occurs in 16–24% of patients treated with agents targeting the PD-1 axis [28]. Although severe fatigue has been reported this is rare and the fatigue typically associated with therapy is usually mild and rarely requires treatment interruption. Given the relatively common incidence of endocrinopathies, it is important to rule out adrenal insufficiency or thyroid dysfunction in patients presenting with fatigue.

The most common irAE associated with checkpoint inhibition is that of dermatologic toxicity which is seen in approximately 30–40% of patients treated [26]. Symptoms typically consist of pruritus and a reticular or maculopapular erythematous rash on trunk or extremities. Severe toxicity with the development of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported but this rarely occurs. For the patients presenting with mild toxicity, these can be typically managed with topical steroids and oral dual antihistamine agents. For those patients who fail to respond to this initial therapy, a referral for dermatology evaluation can be considered [26].

Diarrhea is another fairly common side effect reported in patients treated with immunotherapy. Early detection and treatment can reduce the development of more severe toxicity. Patients with mild grade 1 diarrhea can be managed symptomatically with anti-motility agents. However, grade 2 or higher toxicity may require high-dose steroids and thus a colonoscopy can be considered when the diagnosis is in question [26]. Hepatotoxicity has also been reported and typically manifests as elevation of liver enzymes with or without elevation in bilirubin. In the ini-

tial phase 1 studies of PD-1 blocking agents, the rates of hepatitis were reported as less than 5%. Treatment is based on the severity of the toxicity, but the majority of episodes are asymptomatic. Pneumonitis is another uncommon but potentially fatal irAE. A meta-analysis reported an overall incidence of pneumonitis during PD-1 monotherapy of 2.7% [29]. The most common symptoms include dyspnea and cough but given that such symptoms could also represent progressive disease CT imaging is usually obtained to rule out other causes. Management again involves treatment with corticosteroids as per ASCO guidelines [26].

Endocrinopathies are also associated with checkpoint inhibitor therapy, with immune-related hypothyroidism being the most common, which clinically mimics Hashimoto's thyroiditis. Patients may initially present with symptomatic hyperthyroidism, which will then progress to hypothyroidism requiring permanent thyroid hormone replacement. Less common endocrinopathies that are also reported include hypophysitis, adrenal insufficiency, and rarely type 1 diabetes mellitus. Endocrinopathies related to immunotherapy are considered permanent and typically require lifelong hormone replacement therapy and thus patients should be counseled about these risks. A systematic review which included 7551 patients reported an incidence of approximately 10% for patients presenting with clinically significant endocrinopathies [30].

Additional less common side effects in other organs, such as kidneys, neurological toxicity, and cardiac toxicity (manifesting as myocarditis), have been reported, and in rare cases can be fatal despite aggressive therapy with high-dose corticosteroids. This again highlights the importance of close monitoring and early treatment for irAEs.

Oncologic Monitoring

As with other cancer-directed therapy patients should be monitored for toxicity as well as response to therapy. Tolerance of treatment is important to assess at each treatment cycle, especially early in the course of treatment, while also carefully differentiating from symptoms attributable to disease. Routine blood counts and complete metabolic panel should be checked at each cycle and thyroid function tests at every other cycle (approximately every 6 weeks).

In the studies that led to the approval of atezolizumab, patients underwent response assessment at baseline, every 9 weeks for 12 months and then every 12 weeks until disease progression [18, 20]. In KEYNOTE-045 and 052 patients underwent tumor response assessment by CT or MRI 9 weeks after the first pembrolizumab dose and then every 6 weeks for the first year, followed by every 12 weeks for the second year [13, 21]. Response to treatment should be evaluated after every 3 cycles, longer intervals of imaging can be considered for patients who have achieved a sustained major response and are continuing beyond the first year of therapy.

Defining and Evaluating Recurrence

Oncologic monitoring with serial imaging serves for the evaluation of disease response and assessment of progressive disease. For patients who achieve a CR we continue with clinical surveillance as per clinical practice guidelines [15]. If at any point imaging reveals evidence of progressive disease or new lesions concerning for recurrence a biopsy can be considered particularly if the diagnosis is in question.

Different to patients receiving chemotherapy, patients treated with immunotherapy can develop initial evidence of progressive disease on imaging and later achieve a response. This has been termed pseudo-progression and occurs in approximately 1.5% to 17% of patients with urothelial cancer [31]. For instance, in the IMvigor 210 phase II trial, patients were permitted to continue treatment beyond progression if deriving clinical benefit as determined by the treating investigator. In this study 120 of 310 patients were treated beyond progression and 20 (6%) of them achieved a delayed response [18]. It is important to recognize that pseudo-progression with single-agent PD-1/L1 blockade occurs rarely in urothelial

cancer, and thus, the vast majority of progression noted on initial imaging is real and a change in therapy is warranted. Pseudo-progression is only invoked in a patient with improved laboratory indices and disease-related symptoms but with discordant findings on imaging. In these cases, imaging should be repeated in a short interval of 4–6 weeks to confirm subsequent progression versus treatment response.

Conclusion

Checkpoint inhibitor therapy has transformed the treatment of advanced urothelial carcinoma, and additional FDA approvals in early-stage disease may be expected in the near future. As immunotherapy has moved to the first-line metastatic setting, tumor factors such as disease volume, PD-L1 expression, and other biomarkers as well as patient factors such as comorbidities and patient preference will need to be closely considered in choosing appropriate first-line treatment [32]. Further research is ongoing given the need to better identify the patients that may best benefit from first-line immunotherapy versus chemotherapy, or the combination.

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Novel Therapies

26

Scot Niglio and Matthew D. Galsky

Novel Therapies

Indications

For decades, standard systemic treatment for metastatic urothelial cancer has been limited to cytotoxic chemotherapy. However, high throughput DNA and RNA sequencing strategies have identified a number of novel therapeutic targets that are shared across subsets of urothelial cancers [1–4]. The promise of therapies directed against such targets is an improved therapeutic index of systemic therapies when linked to the molecular of an individual patient's tumor with therapies that might be more selective for tumor- or tumor microenvironment–specific pathogenic mechanisms.

Patient Preparation

A number of experimental therapies discussed in this section are linked to the presence of a specific molecular alteration in a patient's tumor, particularly recurrent somatic genomic mutations. There are a number of commercial targeted exome sequencing platforms currently available including some that have been cleared by the US Food and Drug Administration and potentially covered by payors for patients with advanced/metastatic solid tumors. While such testing has become more widespread in patients with metastatic urothelial cancer, the potential clinical utility of such testing routinely in clinical practice remains to be established. However, with approvals by regulatory authorities for therapies linked to somatic mutations expected in the near term, the role of routine genomic sequencing may be more firmly established. Importantly, because the therapies outlined in this section are not approved by regulatory authorities, their use is not recommended outside of the context of a clinical trial.

Selection of Agent

Several, but not all, of the therapies discussed below have been studied in the context of predictive biomarkers and are expected to confer benefit in a narrowly defined patient population based on molecular diagnostics.

Anti-Angiogenic Pathways

Tumor angiogenesis has a pivotal role in tumor migration, growth, and metastasis, making it an attractive therapeutic target. Multiple ligands, with dysregulated expression in urothelial

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cancers, have shown to be involved in tumor angiogenesis including basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), interleukin-8 (IL8), angiopoietins, and vascular endothelial factor (VEGF) which is one of most characterized [5, 6].

Bevacizumab is a recombinant humanized monoclonal antibody that binds VEGF and has demonstrated improved outcomes in many tumor types. Bevacizumab was combined with cisplatin and gemcitabine in the first-line setting in metastatic urothelial cancer in phase II of 43 patients [7]. The study reported an objective response rate of 72% with a median overall survival (OS) time of 19.1 months. However, the trial failed to meet its primary endpoint of improved progression-free survival compared to historical controls. Based on the promising median OS, a phase III study of gemcitabine + cisplatin with or without bevacizumab was launched by the Alliance for Clinical Trials in Oncology and has completed accrual awaiting final results. A phase II trial of gemcitabine, carboplatin, plus bevacizumab in cisplatin-ineligible patients has also been completed [8].

Ramucirumab is a fully humanized monoclonal antibody that targets the VEGFR2 extracellular domain. A randomized phase II trial of patients with progressive metastatic urothelial cancer despite prior platinum-based chemotherapy to a combination of ramucirimab and docetaxel, docetaxel alone, or icrucumab (VEGFR1 antibody) and docetaxel [9]. The ramicirumab arm demonstrated a significant improvement in progression-free survival compared to docetaxel alone. This led to a phase III study (RANGE) where 530 patients with metastatic urothelial carcinoma progressing despite platinum-based chemotherapy were randomized 1:1 to ramucirumab combined with docetaxel or placebo plus docetaxel [10]. Progression-free survival was prolonged significantly in patients treated with ramucirumab plus docetaxel versus placebo plus docetaxel from a median 4.07 months vs. 2.76 months, respectively. There was no improvement in survival and the role of ramucirimab in the armamenterium remains to be defined.

Sunitinib is a multi-kinase inhibitor targeting VEGF-1,-2,-3 as well as platelet-derived growth factor-α and β, KIT and fms-like tyrosine kinase-2 [11]. A single-agent trial explored sunitinib in patients with metastatic urothelial cancer progressing despite prior therapy. Two different dose schedules (50 mg 4 weeks on/2 weeks off and 37.5 mg continuous dose) were assessed. A partial response was seen in 4 patients for both groups [12].

Pazopanib, another multi-kinase inhibitor with anti-VEGFR activity, has also been studied in urothelial cancer. The phase II PLUTO trial compared the efficacy of pazopanib vs paclitaxel in patients who had received prior platinum therapy. However, the trial failed to demonstrate an improvement in outcomes with pazopanib and revealed a numerical improvement in OS favoring the paclitaxel arm [13].

Cabozantinib is a multi-target kinase inhibitor with activity against VEGFR, c-MET, and other kinases that has shown clinical activity in patient with relapsed or refractory metastatic urothelial carcinoma [14]. Given studies in model systems and patients revealing immunomodulatory effects with cabozantinib, several trials combining this agent with PD-1/PD-L1 blockade have been launched [15].

Together, these trials demonstrate that a subset of patients with metastatic urothelial cancer derive benefit from antiangiogenic therapies including single-agent therapies. However, because the majority of patients do not respond to treatment, the development of predictive biomarkers will be likely necessary to integrate such therapies into standard management for urothelial cancer.

Antibody Drug Conjugates

Antibody-drug conjugates (ADCs) are monoclonal antibodies directed to antigens highly expressed on tumor cells which are conjugated to a cytotoxic with a linker molecule. The antibody portion binds to a specific antigen on the surface of cancer cells, is endocytosed, and releases its cytotoxic payload after cytotoxic degradation [16].

Enfortumab vedotin is an ADC that targets Nectin-4, a type I transmembrane protein that can promote epithelial-to-mesenchymal transition, invasion, and metastasis through integrin, PI3K/AKt and Wnt/β-catenin signaling pathways. Nectin-4 is purported to play a role in the pathogenesis of cancer and is overexpressed in multiple malignancies [17, 18]. In urothelial cancer specimens, increased expression of Nectin-4 protein has been demonstrated in upward of 83% of samples [19]. Enfortumab vedotin consists of a human anti-nectin-4 antibody conjugated to the anti-mitotic agent MMAE. In a phase I trial enrolling 81 patients, 41% achieved an objective response [20]. Preliminary results from a phase II trial confirmed a similar response rate, even among patients previously treated with immune checkpoint blockade, and a phase III compared to chemotherapy is currently underway.

Sacituzumab govitecan is another ADC that targets human trophoblast cell-surface antigen, Trop-2 a cell-surface glycoprotein with expression in many epithelial cancers with higher expression correlating with higher stages of urothelial cancer [21, 22]. Sacituzumab govitecan is an anti-Trop-2 antibody conjugated with SN-38, the active metabolite of irinotecan. Results from a phase I/II in 45 patients with metastatic urothelial cancer showed an overall response rate of 31% [23]. Myelosuppression was the main dose limiting toxicity with neutropenia representing 38% of Grade ≥ 3 adverse events. TROPHY-U-01 a single-arm, open label, global phase II trial of sacitizumab govitecan was launched to confirm this level of activity [24].

PARP Inhibitors

DNA damage response (DDR) proteins help to maintain genomic integrity from continuous environmental and intracellular stressors [25]. Up to 25% of urothelial cancers harbor somatic DDR alterations including ERCC1, BRCA1, BRAC2, and ATM [2]. Poly ADP ribose polymerase (PARP) is a family of proteins involved in a number of cellular processes including DNA repair, particularly repair of single-strand DNA damage. In several solid tumors, DDR alterations have been shown to lead to "synthetic lethality" in the context of treatment with PARP inhibition. Inhibiting PARP leads to accumulation of excessive DNA damage that is lethal to the tumor cell [26]. Case reports have demonstrated single-agent activity of the PARP inhibitor olaparib in patients with metastatic urothelial cancer harboring DDR alterations [27]. Several prospective trials are now assessing the activity of PARP inhibition in patients with metastatic urothelial cancer in either populations of patients selected for tumors harboring DDR alterations or in "all comer" populations.

Fibroblast Growth Factor Receptor Alterations

Fibroblast growth factor (FGF)/fibroblast growth factor receptor (FGFR) signaling is altered in many malignancies promoting oncogenesis, angiogenesis, and drug resistance [28]. FGFR binding leads to receptor dimerization, tyrosine kinase domain transphosphorylation, and activation of downstream signaling molecules. FGFR has been shown to play a role in multiple intracellular pathways including mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/Akt, phosphokinase C (PKC), janus kinase–signal transducers and activators of transcription (JAK-STAT), p38, and ribosomal s6 kinase (RSK) signaling [29]. Urothelial cancers harbor among the highest frequency of somatic alterations in FGFR3, including FGFR3 gene fusions, with such alterations occurring in up to 20% of muscle-invasive tumors [30, 31]. FGFR inhibitors can be separated into three different classes: tyrosine kinase inhibitors (TKI), neutralizing monoclonal antibodies (mAbs), and FGF-trapping molecules [29]. First-generation FGFR TKIs bind to the catalytic site ATP-binding domain but are non-selective and bind various other tyrosine kinase receptors. Second-generation FGFR TKIs are selective to FGFR and were developed to lower off-target effects. Neutralizing mAbs are characterized by a higher specificity than TKIs and may result in reduced

Table 26.1 FGFR inhibitors in development for urothelial cancer treatment

Inhibitor	Class	Target	Phase	Stage	Sample size (pts)	ORR
Infigratinib [32]	TKI	FGFR 1–3	I	Unresectable, metastatic	67	25.4%
Erdafitinib [33]	TKI	FGFR 1–4	II	Unresectable, metastatic	96	42%
Rogaratinib [35]	TKI	FGFR 1–4	I	Locally advanced, metastatic	219	24%
Pemigatinib [34]	TKI	FGFR 1–3	II	Unresectable, metastatic	Cohort A: 64* Cohort B: 36*	Cohort A: 25%* Cohort B: NR*

*Cohort A – patients with FGFR3 mutations/fusions, Cohort B – patients with other FGF/FGFR3 genetic alterations. *FGF* fibroblast growth factor, *FGFR* fibroblast growth factor, *NR* not reported, *ORR* objective response rate, *Pts.* patients, *TKI* tyrosine kinase inhibitor

toxicity. FGF-trapping molecules work by sequestering FGF ligand inhibiting it from binding its receptor [29]. Table 26.1 highlights FGFR inhibitors further along in the development for urothelial cancer. The most common side effects of FGFR inhibition are alopecia, constipation, diarrhea, dry mouth, dysgeusia, fatigue, hyperphosphatemia, and stomatitis [32–35]. While there is not currently a FGFR inhibitor approved by the US Federal Drug Administration for urothelial cancer, several molecules are being tested in late phase trials aimed at achieving regulatory approval.

Human Epidermal Growth Factor Receptor Inhibitors

HER2 is a member of epidermal growth factor receptor family and aberrant signaling leads to cancer cell migration, invasion, adhesion, angiogenesis, and survival through the PI3K/AKT/mTOR and RTK/RAS pathways. HER2 overexpression, amplification, and activating mutations have been reported in urothelial cancer raising the possibility of therapeutic modulation of HER2 as a treatment strategy [6, 36].

Trastuzumab is a monoclonal antibody targeting HER2. In a multicenter phase II trial, patients with metastatic urothelial cancer and HER2 overexpression patients received gemcitabine plus either cisplatin or carboplatin with or without trastuzumab [37]. The addition of trastuzumab had an acceptable safety profile. However, there was no significant difference in objective response rate with or without trastuzumab.

Lapatanib is a small molecule dual EGFR/HER2 kinase inhibitor that has also been explored in urothelial cancer. In a randomized, placebo-controlled phase III trial HER1/HER2 positive patients without progression of disease following first-line chemotherapy for metastatic urothelial cancer were randomized to "switch maintenance" with lapatinib versus placebo. Unfortunately, there was no significant difference in overall survival or progression free survival [38].

Afatinib is an irreversible tyrosine kinase inhibitor of the ErbB receptor family and was investigated in a phase II of patients with metastatic platinum-refractory urothelial cancer [39]. Among 23 patents, 5 achieved the primary end point of 3-month progression-free survival. Next-generation sequencing of 21 available samples showed that molecular alterations in HER2 and ERBB3 were found to be associated with better outcomes; 5 out 6 patients with ERBB molecular alterations with HER2 copy number amplification, and/or ERBB3 somatic mutations achieved 3-month progression-free survival, where none of the 15 without alterations reached this milestone.

The basket trial SUMMIT prospectively sought to define the biologic and therapeutic significance of known HER2 and HER3 mutations and variants of unknown significance using a pan-HER kinase inhibitor neratinib [40]. Specific types of somatic HER2 alterations were found to occur predominantly in certain tumor types with extracellular domain mutations occurring predominantly bladder cancer. Interestingly, this study revealed that although the same type of HER2 alteration may confer sensitivity to small molecule inhibitors of

HER2 in some tumor types and not others. For example, breast, cervical, and biliary cancers with HER2 extracellular domain alterations responded to neratinib, while those with bladder cancer did not.

mTOR Inhibitors

Increased activation in phosphoinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway has been demonstrated in urothelial cancer. PI3K activation is mainly a result of decreased PTEN expression and deregulation through overexpression or activation of growth factor receptors and activating mutations in PI3K. Loss of PTEN is detected in up to 30% of urothelial cancer, associated with more aggressive tumors, and inferior patient outcomes [41–43].

Everolimus, an mTORC1 inhibitor, was explored in a phase II in patients with advanced urothelial cancer after treatment failure of platinum-based chemotherapy [44]. Although the study did not meet its primary endpoint, genomic analysis of an extreme responder helped to define potential molecular alterations associated with sensitivity [45]. Specifically, whole exome sequencing of the archival tumor specimen from a patient who had an ongoing complete response for more than 2 years found a frameshift mutation in tuberous sclerosis complex 1 (TSC1). Preclinical models had shown loss of function mutations like this led to mTORC1 dependence. The investigators went on to analyze 13 bladder cancer patients treated with everolimus in the same trial. Three additional tumors revealed TSC1 nonsense mutations of which two patients had minor responses. A fourth patient with 7% tumor regression had a somatic missense TSC1 alteration. This study suggests that TSC1 could potentially be used as a biomarker to predict everolimus treatment response and has been pivotal advancing precision medicine in urothelial cancer. Several other trials mTOR inhibitors in urothelial cancer have failed to demonstrate appreciable activity in unselected patients [6].

Table 26.2 Notable toxicities of novel therapeutics for urothelial cancer

Class of drug	Notable toxicities
Antibody drug conjugates	*Enfortumab vedotin:* Alopecia, anemia, anemia, decreased appetite, diarrhea, dysgeusia rash, fatigue, hypoglycemia, hyponatremia, hypophosphatemia, nausea, pruritis, urinary tract infection
	Sacituzumab govitecan: Abdominal pain, anemia, constipation, diarrhea, fatigue, febrile neutropenia, hyperglycemia, hypokalemia, hypomagnesemia, hypophosphatama, neutropenia, neutropenia, urinary tract infection
PARP inhibitors	Abdominal pain, arthralgias, fatigue, headache, muscle pain, myelosuppression, nausea, peripheral edema, pneumonitis, vomiting
FGFR inhibitors	Alopecia, anemia, constipation, decrease appetite, diarrhea, dry mouth, dysgeusia, elevated creatinine, fatigue, hyperphosphatemia, nausea, vomiting
HER2 inhibitors	Cardiac toxicity, decreased left ventricular ejection fraction, diarrhea headache, rash, infection, weakness, fatigue, interstitial lung disease, pneumonitis infusion reaction, fever, paresthesia,
mTOR inhibitors	Diarrhea, dyslipidemia, fatigue, hyperglycemia, infection, mouth sore, mucositis, myelosuppression, neutropenic fever, peripheral edema, pneumonitis, rash, stomatitis

Administration

The medications described in this chapter are not yet FDA approved for the treatment of urothelial cancer.

Management of Toxicity

Toxicities for select novel medications currently under investigation are outlined in Table 26.2.

Oncologic Monitoring

Oncologic monitoring of experimental novel therapies should be performed as outlined in the clinical trials exploring these therapies. The

majority of the novel therapeutics are being evaluated in metastatic urothelial cancer where cross-sectional imaging is utilized on a regular basis to assess for response to treatment. Common imaging modalities include computed tomography (CT) scan of the chest, abdomen, and pelvis or CT chest along with magnetic resonance imagine (MRI) abdomen and pelvis.

Defining and Evaluating Recurrence

Given that the novel therapies outlined in this section have been predominantly explored in the setting of metastatic disease, and complete responses to treatment are unusual, serial imaging is more commonly performed to identify progression rather than recurrence per se. Progression of disease is defined Response Evaluation Criteria in Solid Tumors (RECIST) in the setting of clinical trials and in clinical practice the appearance of new tumor lesions or growth of existing lesions is commonly utilized to define treatment failure.

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Variant Histology: Management Pearls

27

Subodh K. Regmi and Badrinath R. Konety

Introduction

The term "variant histology" is used broadly when describing the histological characteristics of neoplasms of the urothelial tract. However, with the recognition of the specific variants in the urothelial cancer histology over the past decade, the 2016 WHO classification of tumors of the urothelial tract has attempted to shed some light into this conundrum (Table 27.1). The grouping of these variations into two distinct categories also has distinct prognostic and possible management implications. *Invasive urothelial carcinoma with divergent differentiation* refers to tumors arising from the urothelial tract where urothelial histology is predominant along with other histologic variations. When the tumor histology is almost exclusively comprised of one or more variant forms other than urothelial, then such tumors are considered as *invasive variants of urothelial carcinoma* [1].

Non-urothelial cancers of the urothelial tract are distinct from variants of urothelial carcinoma. These rare tumors form about 5% of all bladder cancers [2] and the common forms are squamous cell neoplasms, glandular neoplasms, urachal carcinoma, tumors of mullerian type, neuroendocrine tumors, melanocytic tumors, mesenchymal tumors, and other miscellaneous tumors. These neoplasms, though grouped as variant histology,

Table 27.1 Variant histology as per the WHO proposed classification 2016

Invasive urothelial carcinoma with divergent differentiation	**Non-urothelial variants**
With squamous differentiation	*Squamous cell neoplasms*
With glandular differentiation	Pure squamous cell carcinoma
With trophoblastic differentiation	Verrucous carcinoma
With mixed or other types of differentiation	Squamous cell papilloma
Invasive variants of urothelial carcinoma	*Glandular neoplasms*
Nested, including large nested	Adenocarcinoma, NOS
Microcystic	Enteric
Micropapillary	Mucinous
Lymphoepithelioma-like	Mixed
Plasmacytoid/signet ring cell/diffuse	Villous adenoma
Sarcomatoid	*Urachal carcinoma*
Giant cell	*Mullerian tumors*
Poorly differentiated	*Neuro-endocrine tumors*
Lipid rich	Small-cell neuro-endocrine carcinoma
Clear cel	Large-cell neuro-endocrine carcinoma
	Well-differentiated neuro-endocrine tumor
	Paraganglioma
	Melanocytic tumors
	Mesenchymal tumors
	Urothelial tract lymphatic and hematopoietic tumors
	Other tumors

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are distinct from variants of urothelial carcinoma and deserve a separate and detailed discussion.

Though these variations in histology are based on the hematoxylin and eosin–stained preparations, there are distinct molecular features corresponding to the higher incidence of genetic and epigenetic mutations as well as peculiar changes in gene and protein expression patterns [3]. Reports on management outcomes of these histological variants in comparison to conventional urothelial cancer have been conflicting. Pure histological variant tumors are likely to have worse outcomes compared to mixed tumors with urothelial and variant histology [4].

The purpose of this chapter is not only to recognize the distinct nature of these histological entities but also to discuss the implications on management and prognostication of disease. We will focus on the importance of recognition and categorization of correct variant histology, then consider the individual features, and finally discuss the implications in treatment of non-invasive as well as invasive forms of the variants both in the urinary bladder as well as in the upper tracts.

Identifying Variant Histology on Trans Urethral Resection (TUR) Specimens

Historically, the identification of variant histology on TUR specimens was frequently associated with higher stage at diagnosis [5]. Interestingly many of these variants bear some similarity to benign lesions which may pose a challenge to their correct identification [6]. The yield of TUR specimens was previously limited by factors like the amount of tissue that is sampled as well as the skill of the diagnosing pathologist [7] and had been reported to be as low as 39% [8].

In one study, non-academic pathologists were unable to recognize the variant histology in TUR specimens in half the cases, even with 47% of all the specimens in the study having extensive amounts of variant differentiation on subsequent review [9]. These variations in the recognition of variant histology has led to guideline recommendations for more centralized review by genitourinary subspecialized pathologists for a second opinion [10]. It is important to note that up to 1/3 of bladder cancer specimens can harbor variant histology [1]. The presence of variant histology could alter management even in the absence of T2 disease.

Recent TUR biopsy series have noted a rise in the identification of histological variants in non-muscle invasive disease broadly among both academic and community pathologists [8]. A review of second opinion pathology evaluation reported that only 18% of the time the second opinion read identified variants not recognized on the initial pathologic examination by a community pathologist [11]. Another study, which examined the accuracy and prognostic value of variant histology detected at TUR, found a concordance rate of 83.6% between the TUR and subsequent radical cystectomy (RC) specimen [12].

Distinguishing Features of Variants

There are clear distinguishing features of variants as described in the 2016 WHO classification [1]. Several other forms of rare variants are also described in the literature [13], which have not been included in the WHO classification and will not form a part of our discussion. In this section, we highlight these distinguishing features and lay out possible future directions where molecular diagnostics are likely to have an important role in the management of variant bladder cancer.

Urothelial Carcinoma with Divergent Differentiation

Several authors have described the characteristic features of these variants in detail [5, 14–16]. *Urothelial carcinoma with squamous differentiation* is the most frequent variant (20–50%) and expresses urothelial and squamous markers [17–21].*Urothelial carcinoma with glandular differentiation* occurs much less frequently(6–18%) [5, 19] and may even be seen with isolated carcinoma in situ [22, 23]. *Urothelial carcinoma with trophoblastic differentiation* seen in 28–35%, and all divergent forms

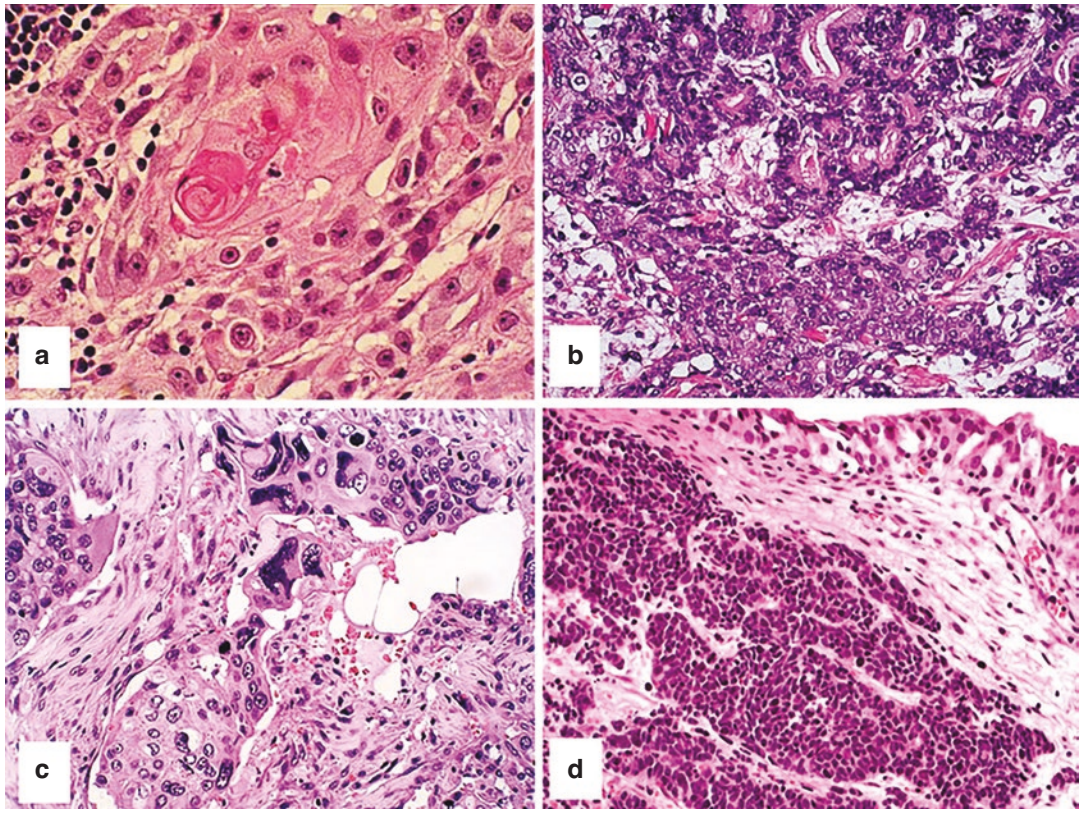

Fig. 27.1 Urothelial carcinoma with divergent differentiation showing squamous (**a**), glandular (**b**), trophoblastic (**c**), and small-cell differentiation (**d**). (With permission from: John Wiley and Sons [13])

are differentiated from their pure counterparts (squamous cell carcinoma, adenocarcinoma and choriocarcinoma, respectively) by the presence of urothelial elements [21, 24] (Fig. 27.1). Other divergent forms can also be present, though not as common as the preceding ones including even small-cell, nested or micro-papillary elements in small amounts.

Invasive Variants of Urothelial Carcinoma

Nested urothelial carcinoma and *microcytic urothelial carcinoma* bear resemblance to benign lesions and therefore need identification of TERT promoter mutations for correct diagnosis [23, 25–28]. *Lymphoepithelioma like urothelial carcinoma* may be present in pure or mixed forms with a prominent lymphoid stroma [13, 23, 25]. *Plasmacytoid/signet ring cell/diffuse urothelial carcinoma* is a rare and a locally aggressive mucin producing variant which also differentiated from adenocarcinoma by the absence of extracellular mucin [26–28] .

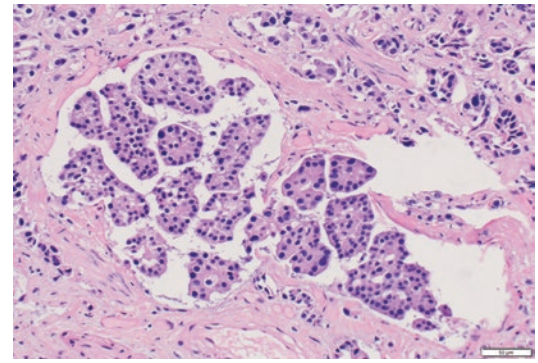

Fig. 27.2 Invasive micropapillary carcinoma. (With permission from Paari Murugan, M.D., Department of Pathology, University of Minnesota)

Micropapillary bladder cancer (MPBC) (Fig. 27.2) bears resemblance to the papillary

serous carcinoma of ovary [29] and presents as invasive and non-invasive forms. It is also consistently associated with conventional urothelial carcinoma and rarely with adenocarcinoma, sarcomatoid carcinoma, or even small-cell carcinoma [30, 31] and is perhaps the most well-described and followed variant. *Sarcomatoid urothelial carcinoma* is an aggressive variant that has features of both epithelial and mesenchymal elements [32–34].Other rare variants like *giant cell urothelial carcinoma, lipid rich urothelial carcinoma, and clear cell (glycogen rich) urothelial carcinoma* are uncommon [28, 35, 36] including *poorly differentiated urothelial tumors,* which have been recently added to the classification [13].

Non-urothelial Variants

The list of non-urothelial variant histology is also quite extensive. Squamous cell carcinoma, adenocarcinoma, and neuroendocrine small-cell carcinoma are the most clinically relevant subtypes. *Squamous cell carcinoma of the urinary bladder* (Fig. 27.3) can either be associated with schistosomiasis or occur denovo (bilharzial vs non-bilharzial). Histologically they may be well, moderately, or poorly differentiated and at times have the characteristic keratin pearls with invasive nests and frequent desmoplasia [37]. *Adenocarcinomas* (Fig. 27.4) can be pure, ura-

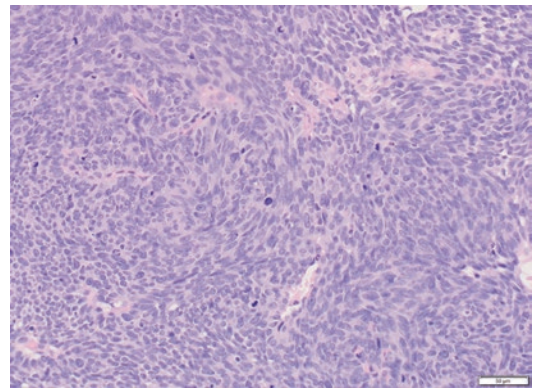

Fig. 27.4 Small-cell bladder cancer. (With permission from Paari Murugan, M.D., Department of Pathology, University of Minnesota)

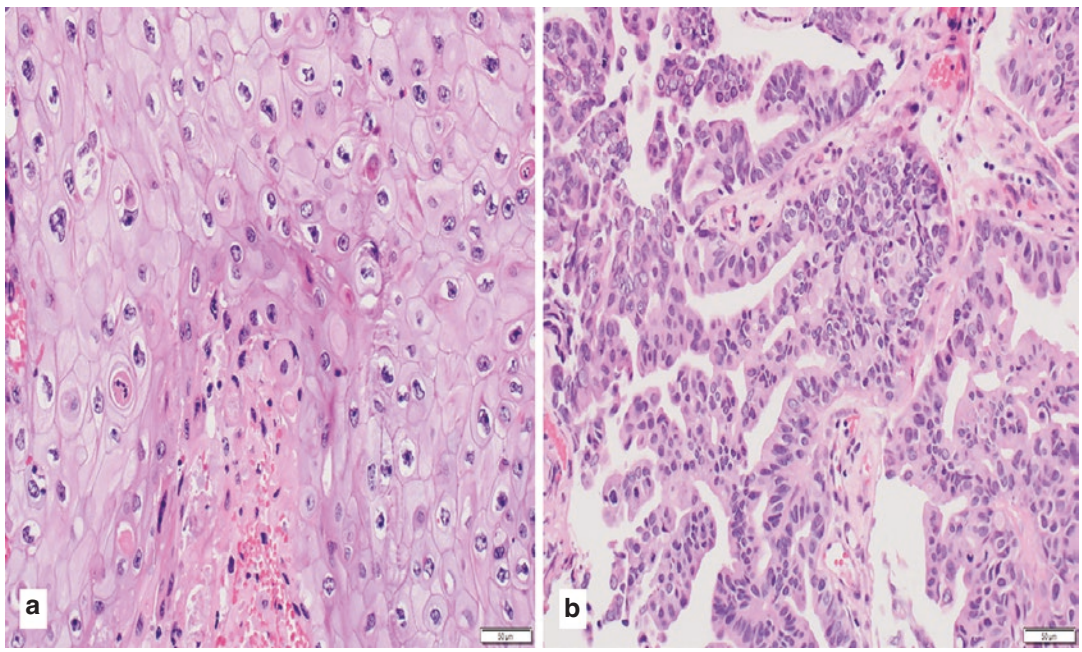

Fig. 27.3 Squamous cell carcinoma (**a**) and adenocarcinoma (**b**) of the urinary bladder. (With permission from Paari Murugan, M.D., Department of Pathology, University of Minnesota)

chal, or mullerian type where the distinction depends upon the tissue of origin. Pure adenocarcinoma is the most common type with classical glandular histological features [37].

Small-cell carcinoma (SmCC) (Fig. 27.4) is a part of the neuroendocrine group of non-urothelial tumors which closely resemble small-cell carcinomas elsewhere and may be seen in its pure form or mixed with other forms of urothelial tumor [37]. It is important to differentiate this from small-cell tumor of the prostate.

Molecular Features of Variants

Urothelial carcinoma has a wide genomic heterogeneity along with the broad phenotypic variations [38]. Recently there has been a sustained effort to describe and catalog this heterogeneity in terms of molecular subtypes by various researchers [39–41]. The ultimate goal of such a classification is to influence management strategies and accurately predict disease prognosis. Prominent work from the group at Lund University [41, 42] and The Cancer Genome Atlas (TCGA) group [39] have greatly increased our understanding of the molecular landscape of bladder cancer. The Lund University group has proposed five distinct phenotypes – urothelial-like, genomically unstable, basal/scc-like, mesenchymal-like, and small-cell/neuroendocrine-like. However, this classification may not necessarily conform to the IHC pattern especially with mesenchymal like and small cell/neuroendocrine like molecular subtypes [41], thus leading the researchers to suggest that a binomial classification with tumor cell phenotype and gene expression cluster would be more appropriate. Warrick et al. [43] studied molecular heterogeneity in 83 histological variants and found that 93% of variants were classified either as basal squamous, urothelial like, or genomically unstable using the immunohistochemistry-based method developed at Lund University [41]. Further research needs to be done to understand the clinical applicability of this knowledge.

Summary Pearls

- *Up to 1/3 of all bladder cancer specimens harbor variant histology.*
- *Presence of variant histology, even in the absence of muscle invasion, can alter disease management.*
- *Second opinion from specialized genitourinary pathologists may be needed upon its identification.*
- *Molecular characterization of tumors suggests distinct variations in gene expression profiles of some of the tumors such as neuroendocrine variants*

Intravesical Treatment for NMIBC with Variant Histology – Is There a Role?

Limited literature is available on the use of either BCG or intravesical chemotherapy in the context of NMIBC with variant histology. Several authors have evaluated the role of intravesical immunotherapy with BCG in variant NMIBC. Shapur et al. [44] have reported that the NMIBC with variant histology was more likely to progress to muscle invasive bladder cancer (MIBC) in comparison to conventional urothelial carcinoma (UC) but had similar 2- and 5-year disease-specific survival rates. They advocated that for less bulky tumors (<4 cm) with variant histology, intravesical immunotherapy may be an option. However, a smaller sample size (n = 22), retrospective nature of the study, and grouping of all the different variants into a common group limit the robustness of the results.

The support for the use of intravesical BCG has usually been limited to those tumors with squamous and glandular differentiation along with possibly nested variants within low-volume tumors with only small foci of variant histology which have been completely resected [45]. This is primarily because of the fact that when matched for the stage and percentage of squamous and glandular elements, disease-specific mortality of

these variant tumors is equivalent to conventional urothelial carcinoma [18]. Support also comes from Yorozua et al. [46], who retrospectively evaluated the role of BCG in tumors with squamous and glandular differentiation and found that patients receiving BCG had significantly higher recurrence-free, progression-free, and cancer-specific survival compared to other (thiotepa and mitomicin C) or no additional intravesical therapy.

Mally et al. [47] studied NMIBC in nested variants and found that patients with < T1 disease on restaging TUR could be candidates for conservative treatment including intravesical instillation. However, among the patients with T1 disease who had early cystectomy, 54% were noted to be upstaged in the bladder or had positive lymph nodes, Gofrit et al. [48], after performing a combined analysis of several variants, have shown that the progression to muscle invasive disease is 40% at 5 years with a 27% risk of dying from the disease. Nevertheless, it is important to remember that these variants of UC are likely to present at an advanced stage and require diligent restaging before considering intravesical BCG. These patients, when considered for intravesical treatment, should be under close surveillance and proceed to immediate radical cystectomy in the event of any failure to respond to intravesical therapy [45].

The role of intravesical treatment is better defined for other variants. Small-cell carcinoma of the bladder is a systemic disease with most patients presenting at an advanced stage. Lynch et al. [49] in their series of 127 patients from MD Anderson Cancer Center found that only 5% had non-muscle invasive disease at TUR and of the 5 patients that had upfront cystectomy, 2 had locally advanced disease, and 1 had metastatic disease (lymph node/distant metastasis). It is an aggressive disease with low overall survival [50] and there appears to be a limited or no role for intravesical treatment [45].

Sarcomatoid and plasmacytoid variants are known to be aggressive. Plasmacytoid variant on the TUR or cystectomy specimen [51] was associated with locally advanced disease, positive surgical margins, and positive lymph nodes in comparison to pure urothelial cancer. It may not be important to identify muscle invasion in view of the aggressive nature of the disease [52]. Sarcomatoid variant is a rare and aggressive tumor with an undefined optimum treatment modality where the approach to treatment should be aggressive rather than conservative [53]. Therefore, intravesical treatment should not have a role to play in the management of these types of variant histologies.

Micropapillary variant (MPBC) is perhaps the most studied, and the most reported variant and thus deserves a special discussion. It was first described by Amin et al. [54] and subsequent reports from Kamat et al. [55] suggested that intravesical BCG was ineffective in view of the of progression being observed in 67% patients in the intravesical BCG group at a median period of 8 months of which 22% had development of metastasis. Another study from Spaliviero et al. [56] suggested that rigorous selection criteria can be applied to identify patients with MPBC who would be good candidates for intravesical BCG therapy. However, they highlighted that in patients with restaged cT1 MPBC who underwent radical cystectomy, there was a higher incidence of node positive disease. Therefore, they advise strong consideration for the high-risk status of MPBC prior to deciding on the management plan of patients. Jackson et al. [57] found that in their series of NMI–MPBC, Ta disease had a significantly better overall survival than T1 disease (63 Vs 47 months), suggesting that perhaps in the absence of invasive disease (T1), immediate radical cystectomy may be deferred.

The identification of the percentage of the MPBC (focal Vs extensive) as well as the presence or absence of carcinoma in situ (CIS) also may have an influence in the selection of patients for BCG intravesical therapy [58]. Over the years, beginning with the initial reports from Samartunga et al. [59] and Alvarado et al. [31], there has been an attempt to prognosticate MPBC based on the percentage of micropapillary component. Gaya et al. [58] have suggested that patients with low micropapillary carcinoma component (<50%) and absence of CIS can be considered candidates for intravesical therapy after a complete transurethral resection. Interestingly, Willis et al. [60] reported that in patients with T1

MPBC who had received intravesical BCG, disease-specific survival (DSS) and progression was worse in those classified as extensive (>25%) vs focal (<25%) MPBC. Others have suggested that like in conventional urothelial cancer the presence of lymphovascular invasion (LVI) may be a significant driver of disease [57]. A recent systematic review conducted by Abufaraz et al. [61] found a lot of heterogeneity in the studies comparing intravesical BCG and early radical cystectomy. They suggested that though early cystectomy seems to be the safest oncological option, consideration for conservative treatment with intravesical BCG should not be completely ruled out.

The rarity of the disease and the small numbers encountered in routine practice makes decision making in variants like MPBC a challenge. With larger case series coming from single center experiences, it is difficult to select the best option for that one patient in question, considering significant disparities in the recommended management options.

In summary, the role of intravesical treatment for the management of variants of NMIBC is based on histologic subtype and should be selectively applied. It is important to consider the presence of coexistent high-risk features (e.g., LVI) as well as the percentage of the variant component (eg.in MPBC) in variant categories eligible for intravesical BCG and the threshold for early cystectomy should be low. An algorithmic approach in the management of variant NMIBC is shown (Fig. 27.5).

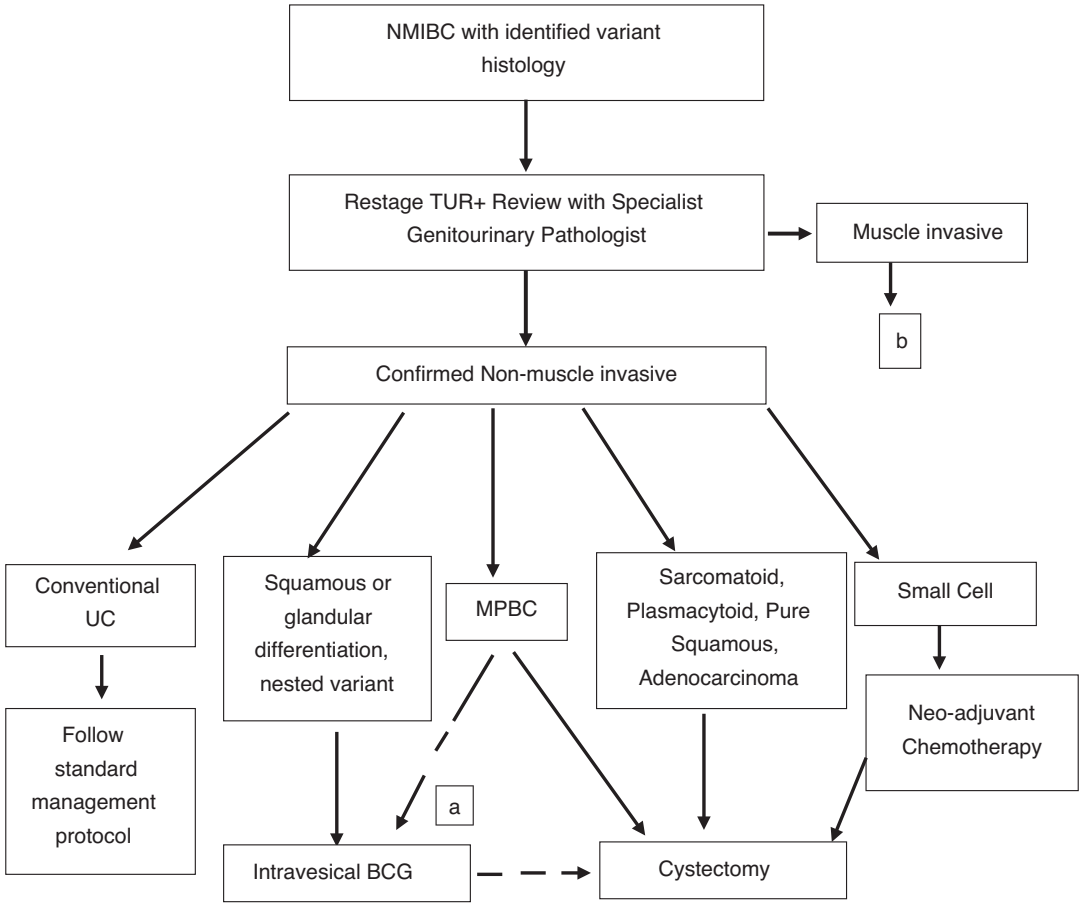

Fig. 27.5 Algorithmic approach to management of NMIBC with variant histology. (**a**) Intravesical BCG may be an option if Ta only, no evidence of lympho-vascular invasion or T1 with <25% micropapillary component. (**b**) Follow management protocol for muscle invasive disease

Summary Pearls

- *The role of intravesical BCG is limited to squamous/glandular differentiation and possibly in low volume disease and fornested variants following complete TUR.*
- *Sarcomatoid, Plasmacytoid and Small cell variants do not respond well to intravesical BCG .*
- *In micropapillary variants, the role of BCG is limited and controversial.*

Muscle Invasive Variant Bladder Cancer: Treatment Paradigm

Conventional urothelial carcinoma (UC) with muscle invasion has clear guidelines for management [62, 63]. However, in these guidelines there is little clarity in the management of variant bladder cancer. The combined set of guidelines from AUA/ASCO/ASTRO/SUO [62] categorically mention that based on *expert opinion* clinicians should consider divergence from standard clinical protocol based on unique clinical characteristics of the variants. The EAU guidelines [63] do not dwell upon the question of variant histology and appropriate management options.

The Role of Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy (NAC) prior to cystectomy for MIBC has a clear survival advantage [64]. The question of whether this advantage extends to the variants of bladder cancer is unclear. Various authors have tried to predict the responsiveness to NAC and have recommended that patients with high-risk features, which included the presence of variant histology, be candidates for NAC as they are more likely to have pathological upstaging at cystectomy and worse survival outcomes [65, 66]. In contrast, however, Pokuri et al. [67] found that tumors with variant and mixed histology were significantly less likely to attain pT0 status on cystectomy after NAC in comparison to conventional UC. It is possible that with the inherent biological variability among the different types of variants, further distinction is needed to understand the role of NAC.

Interestingly a secondary analysis of the South West Oncology Group(SWOG) trial S8071 [68] found a distinct survival advantage for patients with locally advanced tumors and divergent differentiation (squamous and glandular variants) who received neoadjuvant chemotherapy (hazard ratio 0.46; 95% CI 0.25–0.87; $P = 0.02$). Survival in this subgroup was comparatively better than that of conventional UC. This benefit, however, has not been consistently reported for pure squamous cell carcinoma or adenocarcinoma of the bladder. The response of pure squamous cell carcinoma (SCC) to chemotherapy seems to depend on the origin of the tumor; but these inferences have been drawn from relatively small retrospective series. It appears from the results of these studies that the benefit may be limited to bilharzial SCC [69] and not for non-bilharzial SCC [70]. There is limited evidence to support the use of neoadjuvant chemotherapy for pure adenocarcinoma of the bladder and hence these patients are generally recommended to undergo radical cystectomy [71].

Though small-cell carcinoma of the bladder is a non-urothelial bladder cancer in its pure form [1], it is seen in variable proportion as a type of divergent differentiation and perhaps the only variant in which systemic chemotherapy may be the optimal form of initial therapy [2]. This is based on the understanding that more often than not, small-cell carcinoma is a systemic disease that cannot be ideally managed by local therapy in the form of cystectomy alone. In the study by Lynch et al. [49], 62% patients were downstaged to ≤pT1N0 after NAC as compared to 9% who had upfront surgery. The DSS and median overall survival (OS) was also significantly better for patients who had ≤pT2N0M0 at cystectomy. Multivariable analysis revealed that pathological stage (pT) and not clinical stage (cT) was significantly associated with improved overall survival in patients receiving NAC. Similarly,

Vetterlian et al. [72] have also reported that amongst all variants a significant survival advantage is noted in patients with neuroendocrine (small-cell) tumors undergoing NAC (hazard ratio, 0.49; 95% CI, 0.33–0.74 [$p = 0.001$]). The chemotherapy regimen is similar to that used for small-cell carcinoma in the lung and is comprised of cisplatin and etoposide [2]. Several alternative regimens have been used but the results are not significantly better than the classic regimen [49, 73]. Predictably the results of NAC are better for organ-confined disease (pT2M0N0) with good long-term overall survival of 80% [73].

The usefulness of neoadjuvant chemotherapy in micropapillary bladder cancer has also been variably reported. Kamat et al. [74] reported that the median survival for patients receiving NAC was not significantly different (63% at 5 years) from those undergoing cystectomy (71%) and a large portion of patients undergoing NAC had non–organ-confined disease at cystectomy (68.7% Vs 34.8%; $P = 0.0157$) despite having comparable clinical stages. Since this early report, several other authors have analyzed this question. Meeks et al. [74] have reported the beneficial effects of NAC where they found a 45% rate of tumor downstaging and improved recurrence-free and overall survival at 24 months. Joshi et al. [75] found that 23% of patients with MPBC received neoadjuvant chemotherapy but had no significant benefit in terms of overall survival.

A retrospective single institutional review from the M. D. Anderson Cancer Center [76] reported that of the 103 patients who had surgically resectable MPBC (≤cT4a cN0 cM0) at presentation, 29 received NAC. 55% of patients undergoing NAC were downstaged to T0 in the final pathology as compared to 23% of those undergoing TUR only. This downstaging (<pT1) was prognostic of the survival outcomes (5-year OS 76% vs 42%, $P = 0.003$; 5-year DSS 96% vs 45%, $P < 0.001$), regardless of the precystectomy treatment (NAC Vs No NAC). However, in patients with NAC who were not downstaged, the prognosis was dismal with a 5-year DSS of only 17%. The addition of adjuvant chemotherapy did not improve survival. The authors have thus advocated for identifiers of aggressiveness and chemosensitivity to avoid delays in radical cystectomy in patients who are unlikely to benefit from chemotherapy. A systematic review conducted recently [61] concluded that though NAC results in pathological downstaging the survival benefit derived from such downstaging may be limited.

There is a paucity of data regarding the relevance of NAC for other variant histologies such as sarcomatoid, plasmacytoid, and even nested variants [26, 51, 52, 77–79]. These are rare tumors and limited to small retrospective case series or case reports.

In summary, the role of neoadjuvant chemotherapy is well defined for small-cell carcinoma. The regimen typically uses a combination of cisplatin and etoposide and is different from UC. Squamous and glandular variants of UC may have some benefit derived from NAC that is typically the same regimen as for pure urothelial carcinoma. Pure adenocarcinoma of the bladder does not respond to NAC and limited evidence exists for benefit in pure squamous cell carcinoma (Bilharzial). However, the role of NAC is controversial for MPBC and for the other variants there is sparse evidence in the literature to come to a conclusion.

Summary Pearls

- *NAC has an established role in the treatment of SmCC where the regimen typically uses a combination of cisplatin and etoposide.*
- *For most other forms of variant bladder cancer the role of NAC, possibly beneficial, is less well defined or conclusive.*
- *NAC is not useful in pure Adenocarcinoma of the bladder.*

Radical Cystectomy: The Way to Go!

Radical cystectomy (RC) forms the basis of management of most variants of bladder cancer. In fact, most retrospective studies have continuously

found that when controlling for stage, upfront radical cystectomy in variant MIBC has similar outcomes in terms of overall survival as conventional urothelial carcinoma [80–82]. In the absence of benefit from the use of neoadjuvant chemotherapy in sarcomatoid, plasmacytoid, and nested variants, radical cystectomy remains the first line of treatment. Cystectomy with or without prior NACT should be the standard treatment strategy in UC with glandular and squamous differentiation based on the existing evidence [67, 68]. In patients with muscle invasive MPBC, cystectomy is still the cornerstone of treatment.

Earlier reports had reserved primary chemotherapy for metastatic small-cell bladder cancer and recommended upfront radical cystectomy for all other stages [83]. Subsequent findings suggested the survival benefit of the combination of adjuvant chemotherapy with radical cystectomy (43% vs 20% 5 year OS) [84]. Interestingly, when the National Cancer Database (NCDB) was reviewed to understand the existing treatment patterns for small-cell bladder cancer, it was seen that only 12% of the 625 patients were treated with multimodality therapy (MMT) in conjunction with radical cystectomy [85]. There was superior 3 year OS for patients who had bladder preservation and multimodality treatment (chemotherapy and/or radiation therapy) when compared to RC with MMT (35% Vs 30.1%) but the best results were for NAC with RC (53%).

The single institutional experience from MD Anderson has also been in favor of neoadjuvant chemotherapy followed by radical cystectomy with both prospective [73] and retrospective data [86] confirming the benefit of the combination and the order of these approaches. In the prospective phase II trial reported in 2009 [73], the authors reported a 2- and 5-year OS rates of 87% and 77%, respectively. Thus, in patients with small-cell variant pathology, it is wise to offer upfront chemotherapy prior to surgery in eligible patients. A pT0 status on cystectomy following NAC is also associated with improvement in survival in these patients [49]. Having said this, the evidence to support the use of cystectomy as an integral part of treatment for SmCC after systemic chemotherapy is not very strong [87]. Therefore, based on limited retrospective series both NAC followed by radical cystectomy and neoadjuvant and/or concurrent chemotherapy with radiation therapy are reasonable treatment options [88].

For patients with pure squamous cell carcinoma and pure adenocarcinoma of the bladder, radical cystectomy is the first line of management even for NMIBC [73]. So what does this mean in terms of the sequence of cystectomy in the management of the patient at hand? It is recommended that, based on existent literature, stage-matched treatment algorithms similar to conventional UC can be followed for most variants [18, 49, 51, 77, 80–82].

There are no definite answers to the question of the extent of lymph node dissection (LND) in the case of variant histology. Recent evidence favoring a standard template lymph node dissection in conventional UC can be followed for these variants as well [89, 90].

The Role of Radiation

The role of radiation therapy in the treatment of bladder carcinoma is limited, especially due to concerns of toxicity [91, 92]. The use of radiation as a form of local treatment has been studied in SmCC. Older studies examining radiation therapy have reported on recurrence in the bladder that required salvage treatment [93]. The reason for this has been attributed to presence of mixed histology as well as carcinoma in situ (which is radio-resistant) that are frequently encountered with small-cell bladder cancer [73]. However, there are several studies which have also reported the beneficial effects of external beam radiation herapy (EBRT) as a form of local treatment along with systemic chemotherapy. Mattes et al. [94] have reported 2-year disease-free and overall survival of 51% and 78%, respectively along with 2-year distant metastasis-free survival of 76% and 26%, for node-negative and node-positive patients, respectively (P = 0.04). Similarly, Lohrish et al. [93] and Bryant et al. [97]have also reported on the survival benefits of EBRT along with combination chemotherapy and have sug-

gested its role in bladder preservation in SmCC. These authors have further commented that this benefit may largely be due to the use of systemic chemotherapy [94, 95]. Nevertheless, EBRT does seem to have a role which needs to be substantiated by larger studies.

Some reports have also shown beneficial effects of radiation in Bilharzial SCC [96, 97]. The benefits were mostly in terms of improvement in local control as well as survival. Therefore, recommendations do exist for the use of radiation therapy in the neoadjuvant as well as adjuvant setting in the treatment of squamous cell carcinoma with schistosomiasis. In non-bilharzial SCC, the role of radiation may be restricted to a palliation [2]. A weak recommendation also exists for radiation to be used for adjuvant treatment in locally advanced adenocarcinoma of bladder [2].There have also been some reports examining the use of radiation as a part of multimodal management in patients with sarcomatoid carcinoma. However, there was no survival advantage documented in one small retrospective series [53]. Moschini et al. [92] found that variant histology was one of the predisposing factors for local failure in patients following radical cystectomy and suggested that these patients, who are at high risk of local failure, may find benefit with the addition of radiation to the treatment. Others have also recommended that a combined clinicomolecular stratification model be used in selecting patients for adjuvant radiation therapy [98].

Is Bladder Preservation Possible with Variant Histology (VH)?

The answer to this question is a little more complex when compared to patients with conventional UC where trimodality treatment (TMT), which encompasses maximal TURBT with NAC and radiation, has similar survival outcomes compared to standard treatment protocols in a select group of patients [99]. A recent report from Massachusetts General Hospital found comparable survival outcomes in patients undergoing TMT for conventional as well as variant bladder cancer [100]. They reported a complete response rate after induction TMT of 83% and 82% in UC and VH respectively. The 5-yr and 10-yr DSS (75% & 67% in UC Vs 64% each in VH) and OS (61% & 42% in UC Vs 52% & 42% in VH) were similar between the two groups. VH was also not found to be significantly associated with DSS (hazard ratio: 1.3, 95% confidence interval: 0.8–2.2, $P = 0.3$) or OS (hazard ratio: 1.2, 95% confidence interval: 0.8–1.7, $P = 0.4$) on multivariate analysis. Forty Nine of the 66 patients in this series, however, had glandular or squamous histology and apart from 8 sarcomatoid variants, the number of other variants was very less [100]. Glandular and squamous VH are known to have better response to neoadjuvant chemotherapy [68], and thus their favorable biology may be an important factor in the response to TMT.

In another study using data from the NCDB [85], 53.3% of small-cell cancer patients were treated with bladder preservation using multimodality therapy where 71.8% had disease that was cT2 or more. This report also reflected a preference toward conservative management for the treatment of small cell bladder cancer, which was largely metropolitan, or urban (82.3% and 16%) and predominantly in comprehensive community cancer centers or academic centers (53.2% and 27.7%). Other smaller series have also suggested that bladder preservation strategies with chemoradiation therapy can be considered in eligible patients with SmCC [93–95].

Bertz et al. [101] retrospectively evaluated 238 patients who had undergone TMT according to the "Erlanger Schema" and found that 45 patients had VH on pathology review. They did not include squamous and glandular differentiation as VH and found that micropapillary was the most common VH in their series (17/45). Only MPBC was included for survival analysis which revealed that the cancer-specific survival, on Kaplan Meier analysis, was worse for patients ≥30% micropapillary morphology compared to UC (mean survival: 97 months Vs 229 months; $P = 0.010$). Therefore, with the inherent issues associated with VH such as limited number, differences in the biological behavior as well as limited reported experience, the role of TMT needs further validation [102].

Summary Pearls

- *It is recommended, based on existent literature, that stage matched treatment algorithms similar to conventional UC can be followed for most variants.*
- *In SmCC both NAC followed by radical cystectomy and neoadjuvant and/or concurrent chemotherapy with radiation therapy are reasonable treatment options.*
- *The role of radiation therapy, at best, is limited and used mostly in conjunction with bladder preservation protocols, which need further validation.*

Prognostic Implications and Variations

This section highlights perhaps the most important aspect of management of VH bladder cancer. The inherent difficulty in prognosticating these tumors is the paucity of large studies with significant follow-up period. Traditionally VH has been viewed to be an independent predictor of progression and mortality following RC, and this was attributed to their inherently aggressive biologic behavior [103, 104].

In the early reports from Rogers et al. [104], patients with non-transitional cell carcinoma/non-squamous cell carcinoma (non TCC/SCC) were found to have increased risk for progression and death than patients with TCC or SCC. This increased risk was present for both organ confined as well as non-confined disease. However, subsequent large retrospective studies have drawn different conclusions. Mitra et al. [18], from the University of Southern California (USC), reported similar OS and recurrence-free survival (RFS) for patients with UC compared to UC with glandular, squamous, or both differentiation after intensive matching. The pathological stage was the only predictor influencing outcomes in UC with differentiation and when compared to an independent control cohort had higher pathologic stage at cystectomy. Kim et al. [15] have also reported that patients with squamous and glandular differentiation were more likely to present with pT3-T4 tumors (70% Vs 38%, $P < 0.001$) and pN+ disease (35% Vs 30%, $P = 0.05$) when compared to pure UC. However, there was no statistically significant difference in the 10-year CSS (52% Vs 51%, $P = 0.71$) and after adjusting for clinico-pathological stage there was no difference in the risk of death from bladder cancer (Hazard Ratio [HR] = 0.79, $P = 0.10$).

A multi-institutional study [82] reported that nonsquamous VH patients were noted to have higher disease recurrence and cancer-specific mortality as compared to conventional UC ($p = 0.001$) and squamous differentiation ($p = 0.04$) on univariate analysis. However, this association was not seen on multivariable analyses adjusted for the effects of standard clinicopathologic characteristics. Moschini et al. [4] went a step further to better understand this conundrum and classified the variants as either pure or mixed (when more than 1 variant is identified). They reported that out of 1067 patients of radical cystectomy, 201(19%) and 137 (13%) had mixed variants and pure variants respectively. Upon analysis, pure variants were found to have worse recurrence rate, cancer-specific mortality (CSM), and overall mortality (OM) than pure UC ($P < 0.01$). In contrast, mixed variants did not have any difference in the survival outcomes.

Kamat et al. [74] reported the 5- and 10-year overall survival at 54% and 27%, respectively, for MPBC following RC. Sui et al. [105] upon the evaluation of the NCDB found that the median OS was 44.7 months (95% CI, 33.4–56.0) and 91.9 months (95% CI 91.1–92.7) for MPBC and UC, respectively. On sub-analysis by clinical T stage, however, the difference was not statistically significant. Fairley et al. [81] also found the predicted 5-year OS (61% and 67%, Log rank $P = 0.96$) and RFS (69% and 58%, Log rank $P = 0.33$) rates were similar between patients with UC and MPBC. MPBC in this study was associated with an advanced clinical (cTanyN1–3: 2% vs. 9%, $P = 0.03$) and pathologic (pTanyN1–3: 22% vs. 46%, $P = 0.01$) TNM stage and multifocality (38% vs. 58%, $P = 0.02$). Interestingly, the MD Anderson group has noted poor prognosis for MPBC patients who opted for intravesical therapy with pT1 disease where 67% noted progression pT2 or more) and 22% had metastatic disease compared to patients who had upfront RC. They had a 5-year CSS rate of 60% compared to 72% of those who had initial cys-tectomy [55].

The prognosis of small-cell cancer of the bladder is rather dismal. The report from Patel et al. [85] found 33% 3-year OS in a cohort of patients from NCDB who were treated between 1998 to 2010. With the addition of neoadjuvant chemotherapy, however, this significantly improved especially in patients with resectable disease at diagnosis. Lynch et al. [49] have reported a median OS of 159.5 months and 5-year DSS of 79% in patients with resectable disease receiving NAC. Older series, where most patients had metastatic disease at presentation, have noted 5-year OS and RFS of 10% and 13%, respectively [106]. Moschini et al. [80], on retrospective evaluation and comparison with conventional UC, found that small-cell cancer was the only variant associated with higher recurrence (HR =3.47, $P < 0.001$), cancer-specific mortality (HR = 3.30, $P < 0.04$), and overall mortality (HR =2.97, $P < 0.003$).

The clinical outcomes of nested variant are similar to conventional stage-matched urothelial carcinoma following surgical treatment [79]. Microcystic urothelial shares also similar survival statistics [107] to conventional urothelial carcinoma. In contrast, pure forms of lymphoepithelioma may have better prognosis as compared with the mixed histological forms where the outcomes are similar to conventional urothelial cancer [23, 108]. Presentation is usually advanced in plasmacytoid variant with high relapse rate and evidence of peritoneal carcinomatosis [13, 26, 27, 109]. Other rare variants like giant cell urothelial carcinoma, lipid rich urothelial carcinoma, and clear cell (glycogen rich) urothelial carcinoma are uncommon and present at advanced stage and are associated with worse outcomes [28, 35, 36]. Poorly differentiated urothelial tumors also have aggressive presentation and poor outcomes [13]. The survival statistics of the common variants are outlined below (Table 27.2).

Follow-up and Surveillance Strategies

There are no specific recommendations within existing guidelines for the follow-up and surveillance strategies of variant histology bladder cancer. All non-muscle invasive VH should be considered as high risk and surveillance schedule as well as investigations follow that of high-risk bladder cancer. There are also no unique set of recommendations for VH bladder cancer following radical cystectomy. The use of serum and urinary markers like CA-19.9 have not been specifically studied apart from case reports [110] in VH. Chromogranin A, which was initially thought of as a promising tumor marker for neuroendocrine VH, has lost its standing as a stand-alone tumor marker [111]. The challenge in making recommendations for surveillance is not only limited by the small numbers encountered but also by the strength of existing evidence even for conventional UC [62]. Therefore, unique clinical characteristics of these variants should be taken into account and divergence from the standard management principles of conventional UC may be necessary [62].

Conclusion

Variant histology bladder carcinoma presents a difficult management problem to the treating physician. It is important to realize that a centralized pathology review by a genitourinary pathologist can be critical for the identification of these variants in the TUR specimen. Quantification of the volume of the tumor comprised by the histologic variant may be helpful in prognostication. The role of molecular subtyping is still investigational and may provide some insights as we continue to expand our existing knowledge. Intravesical immunotherapy with BCG has a limited role in some variants and requires good communication between the patient and the physician about the possible need for radical cystectomy and a worse prognosis in the event of disease progression. Radical cystectomy with urinary diversion is the cornerstone of the management paradigm and neoadjuvant chemotherapy has shown consistent results only with small-cell neuroendocrine variants. Radiation therapy has an adjuvant role only in specific squamous cell variants.

Table 27.2 Survival statistics of variant histology

Investigator, year	Pathology, no. of cases	RFS	CSS/DSS	OS	Comments
Linder et al., 2013 [79]	Nested, 52	77% Vs 75% ($p = 0.46$)	41% Vs 46% ($p = 0.75$)	29% vs 23% ($p = 0.89$)	10-year survival statistics, matched 1:2 with UC
Lopez-Bertran et al., 2014 [107]	Microcystic, 20	–	–	–	Mean duration of follow-up = 30 months 11 deaths at 30 months, 3 alive with disease at 32 months, 6 alive without disease at 34 months (mean duration)
Lopez-Bertran et al., 2001 [108]	Lympho-epithelioma like, 13	–	–	–	No difference on univariate survival analysis with UC ($p = 0.548$)
Keck et al., 2011 [26]	Plasmacytoid, 32	–	–	–	Median overall survival = 23.4 months (less than UC)
San Francesco et al. 2016 [33]	Sarcomatoid, 28	–	–	–	46% developed distant metastasis (11/24) Median survival and mean survival = 10.2 months and 9.1 months, respectively (95% CI = 5.0–31.0)
Mitra et al., 2014 [18]	Squamous, 141 Glandular, 97 Both, 21	62% vs 64% 50% vs 55% 63% vs 53%	–	43% vs 39% 38% vs 39% 32% vs 22%	5-year survival statistics compared with UC (p values were not significant)
Kim et al., 2012 [15]	Squamous, glandular, and mixed, 186	84% vs 79% ($p = 0.14$)	–	52% vs 51% ($p = 0.7$)	10-year survival statistics compared with UC
Kamat et al., 2007 [74]	MPBC, 100	–	–	5 year = 54% 10 year = 27%	–
Sui et al., 2016 [105]	MPBC, 869	–	–	–	Median OS vs UC: Overall: 44.7 vs 91.9 months ($p < 0.001$) T2 disease: 30 vs 27.7 months ($p = 0.51$) T3 disease: 16.4 vs 16.8 months ($p = 0.38$)
Fairey et al., 2014 [81]	MPBC, 33	69% vs 58% ($p = 0.33$)		61% vs 67% ($p = 0.96$)	UC vs MPBC 5-year survival outcomes
Patel et al., 2013 [85]	SMCC, 625			33%	3-year overall survival
Lynch et al., 2013 [49]	Small-cell carcinoma, 125		79% vs 20% (5 year)	159.5 vs 18.3 months (median)	Comparison of NACT +cystectomy VS cystectomy alone

RFS recurrence-free survival, *CSS* cancer-specific survival, *DSS* disease-specific survival, *OS* overall survival

Summary Pearls

- *Most VH share similar stage matched survival statistics with conventional UC.*
- *However, there is evidence to suggest that pure forms of VH fare worse as compared to mixed VH.*
- *SmCC is perhaps the only variant that has worse overall survival statistics as compared to conventional UC.*

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28 Clinical Trials in Bladder and Upper Tract Cancer – Bladder Cancer Disease States

Seth P. Lerner

One of the many challenges in clinical trial design is identifying the target patient population for a particular intervention and designing a set of inclusion criteria that are accurate and verifiable. Too often our trials include a heterogeneous population with heterogeneous disease characteristics that cannot be fully accounted for in the design and analysis. One example that has plagued progress in trials of non-muscle-invasive bladder cancer (NMIBC) is treating patients with carcinoma in situ (CIS) and papillary disease (Ta, T1) without CIS in the same trial. The therapeutic efficacy in a single-arm trial can only be established in CIS which is biopsy proven and present at the beginning of treatment. We require that papillary disease be completely resected prior to initiating treatment so it is hard to determine the magnitude of treatment effect compared to that achieved with transurethral resection of the bladder tumor (TURBT) alone. This can be accomplished, for example, in randomized trials of single-dose perioperative intravesical therapy where there is a no-treatment or placebo control arm. Another example is tumor heterogeneity in trials of muscle-invasive bladder cancer (MIBC). While the majority of patients have a urothelial cancer, mixed histology is common and may be present in up to a third of patients [1]. Furthermore, the percentage of mixed histology varies considerably, and this may impact the likelihood of treatment response and outcome [2]. Genomic heterogeneity is also common and multiple groups have reported expression-based subtypes that vary considerably in response to cisplatin-based chemotherapy and immunotherapy [3–5].

NMIBC Disease States

Beginning in 2012, the bladder cancer community began working with the US Food and Drug Administration (FDA) to define a registration pathway for patients that recurred with high-grade NMIBC following adequate BCG treatment. This led to adoption of a single-arm trial design, acknowledging that there was not an adequate comparator for randomized trials and that there was an urgent unmet need for drug development for this patient population for whom the alternative was radical cystectomy [6]. Through a highly iterative process, we defined the target population as "BCG Unresponsive" characterized by patients for whom BCG was no longer appropriate treatment [7]. In a final guidance document issued in 2018, the FDA clearly laid out the single-arm trial design for patients with BCG unresponsive disease [8]. In a previous white paper, the FDA also described other disease

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states in NMIBC and appropriate clinical trial designs for these populations [9].

Patients with NMIBC can be risk stratified regarding probability of progression and these strata can also be used to define disease states for clinical trial design [10, 11]. Patients with low-risk disease typically have a first occurrence of a Ta low-grade (LG) tumor and standard of care is a single dose of perioperative intravesical chemotherapy. Small tumors up to 1 cm can be left in place as a marker lesion for testing novel therapies. Randomized phase III trials are required for registration with either placebo or standard-of-care intravesical chemotherapy as a comparator. Patients who recur with Ta LG disease or present with multifocal disease at first presentation should be treated with intravesical chemotherapy. BCG with maintenance is a standard of care but with the current BCG shortage, this should be reserved for patients with high-risk disease. An "add-on" clinical trial design is appropriate comparing standard of care treatment with or without the experimental treatment.

BCG is standard of care for patients with high-grade Ta, T1, or CIS. Disease states are characterized as BCG naïve, BCG failure, or BCG unresponsive. Patients who are BCG naïve may have received prior intravesical chemotherapy. Clinical trials testing novel agents generally require comparison to standard of care BCG induction plus 3 years maintenance. Patients who recur after induction only may respond to additional BCG, and the FDA recommends an "add-on" trial design comparing BCG with or without the experimental treatment [9]. Stratifying by papillary only or CIS with or without papillary allows inclusion of all patients with high-risk disease for the primary outcome assessment. Patients with BCG unresponsive disease have high-grade (HG) disease and either recur after at least five of six induction and two of three maintenance treatments or never achieve a complete response (CR) [7]. The original definition required time from last BCG to recurrence to be less than 6 months, but this has been extended to 12 months. Patients who recur with T1HG after induction BCG only are included in this disease state.

MIBC Disease States

Patients with MIBC are treated with either radical cystectomy (RC) or radiation therapy with or without chemotherapy. Elderly patients frequently do not undergo definitive treatment and there is a small population of patients that achieve a clinical CR to systemic chemotherapy alone that are observed without additional therapy [12, 13]. Neoadjuvant chemotherapy (NAC) is the current standard of care for patients that can be treated with cisplatin-based multiagent chemotherapy [14]. NAC is most commonly used prior to RC but may also be used in conjunction with RT in patients who are not medically fit or refuse RC. This pre-NAC disease state is ideal for clinical trials comparing standard of care cisplatin-based NAC with or without an experimental treatment. Patients who are not cisplatin eligible and pre-RC may be treated in single-arm phase II clinical trials testing an experimental treatment or randomized to RC with or without an experimental treatment. The standard of care for patients undergoing bladder-sparing treatment is maximal TURBT followed by chemotherapy plus radiation [15]. This pre-RT disease state is appropriate for testing a novel treatment in an "add-on" trial design with chemoradiation with or without the experimental treatment. Patients with residual NMIBC after chemoradiation can be treated with standard-of-care intravesical therapy based on their risk strata. As an example, patients with persistent or recurrent CIS can be managed with BCG.

Following RC, patients can be risk stratified based on pathologic staging of the primary tumor and lymph nodes and whether or not they received NAC. If no NAC was given, then patients with pT3,4 or N+ disease are considered high risk for progression. If NAC was given, then patients with residual pT2 disease or greater or N+ disease are considered high risk. There is no standard of care for adjuvant therapy, so randomized trials comparing experimental treatment to placebo or observation are required for approval of novel treatments.

Metastatic Disease States

Patients may present with de novo metastatic disease or progress from organ-confined disease post definitive loco-regional treatment. Patients with locally advanced defined as T4b and any N are also included in trials for patients with measurable metastatic disease. Patients with adequate renal function and no contraindication to cisplatin or poor performance status should be treated with combination chemotherapy with either M-VAC or GC [14]. Patients who are not candidates for cisplatin-based chemotherapy may be treated with one of two single agent–approved checkpoint inhibitors. Eligible patients must have tumors that are positive for PD-L1 expression. Treatment-naïve patients with metastatic disease are suitable for clinical trials combining cisplatin-based chemotherapy and an experimental agent compared to cisplatin-based chemotherapy alone. Patients who are "platinum ineligible" are suitable for randomized trials of experimental therapy alone or in combination with non-cisplatin-based chemotherapy. Patients who progress following platinum-based chemotherapy administered either perioperative (neoadjuvant or adjuvant) or for measurable metastatic disease may be treated with one of five approved immune checkpoint inhibitors or an approved FGFR inhibitor. These patients are also suitable for clinical trials of single-agent experimental therapy alone or in combination with a checkpoint inhibitor or chemotherapy. So-called third-line therapies are being developed in the post-platinum/post-immune checkpoint inhibitor space as well.

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29 Practical Approaches to Clinical Trials in Non-muscle-Invasive Bladder Cancer

Robert S. Svatek and John A. Taylor III

Background

The randomized, controlled trial emerged in the 1940s, following its predecessor – the alternate allocation trial. In alternation, patients are allocated to the intervention in time-dependent sequential clusters. For example, treating every other patient and withholding treatment from the other patients and then comparing their outcomes. The problem with alternate allocation trials is that foreknowledge of treatment allocation leads to bias, including patient selection. Concealing allocation through randomization emerged as a means to solve this limitation. The number of randomized controlled trials in bladder cancer has risen dramatically over the last several decades (Fig. 29.1).

Biases in Clinical Trials

Selection bias designates the bias that occurs due to selection of certain individuals, groups of individuals, or data to be analyzed. Most observational cohort studies of NMIBC are subject to selection bias because they report data on individuals that were selected for inclusion through some method. For example, suppose an investigator reported on the outcomes of patients treated with intravesical BCG versus intravesical mitomycin C using an observational cohort analysis. The investigator may choose only patients with high-grade NMIBC to try to limit the amount of selection bias, but other factors such as tumor volume, tumor multifocality, etc., also influence treatment selection and it is not possible to account for all potential confounders in such an analysis. Randomization reduces the likelihood of selection bias significantly but not completely as described below.

Performance bias occurs when patients or providers receive different care based on the knowledge of which group (treatment or control, for example) the subject is in. As an example, persons placed into an improved diagnostic treatment group could undergo more intense biopsies and sampling compared to patients in the control group.

Detection bias occurs when a cancer detection performs differently according to some characteristic of the study patient. For example, patients undergoing blue-light cystoscopy can have more complete assessment of the bladder which can improve detection of bladder cancer.

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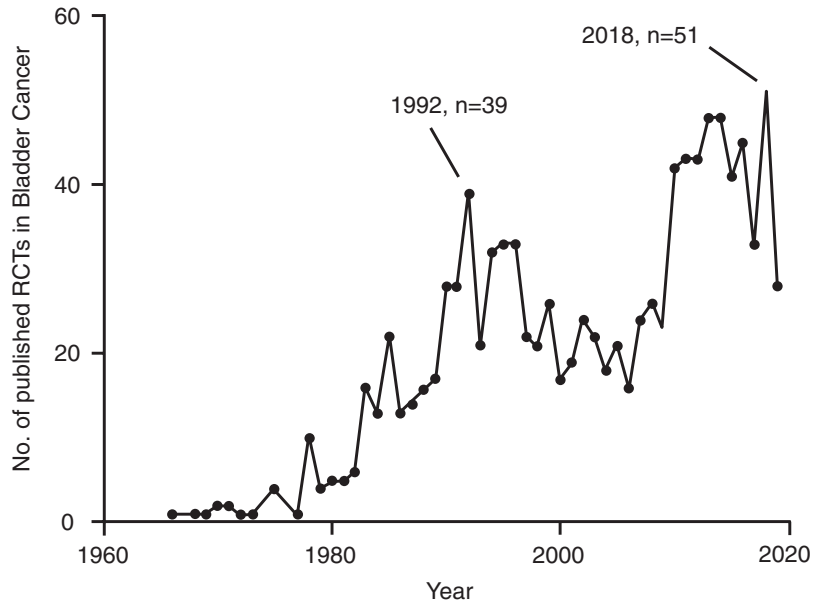

Fig. 29.1 *Quantity of published bladder cancer RCTs per year.* Pubmed search was conducted August 1, 2020, using the search phrases ("Urinary Bladder Neoplasms"[Mesh]) AND ("Randomized Controlled Trial" [Publication Type]). Number of published papers was plotted as a function of the year published. Two high points in 1992 and 2018 are designated

Attrition bias refers to systematic error caused by unequal removal or loss of participants from one or more arms of a trial. For example, patients randomized to one particular intravesical intervention may be more likely to stop treatment than another arm, thereby compromising the ability of the intervention to be effective.

Key Elements in Clinical Trial Design

Randomization The purpose of randomization is often misunderstood as a means to eliminate selection bias or to balance covariates across treatment groups. In fact, selection bias is still possible in randomized controlled trials. For example, investigators may select certain types of patients to be included in a particular trial, thereby systematically biasing the study. While randomization does help with balancing variables across the treatment groups, it does not assure equal balancing and by chance alone certain variables will be unequally distributed. For this reason, stratification is performed to make certain that an equal number of patients are placed into treatment versus control groups for critical variables. The purpose of randomization is linked to the origin of the randomized controlled trial, namely allocation concealment. As mentioned above, randomized controlled trials replaced alternate allocation trials as a means to ensure allocation concealment. Although randomization does improve allocation concealment over other trial approaches, there remain situations where allocation concealment is not fully protected, including in certain block randomization trials.

Block randomization This method of randomization is performed in order to balance the number of subjects placed into treatment groups. This is especially important for randomized trials with small number of patients. For example, without block randomization, the first 10 patients could, by chance, all be placed into one treatment group. For small, randomized trials, this could result in a large imbalance in the number of patients in each group. To mitigate that imbalance, block randomization trials randomize a block of subjects (e.g., $n = 4,6,8$) and each block contains an equal number of subjects in each treatment/control group. The block size is determined by the researcher. With small block sizes, especially $n = 2–4$, it is sometimes possible for the investigator to conjecture the next treatment assignment, thereby violating allocation concealment. This is especially

true when there is no blinding or in trials where unmasking is common. For example, if the treatment arm is testing an intravesical chemotherapy agent that has a known high side-effect profile, then unmasking is higher as investigators can figure out which arm the patient was randomized to because of the side-effect profile and if the block size is small, then the investigator can predict the next treatment assignment.

Stratification randomization Stratification is performed to balance patient assignment for certain variables. For example, patients with cystoscopic-appearing, low-grade bladder tumors were randomized in a blinded 1:1 fashion to receive gemcitabine or placebo (saline) intravesical instillation immediately following TURBT with balancing for two stratification factors: disease status (newly diagnosed vs. recurrent) and number of lesions (single vs. multiple). As a result, the study comprised an equal number of newly diagnosed and recurrent subjects in both the gemcitabine and saline arms. Similarly, an equal number of patients presenting with single and multiple lesions was present in the gemcitabine and saline arms, respectively. On the other hand, the stratification was not performed for smoking history and, by chance alone, the gemcitabine arm enrolled more never-smokers ($n = 54$, 27%) compared to the saline arm ($n = 46$, 22%). Stratification should be performed on confounding variables that could significantly influence the results of the study should an imbalance occur. Common confounding variables in NMIBC trials include grade (e.g., high versus low), stage (e.g., T1 versus Ta), presence of CIS, prior intravesical therapy, prior recurrence, and multifocality.

Blinding Trials may blind the patient, investigator, study team, or everyone involved. In this case, often the pharmacy or dispensing service is responsible for over labeling the drug and keeping track of subject ID and treatment assignment. How could lack of blinding influence the results of a trial in NMIBC? Investigators can be biased consciously or unconsciously by the knowledge of treatment assignment, and these could influence the approach to follow-up in subtle but important and systematic processes. For example, during cystoscopic follow-up, providers could influence the timing or type of disease assessment for disease recurrence, especially if office-based fulguration or blue-light cystoscopy is allowed in the context of the trial.

Intention-to-treat versus per-protocol analysis The method for analysis can influence the results. In the intention-to-treat method, subjects are analyzed according to which group they were originally assigned, regardless of whether or not they received the assigned treatment. For example, in a randomized controlled trial of 2243 patients with NMIBC were randomized to immediate versus 2-week postoperative MMC. The primary outcome was recurrence at 3–5 years after randomization. Some patients randomized to immediate instillation were unable to receive treatment for various reasons (e.g., large bladder perforation) but these patients were still included in the analysis. Similarly, patients randomized to 2-week postoperative MMC may have declined or not received MMC but were still included in the ITT analysis. In this way, ITT analysis protects against biases that may occur from excluding certain patients from protocol treatment or analysis. ITT analysis provides the most unbiased conclusions regardless of the effectiveness of the intervention [1]. Per-protocol analysis, on the other hand, conducts analysis only on patients who actually received protocol treatment. If there is substantial number of patients who were not treated per-protocol, then ITT may be unable to identify a potential benefit of treatment. However, per-protocol analysis is subject to biases as mentioned. Whenever possible, ITT analysis should be conducted and represents the more rigorous and less-biased analytical approach.

Pathologic evaluation Because the primary endpoint in most NMIBC trials requires an assessment of pathology, the method of pathologic examination is important. Transurethral resections or bladder biopsies are required to assess suspicious lesions as visible determination of presence/absence requires

histopathologic assessment regardless of what is seen grossly. In an ideal setting, central pathology review and evaluation of tissue by an expert GU pathologist would be conducted on baseline tissue to confirm the pathologic grade/stage and confirm eligibility. In addition, central pathology review for all biopsies conducted on study by a central GU pathologist blinded to the treatment assignment provides an unbiased and accurate evaluation. However, this is rarely feasible in the setting of large phase III clinical trials.

Features of NMIBC That Influence Clinical Trial Designs

Common Types of Trials in NMIBC

There are biologic aspects of NMIBC that led to unique types of clinical trials. Generally, papillary NMIBC (Ta and T1) tumors are completely resected at the time cystoscopy/TURBT under anesthesia. Recurrence of papillary tumors is relatively common. Thus, most clinical trials address agents to decrease the disease recurrence rate for patients by giving agents following tumor removal (see Adjuvant Trials below). The most common trials are adjuvant trials, where therapy is given either immediately following tumor resection (i.e., postoperative instillation) or later in an office-based setting (e.g., induction +/− maintenance adjuvant therapy). On the other hand, CIS is not typically completely resected because it tends to be diffuse and multifocal. In CIS, agents are given to eradicate the disease, therefore, complete response is an appropriate endpoint to assess the effectiveness of an agent in treating CIS.

Early-Phase Trials

Bladder tumors almost always declare themselves clinically due to hematuria or new onset irritative voiding symptoms. As such they are diagnosed prior to initial treatment with complete excision by TURBT. This affords the opportunity to exploit the time from visual to pathologic diagnosis in window of opportunity trials (WOT). The unique aspects of these trials are that newly diagnosed tumors are treatment-naïve and permit exploration of novel therapy on disease state as defined radiologically/visually or pathologically. Additionally, biopsies are easily obtained prior to therapy to allow for tissue activity to be determined. In most circumstances, standard-of-care therapy, in this case TURBT, is not significantly delayed.

By nature of the disease state and trial design, it is not anticipated that participants will see benefit from WOT trials. However, these types of trials are of value in that they are critical components in early phase drug development, allow for early pharmacokinetic/dynamic evaluation of lead candidate compounds and may facilitate biomarker discovery for improved patient selection [2].

Adjuvant Trials

By virtue of the disease state and patterns of recurrence, NMIBC lends itself to unique types of clinical trials, including adjuvant, immediate postoperative, and marker lesion studies. Adjuvant trials include any treatments given after TURBT, which serve to improve the efficacy of the TURBT (hence adjuvant term). This could be one instillation or several instillations. Drawing from terminology used in systemic chemotherapy, we sometimes characterize the first set of instillations as “induction” and subsequent instillations as “maintenance” therapy. The goal of adjuvant therapy is to decrease disease relapse and progression. The most common outcome of primary study used in adjuvant NMIBC trials is recurrence-free survival (RFS). While progression-free survival may be considered as a secondary objective, progression events are too low to justify use as a primary study objective in most cases. For similar reasons, overall survival is also not used for NMIBC trials. Regarding adjuvant trials, it is important to understand distinctions in managing papillary (Ta and T1) tumors from non-papillary carcinoma in situ (CIS). As mentioned, papillary tumors should be completely resected while CIS is often not completely fulgurated because in many cases the amount of CIS is too diffuse. Therefore, intravesical treatment after TURBT could be considered preventative (in the case of resected papillary

tumors) or active treatment (in the case of incompletely resected CIS). Advantages of adjuvant NMIBC trials include the potential high impact on disease relapse and progression from repeated instillations. Randomization is feasible and allocation concealment and blinding are possible (see examples below).

One interesting type of adjuvant trial is the immediate postoperative instillation trial. In this approach, agents are instilled into the bladder in the operating room or post-anesthesia care unit immediately following a TURBT. Several trials have shown efficacy of this approach to decreasing disease relapse. Benefits of immediate or postoperative therapy instillation is the ease of double-blinding, relatively decreased cost because of one-time instillation, simplicity, and the lack of long-term therapy. Adherence to complete regimen is straightforward unlike maintenance regimens for which the vast majority of patients do not complete the prescribed regimen, which can last for several years. Another benefit of immediate postoperative instillation trials is the ability to assess side effects and tolerability because treatment occurs at a specified time point. Thus, the time from therapy administration to side effect can be calculated in a straightforward manner. The major disadvantage to postoperative instillation trials is that, generally, the effect of one instillation on the natural history of the bladder cancer and disease relapse is relatively modest. As a result, these trials required relatively large sample sizes to identify small effect sizes.

Marker Lesion Studies

Marker lesion studies are a unique type of trial in NMIBC. Typically, a patient presenting with two or more tumors are eligible. All tumors except one "marker lesion" are removed per standard of care. Removing the tumors allows for proper staging of the bladder cancer. Then treatment is commenced and the outcome is determined based on the ability of the treatment to eradicate the tumor. Remarkably, the results of marker lesion studies indicate considerable efficacy of many agents to eliminate tumors in this setting. These studies tend not to be randomized and make the important assumption that no tumor would spontaneously disappear without treatment. The downside to this trial is generally patient and provider acceptance/willingness to allow a tumor to remain in the bladder, since in some cases this could mean another unnecessary procedure if the tumor does not respond to the treatment. This study approach, however, can provide a very rapid read-out of a treatment and help development of that agent for subsequent study.

Second-Line Trials

Disease relapse in NMIBC is common, even for patients treated with intravesical agents. If tumors relapse despite adjuvant therapy, patients may be eligible for second-line agents. Clinical trials in the second-line setting for NMIBC are susceptible to substantial heterogeneity in the cohort because of the wide variability in amount, type, and extent of prior therapies. For these reasons, investigators have designated certain disease states and entry criteria for determining eligibility in clinical trials. For example, in the ad-IFN clinical trial, patients with BCG-unresponsive disease were eligible if they experienced relapse after at least five of six induction BCG courses and two of three maintenance BCG courses [2]. In this disease setting, it will be difficult to assess the efficacy of therapy without a randomized clinical trial because some patients are cured with TURBT and this population is very heterogeneous (e.g., small volume disease and large volume disease). Nevertheless, in the current climate, phase II noncomparative trials in this setting have become the norm. It follows that there has been poor clinical utilization of these agents following published results of these noncomparative trials.

Landmark Studies in NMIBC

BCG Versus Doxorubicin [3]

Randomized trial of intravesical doxorubicin versus BCG (intravesically and percutaneously) for patients with "rapidly recurrent" Ta or T1 or CIS of the bladder. Treatment was given intravesically weekly for 6 weeks.

Percutaneous BCG was given to the upper part of the inner thigh by four punctures with a 28-gauge needle, usually at the time of the first intravesical BCG administration. A total of 262 patients were followed for 5 years and the median time to treatment failure was 10.4 versus 22.5 months for the doxorubicin versus BCG group, respectively. For patients with CIS, complete response was observed in 34% and 70% of patients for the doxorubicin and BCG groups, respectively. Limitations of this trial included lack of central pathology review for pre- and post-treatment tissues and lack of blinding. Nevertheless, this trial was a well-conducted RCT and provided validation of the efficacy of BCG over intravesical chemotherapy for treating NMIBC and helped to establish BCG as the standard of care. Since this trial, there have been multiple head-to-head comparisons of intravesical BCG versus intravesical chemotherapy and BCG consistently outperforms chemotherapy.

SWOG 8507 BCG Maintenance [4]

Preclinical data suggested that repeated instillations of BCG after induction, termed maintenance BCG instillations, would provide improved control over induction BCG alone. To test, patients were randomized to induction versus maintenance BCG where maintenance BCG of 3 weekly instillations were given at months 3, 6, 12, 18, 24, 30, and 36 following trial registration. Patients who completed induction BCG underwent PPD testing and stratified by the outcome (less than 5 mm versus ≥5 mm) and by presence/absence of CIS, then randomized to +/− maintenance BCG.

The trial reported on 384 patients, finding that the estimated median RFS was 35.7 months versus 76.8 months for the induction versus maintenance arms ($p < 0.0001$). This represents one of the most significant and substantial differences in outcomes for any urologic treatment and established maintenance BCG as the standard of care for patients with high-grade NMIBC.

Limitations of this study include lack of blinding and lack of central pathologic review for pre- and post-treatment tissue assessments. The strengths of the study included its rigorous design and the large magnitude of benefit.

A caveat to the terms induction and maintenance are that these are actually misnomers for papillary NMIBC. Induction indicates "successful treatment" of the disease with disappearance of tumor or resolution of symptoms. Maintenance refers to additional treatment given after induction which aims to keep the disease from re-emerging. In papillary NMIBC disease, however, tumors are successfully removed with surgery. Any therapy given afterwards is given to prevent disease relapse. Thus, induction is not truly induction in the true since of the word, but rather is the first component of maintenance therapy. In CIS NMIBC, induction therapy is given to treat the active disease and induce successful clearance.

Immediate Postoperative Intravesical Gemcitabine [5]

Investigators enrolled patients suspected of having low-grade NMIBC (based on cystoscopic appearance) into a RCT of postoperative one-time immediate instillation of intravesical gemcitabine versus saline placebo. The primary outcome was based on time to disease relapse. A total of 383 patients completed the trial. Of 201 patients randomized to gemcitabine and 205 to saline, 67 patients in the gemcitabine arm (4-year estimate, 35%) and 91 patients in the saline arm (4-year estimate, 47%) experienced a recurrence by 4-year median follow-up (HR, 0.66; 95% CI, 0.48–0.90; $P < 0.001$ by one-sided stratified log-rank test for time to recurrence). Strengths of the study included randomization, blinding of patients and investigators, and rigorous study design. Limitations included selection bias (enrollment based on cystoscopic appearance) and lack of centralized pathology review. While it was established that immediate postoperative instillation of mitomycin C was effective at preventing disease relapse in patients with

NMIBC, this study supported using gemcitabine, which is safer as MMC has been associated with severe reactions in some cases.

Endpoints Various endpoints are used in NMIBC, including endpoints based on tumor assessment, symptom assessment, and biomarkers. FDA approval of agents treating NMIBC utilize time-to-event endpoints (e.g., recurrence-free survival and progression-free survival) and complete response for CIS. Time-to-event provides more information than event alone. Evaluation of proportion of patients who recurred across groups provides some detail but is not as informative as a time-dependent endpoint. For example, a patient who recurs at 3 months after randomization compared to a patient who recurs at 18 months after randomization. Both of these patients are designated as recurrence but the person with the later recurrence benefitted greater because they went for a longer interval of time without disease.

For NMIBC, most often the primary endpoint is based on time to disease recurrence while time to progression is usually a secondary endpoint. Because high-grade disease is more dangerous than low-grade recurrence, some trials have used time to high-grade recurrence endpoint. Secondary endpoint considered in NMIBC clinical trials include time to disease progression, which could be defined as any stage progression or progression to muscle-invasive disease, time to death from bladder cancer, and time to any death (i.e., overall survival). This is because progression is infrequent in NMIBC whereas recurrence is more common. There is no universal definition of progression in NMIBC. It is well accepted that disease stage of ≥T2 represents progression. However, stage change from Ta to T1 or CIS to T1 could also be considered as progression. Further, grade progression is defined as low-grade changing to high grade. Time to recurrence can be assessed by comparing the median RFS between groups or by comparing the prevalence of recurrence at a specified time (e.g., 36 months). Often, the effect of a treatment over control is expressed as a hazard ratio (HR). Graphically, the difference between treatments are commonly depicted with a Kaplan–Meier curve. In this curve, the median survival is shown as the time at which 50% of the cases experienced the event (e.g., recurrence, progression, or death). The log-rank test statistic is used to estimate the significance of the difference between the 2 KM curves.

Although overall survival (OS) is the "gold standard" endpoint in oncology trials, OS is rarely used as a primary endpoint in NMIBC because of the relatively small impact that NMIBC has on OS. Generally, tumor assessment is evaluated with office-based cystoscopy with or without urine cytology. If office-based cystoscopy reveals a tumor, biopsy is required in order to define the tumor stage and grade. Usually, in the context of a clinical trial, performing an office-based tumor fulguration is not recommended because the tumors need to be evaluated by histopathology. In some trials, biopsies are mandated per protocol regardless of the cystoscopy findings. This is particularly the case with CIS which can, in some cases, elude routine cystoscopic detection. For example, in SWOG-8507, biopsies were mandated at 3 and 6 months after randomization for patients with CIS [4]. In this trial, CR for patients with CIS was defined as histological disappearance of malignancy on bladder biopsy and resolution of abnormal cytology.

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30 Clinical Trials in Localized Muscle-Invasive Bladder Cancer

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Introduction

With international regulatory approval of multiple new drugs for metastatic bladder cancer patients in recent years, a dramatic increase in clinical trial options for patients with localized muscle-invasive bladder cancer (MIBC) has resulted. These trials are testing both innovative designs and novel therapeutic agents. This chapter will provide an updated overview of these exciting development efforts with an emphasis on studies with practice-changing or transformative biologic understanding impact. These trials are summarized in Table 30.1 and their schemas are collectively presented in Figure 30.1.

Surgical Trials

It is appreciated that the number of lymph nodes examined at each lymph node station and the extent of lymph node stations assessed can provide more accurate staging information on MIBC patients who undergo cystectomy [1, 2]. It is postulated that extensive lymph node dissections may also provide therapeutic benefit [3]. Two randomized trials have tested this hypothesis. In the Association for Urologic Oncology of the German Cancer Society LEA AUA AB 25/02 phase 3 trial, 401 patients with MIBC or T1 high-grade tumors undergoing cystectomy were randomized to undergo a standard pelvic lymph node dissection (obturator, internal iliac, external iliac nodes) versus an extended lymph node dissection (standard dissection plus deep obturator, common iliac, presacral, paracaval, interaortocaval, and para-aortic nodes up to the inferior mesenteric artery) [4]. The study aimed to show an improvement from 50% to 65% in the primary endpoint of 5-year recurrence-free survival (RFS). After a median follow-up of 43 months, no significant difference in 5-year RFS estimate was observed with 64.6% and 59.2% remaining recurrence free in the extended vs. standard dissection groups respectively ($p = 0.36$). Secondary endpoints of cancer-specific survival and overall survival trended toward a benefit in the extended lymph node dissection arm; however, neither reached statistical significance. In a similar effort, the Southwest Oncology Group trial S1011 (NCT01224665) randomized 659 MIBC patients undergoing cystectomy to extended versus standard lymph node dissection defined according to the LEA AUA AB 25/02 trial definitions with the exception that dissection of lymph nodes between the aortic bifurcation and the inferior mesenteric artery was at the treating surgeon's preference. In S1011, investigators targeted a 28% improvement

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in disease-free survival (DFS) with the addition of an extended node dissection corresponding to an improvement in 3-year DFS from 55% to 65%. This study reached its full enrollment in April 2017 with results eagerly anticipated along with important translational biomarker work imbedded in both trials to discern any patient subsets that may derive greatest benefit.

Neoadjuvant Trials

Given the stalemate in bladder cancer drug development that existed for over a quarter century, the recent approval in metastatic bladder cancer patients of several new therapeutic options creates a new sense of optimism for bladder cancer patients of all stages. These new treatments

Table 30.1 Summary of recently reported and ongoing MIBC clinical trials with potential practice-changing impact

MIBC trial type	Trial	Intervention	N	1° Endpoint	Status
Surgical	LEA AUA AB 25/02	Extended vs standard PLND	401	5-yr RFS	Completed 5-yr RFS 65% vs 59% ($p = 0.36$) w/extended PLND
	S1011 (NCT01224665)	Extended vs standard PLND	659	DFS	Fully accrued, data maturing
Neoadjuvant	PURE-01 (NCT02736266)	Pembrolizumab	71	pCR	pCR = 42%
	ABACUS (NCT02662309)	Atezolizumab	74	pCR and CD8+ TILs	pCR = 29%, post-tx CD8+ TILS increased
	HCRN GU 14–188 (NCT02365766)	CG + pembrolizumab (Cis-Elig) Or G + pembrolizumab (Cis-Inelig)	81	≤pT1N0	≤pT1N0 = 62%, pCR = 44% (Cis-Elig arm) < pT1N0 = 52%, pCR = 45% (Cis-Inelig arm)
	NIAGARA (NCT03732677)	CG + durvalumab vs CG (Cis-Elig)	1050	pCR and EFS	Ongoing
	KEYNOTE-866 (NCT03924856)	CG + pembrolizumab vs CG + placebo (Cis-Elig)	870	pCR and EFS	Ongoing
	CA017–078 (NCT03661320)	CG + nivolumab + BMS986205 vs CG + nivolumab + placebo vs CG (Cis-Elig)	1200	pCR and EFS	Ongoing
	KEYNOTE-905 (NCT03924895)	Pembrolizumab + enfortumab vedotin vs pembrolizumab vs no neoadjuvant treatment	836	pCR and EFS	Ongoing
	EA8192 (NCT04628767)	AMVAC + durvalumab vs AMVAC (Cis-Elig UTUC) Gemcitabine + durvalumab (Cis-Inelig UTUC)	249	EFS (Cis-Elig) pCR (Cis-Inelig)	Ongoing
Adjuvant	IMVigor010 (NCT02450331)	Atezolizumab vs observation	809	DFS	Median DFS 19.4 m (Atezolizumab) vs 16.6 m (observation) HR 0.89 (95% CI 0.74–1.08 $p = 0.24$)
	CheckMate-274 (NCT02632409)	Nivolumab vs placebo	709	DFS	Median DFS 21.0 m (Nivolumab) vs 10.9 m (placebo) HR 0.70 (98.31% CI 0.54–0.89 $p < 0.001$)
	AMBASSADOR A031501 (NCT03244384)	Pembrolizumab vs observation	739	DFS and OS	Ongoing

(continued)

Table 30.1 (continued)

MIBC trial type	Trial	Intervention	N	1° Endpoint	Status
Bladder sparing	KEYNOTE-922 (NCT04241185)	TMT + pembrolizumab vs TMT	636	BIEFS	Ongoing
	SN1806 (NCT03775265)	TMT + atezolizumab vs TMT	475	BIEFS	Ongoing
	RETAIN (NCT02710734)	AMVAC ➔ surveillance in DDR+ cCR pts	71	2-yr MFS	17/26 (65%) DDR+ patients with cCR who opted for surveillance recurred (10 NMIBC, 6 MIBC, 1 metastatic disease, mature follow up ongoing
	A031701 (NCT03609216)	ddGC ➔ surveillance or intravesical tx in DDR+ cCR/tis/ta pts	271	3-yr RFS	Ongoing
	HCRN GU16–257 (NCT03558087)	GC + nivolumab ➔ surveillance + nivolumab in DDR+ cCR/ta pts	63	2-yr MFS	Ongoing

PLND pelvic lymph node dissection, *RFS* recurrence-free survival, *yr*. year, *DFS* disease-free survival, *pCR* pathologic complete response, *TILs* tumor infiltrating lymphocytes, *CG* cisplatin + gemcitabine, *G* gemcitabine, *p* pathologic stage, *Cis-Elig* cisplatin eligible, *Cis-Inelig* cisplatin ineligible, *EFS* event-free survival, *DFS* disease-free survival, *OS* overall survival, *TMT* trimodality therapy (chemoradiation), *BIEFS* bladder-intact event-free survival, *MFS* metastases-free survival, *AMVAC* accelerated MVAC (methotrexate, vinblastine, doxorubicin, cisplatin), *DDR+* DNA damage repair mutation positive tumor, *cCR* clinical complete response, *ddGC* dose-dense gemcitabine + cisplatin, *tx* treatment

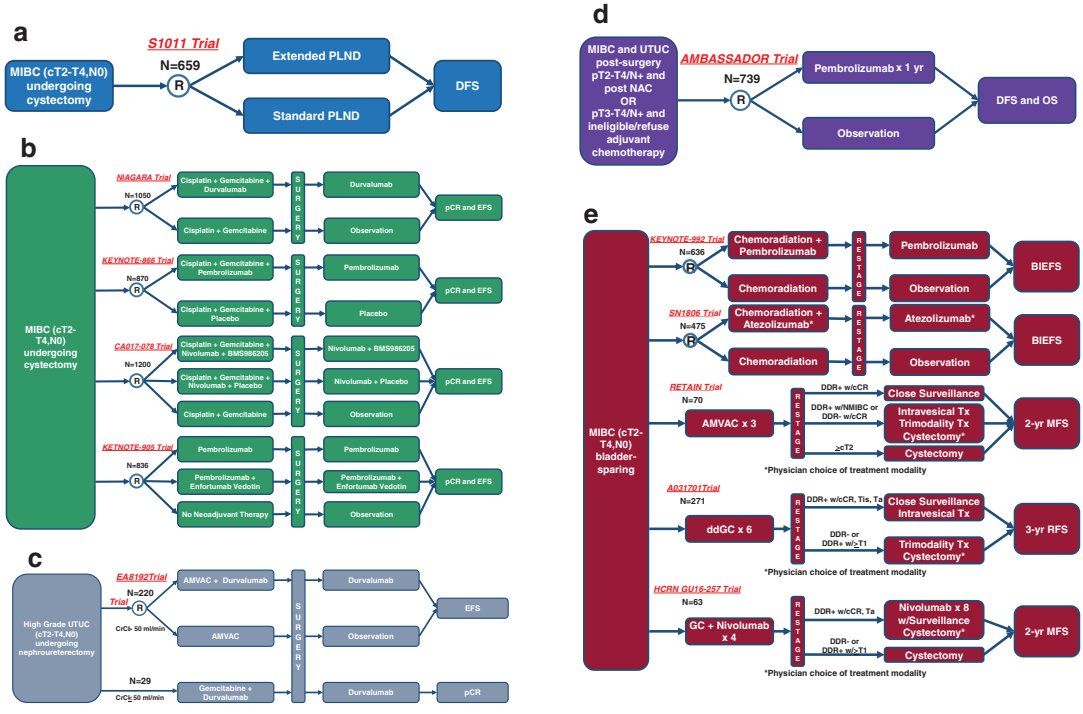

Fig. 30.1 Key ongoing MIBC clinical trial schemas: (**a**) surgery trials; (**b**) neoadjuvant bladder trials; (**c**) neoadjuvant upper tract trials; (**d**) adjuvant trials; (**e**) bladder-sparing trials. (*c* clinical stage, *R* randomize, *PLND* pelvic lymph node dissection, *DFS* disease-free survival, *pCR* pathologic complete response, *EFS* event-free survival, *UTUC* upper tract urothelial carcinoma, *CrCl* creatinine clearance, *p* pathologic stage, *N+* node positive, *NAC* neoadjuvant chemotherapy, *yr*. year, *OS* overall survival, *BI-EFS* bladder-intact event-free survival, *AMVAC* accelerated MVAC (methotrexate, vinblastine, doxorubicin, cisplatin), *MFS* metastasis-free survival, *ddGC* dose-dense gemcitabine + cisplatin, *RFS* recurrence-free survival, *GC* gemcitabine + cisplatin)

include immunotherapies (atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab) targeting the PD-1/PD-L1 immune checkpoint signaling pathways as well as novel antibody drug conjugates (ADCs) that exploit urothelial cancer-specific targets (e.g., Nectin-4 and Trop2) [5–14]. The favorable side-effect profiles of these immune checkpoint inhibitors (CPIs) compared to traditional cytotoxic chemotherapy options provide the opportunity to offer CPI treatment to a large proportion of bladder cancer patients who cannot tolerate or refuse chemotherapy treatment. Furthermore, while less than one-third of metastatic bladder cancer patients respond to CPI monotherapy, the high percentage of durable responses among those who achieve a response indicates that long-term disease control with maintenance of high quality of life is possible. Moreover, the encouraging clinical responses seen with ADCs in post-platinum- and post-CPI-treated metastatic bladder cancer patients combined with their absence of renal toxicity provide much needed non-platinum therapy options. These promising breakthroughs in metastatic bladder cancer patients provide rationale for the initial clinical trials demonstrating proof of concept in MIBC patients and support ongoing phase 3 trials with practice-changing potential.

Current clinical guidelines recommend upfront cystectomy for MIBC patients in whom cisplatin-based neoadjuvant chemotherapy (NAC) is not feasible due to concurrent comorbidities such as renal insufficiency [15]. In addition, up to half of patients eligible for cisplatin-based NAC choose not to receive it [16]. Due to the opportunity to assess clinical efficacy early in the form or pathologic response status and the ability to obtain pre- and post-treatment tumor tissue as part of standard of care management, initial investigations of the merits of CPI therapy in MIBC have focused on neoadjuvant approaches. Important proof-of-concept neoadjuvant CPI trials have recently been reported in MIBC patients. In the PURE-01 trial (NCT02736266), results are available from the first 50 patients of a planned enrollment of 71 patients [17]. MIBC patients (both cisplatin-eligible and cisplatin-ineligible were allowed to enroll) with baseline bladder tumor intentionally incompletely resected at transurethral resection of bladder tumor (TURBT) received three cycles of anti-PD-1 antibody, pembrolizumab, followed by cystectomy. Pembrolizumab was administered per the standard metastatic bladder cancer dosing schedule at 200 mg intravenously once every 21 days. Patients who demonstrated treatment failure per the treating physician's interpretation were treated with dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) followed by cystectomy. Pathologic complete response (pCR) was the primary endpoint with a goal pCR rate of 25%. Within the first 50 patients, the pCR rate observed was 42% (95% CI 28-57%) with 54% (95% CI 39-68%) of patients down-staged to non-muscle invasive stages (≤pT1N0). Ten patients (20%) demonstrated lymph node involvement with no metastatic development observed while on study. Importantly, treatment was well tolerated with only three patients (6%) experiencing grade 3 treatment-related adverse events (elevated transaminases, hyperkalemia, diarrhea – one event each) of which only one patient (2%) had to discontinue pembrolizumab treatment (elevated transaminases).

Using a similar neoadjuvant strategy with the anti-PD-L1 antibody atezolizumab, results from the neoadjuvant ABACUS trial (NCT02662309) have also been reported [18]. MIBC patients ineligible for or refusing cisplatin-based NAC with residual tumor still present following standard of care TURBT were enrolled (n = 74). Patients received two cycles of atezolizumab administered intravenously every 3 weeks at a dose of 1200 mg. Co-primary endpoints included a goal pCR rate above 20% and post-treatment increases in tumor tissue CD8+ T-cell infiltration. Of the 68 patients evaluable for pathologic response, the pCR rate observed was 29% (95% CI 19-42%). In patients with paired pre- and post-treatment tumor tissue available for analysis, a significant increase in CD8+ T-cells was observed post-atezolizumab treatment ($p < 0.001$). Four patients (6%) had progression to lymph node positive status at surgery. Treatment-related adverse events leading to discontinuation of the second atezoli-

zumab dose occurred in eight patients (11%) including one on-study death due to myocardial infarction and pulmonary embolism.

In an attempt to understand the potential benefits of combining traditional NAC with CPI therapy, the Hoosier Cancer Research Network (HCRN) GU 14-188 trial (NCT02365766) results provide additional data supportive of further investigation of NAC and CPI combinations in MIBC patients [19]. In this study, cisplatin-eligible MIBC patients ($n = 40$) were treated with traditional cisplatin 70 mg/m^2 on day 1, gemcitabine 1000 mg/m^2 on days 1 and 8, and pembrolizumab 200 mg on day 8 every 3 weeks with four cycles of chemotherapy and five cycles of pembrolizumab administered prior to cystectomy. The rate of patients with non-muscle invasive pathologic staging (≤ypT1N0) served as the primary endpoint with a target rate above 48%. Within the study population, the ≤ypT1N0 rate observed was 61% (95% CI 45-75%) with a ypCR (ypT0N0) rate of 44%. Spread of tumor to resected lymph nodes was seen in five patients (14%). Treatment-related toxicity was similar to that observed with traditional cisplatin and gemcitabine NAC with 31% of patients experiencing at least one grade 3-4 non-hematologic event and 57% of patients experiencing a grade 3-4 hematologic event. One death occurred 9 days after surgery due to mesenteric ischemia that was not attributed to study therapy. One grade 4 immune-related adverse event (3%) of thrombocytopenic purpura was observed that prevented cystectomy with the patient's tumor in remission at 14 months of follow-up. Within the same study, cisplatin-ineligible MIBC patients ($n = 37$) were treated with gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks for three cycles with pembrolizumab 200 mg administered every 3 weeks for five doses [20]. Promising clinical activity was observed with a <ypT1N0 rate of 52% and a ypCR (ypT0N0) rate of 45%. Grade 3/4 treatment-related events included neutropenia (24%), anemia (13%), and thrombocytopenia (5%). Four grade 3 immune-related adverse events were observed including pneumonitis (5%), colitis (3%), and elevated liver enzymes (3%) leading to therapy discontinuation in three patients.

With the promising initial signs of anti-tumor activity demonstrated with CPI monotherapy in the PURE-01 and ABACUS studies and with CPI combination therapy in the HCRN GU 14-182 study, international registration trials are now underway examining the merits of perioperative CPI approaches in MIBC patients. In the NIAGARA open-label phase 3 trial (NCT03732677), 1050 cisplatin-eligible MIBC patients will be randomized to receive neoadjuvant cisplatin and gemcitabine combined with the anti-PD-L1 antibody durvalumab (both during the neoadjuvant time frame and the adjuvant setting following cystectomy) compared to standard-of-care neoadjuvant cisplatin and gemcitabine therapy. The study will be examining co-primary endpoints of pCR rates at cystectomy as well as event-free survival (EFS) rates following cystectomy. Similarly, in the KEYNOTE-866 randomized, placebo-controlled, phase 3 trial (NCT03924856), 870 cisplatin-eligible MIBC patients will be randomized to receive either neoadjuvant pembrolizumab or placebo in addition to standard cisplatin and gemcitabine therapy in both arms. The primary endpoints of pCR rates and EFS rates will be examined. In the randomized, placebo-controlled, phase 3 CA017-078 trial (NCT03661320), cisplatin-eligible MIBC patients will be randomized between three arms with all patients receiving standard cisplatin and gemcitabine neoadjuvant treatment. In addition, patients in the two experimental arms will receive nivolumab with BMS986205 (an oral IDO1 inhibitor) or placebo. Again pCR and EFS rates will serve as the primary study endpoints. The enthusiasm for these new therapy options is further evidenced by new registration trial investigations in both the cisplatin-ineligible and the upper tract urothelial carcinoma (UTUC) populations. In the phase 3, randomized KEYNOTE-905 trial (NCT03924895), cisplatin-ineligible MIBC patients ($n = 836$) will be randomized to neoadjuvant treatment with pembrolizumab with or without the Nectin-4 targeting ADC enfortumab vedotin versus proceeding straight to surgery with pCR and EFS serving as the primary endpoints. In high-grade UTUC patients, the randomized phase 3 EA8192 trial (NCTN04628767)

will evaluate an EFS primary endpoint in cisplatin-eligible patients treated with accelerated methotrexate, vinblastine, doxorubicin, and cisplatin with or without the addition of durvalumab. A small, parallel, phase 2 portion of the study in cisplatin-ineligible patients will assess the pCR rate of the gemcitabine and durvalumab combination. Other phase 3 chemotherapy and CPI combination trials are in development with numerous phase 2 combination investigations already ongoing particularly in the cisplatin-ineligible MIBC population.

Adjuvant Trials

While the neoadjuvant setting provides advantages with regard to pre- and post-treatment tissue biomarker investigations, bladder cancer patients with high-risk disease remaining following cystectomy represent another population with large unmet needs. Rather than wait 3–5 years to interpret results of randomized phase 2 trials, several agents have been thrust directly into practice changing randomized phase 3 designs. In the IMvigor010 trial (NCT02450331), the role of adjuvant atezolizumab 1200 mg administered intravenously every 3 weeks for 1 year following cystectomy was compared to standard observation [21]. Eligible patients (n = 809) included MIBC patients with either ypT2-T4 tumors following neoadjuvant chemotherapy, pT3-T4 tumors in the absence of neoadjuvant chemotherapy, or node-positive (N+) disease in either setting. In addition, patients with upper tract urothelial carcinoma with similar high-risk staging were allowed to enroll up to a limit of approximately 10% of the total study population. The trial assessed the primary endpoint of investigator-assessed disease-free survival (DFS). At a median follow-up of 21.9 months, a median DFS of 19.4 months was observed in patients treated with atezolizumab compared to 16.6 months for patients randomized to observation. This difference was not statistically significant (HR 0.89, 95% CI 0.74–1.08, p = 0.24). In a similar trial design, but with incorporation of a placebo arm, the phase 3, placebo-controlled CheckMate-274 trial (NCT02632409) randomized high-risk post-surgery urothelial carcinoma patients to treatment with nivolumab 240 mg intravenously every 2 weeks for 1 year versus placebo [22]. With a median follow-up of 20.9 months, a statistically significant improvement from 10.9 months with placebo to 21.0 months with nivolumab treatment (HR 0.70, $p < 0.001$) was observed with no new safety concerns and no significant detriments to patient-reported quality-of-life measures. Lastly, the Alliance A031501 AMBASSADOR phase 3 trial (NCT03244384) being conducted through the National Clinical Trials Network (NCTN) is analyzing the clinical utility of adjuvant pembrolizumab 200 mg intravenously administered for 1 year versus observation. Patients (n = 739) with MIBC or invasive upper tract urothelial carcinoma who received neoadjuvant chemotherapy with residual ypT2-T4 disease, with residual pT3-T4 disease without neoadjuvant chemotherapy, or any node-positive (N+) patients are randomized to 1 year of adjuvant pembrolizumab versus observation. The study will assess the co-primary endpoints of overall and disease-free survival. Given the conflicting results observed in the ImVigor010 and CheckMate-274 studies, the AMBASSADOR trial results are eagerly anticipated.

Bladder-Sparing Trimodality Trials

In addition to the clinical benefits demonstrated to date with CPIs in the metastatic bladder cancer populations, preclinical investigations have shown improved anti-tumor control rates when CPIs are combined concurrently with external beam radiation therapy (EBRT) [23]. With traditional bladder-sparing trimodality therapy (TMT) approaches incorporating maximal up-front transurethral resection of bladder tumor (TURBT) followed by concurrent chemoradiation, long-term eradication of high-grade bladder cancer while maintaining an intact native bladder is achieved in 55% of patients [24]. In recent years, both patients and physicians have advocated to offer bladder-sparing TMT to a higher percentage of appropriately selected MIBC patients.

Indeed, the NCCN guidelines for MIBC now place a category 1 recommendation of TMT therapy in the management of MIBC patients [25]. Given the preclinical rationale suggesting synergistic benefits of combining CPI therapy with EBRT and the increased interest in TMT bladder-sparing approaches by patients and physicians, the SN1806 phase 3 trial (NCT03775265) conducted through the NCTN will randomize 475 MIBC patients to TMT in combination with atezolizumab versus standard-of-care TMT. Patients will be allowed to receive any of three standard intravenous chemosensitizing regimens (weekly cisplatin, mitomycin C combined with continuous infusion of 5-fluoruracil, twice weekly gemcitabine). In addition, both cisplatin-eligible and -ineligible patients will be enrolled. The primary endpoint is bladder-intact event-free survival (BI-EFS) with a goal of improving the median BI-EFS by 46% (HR = 0.68) compared to historical rates corresponding to an improvement in 3-year BI-EFS from an expected 52% to 64% with the addition of atezolizumab therapy. Utilizing a very similar strategy, the KEYNOTE-922 randomized phase 3 trial (NCT04241185) will also examine the role of TMT with or without CPI therapy. MIBC patients (n = 636) will be randomized to treatment with standard TMT with one of three standard chemosensitizing regimens combined with or without pembrolizumab. As in SN1806, BI-EFS will be the primary efficacy endpoint examined.

Bladder-Sparing Genomically Selected Chemotherapy Trials

Taking advantage of recent bladder cancer biomarker discovery efforts, several investigators are now conducting novel trials in which an individual's tumor mutation profile combined with their clinical response to neoadjuvant cisplatin-based chemotherapy can be used to identify patients most likely to achieve a pathologic complete response. In such patients, the opportunity to forego cystectomy and be followed with very close surveillance is being offered within clinical trials for the first time. The rationale for these studies stems from evidence that patients harboring deleterious mutations in DNA damage repair (DDR) genes (e.g., *ERCC2, ATM, FANCC, RB1*) have increased pCR rates to NAC. Thus, the possibility may exist for cure with chemotherapy alone in such patients with DDR+ mutant tumors. In the RETAIN trial (NCT02710734), patients (n = 71) with MIBC received three cycles of accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) every 2 weeks [26]. While they were receiving their AMVAC treatments, their baseline TURBT tumor specimen was tested for DDR+ mutations in *ERCC2, ATM, FANCC*, and *RB1*. Furthermore, all patients underwent repeat clinical staging after completion of their AMVAC treatments including cystoscopy, urine cytology, and repeat TURBT. Patients with DDR+ mutations and a complete response on clinical restaging had the option to forego cystectomy. Patients with residual non-muscle-invasive bladder cancer (NMIBC) on clinical restaging or a clinical complete response in a DDR- patient could be managed by the treating physician's choice with intravesical therapy, bladder-sparing TMT, or cystectomy. Those patients with residual T2 MIBC could be offered bladder-sparing TMT or cystectomy. All T3 or greater patients were offered cystectomy. The RETAIN study aimed to demonstrate a 2-year metastasis-free survival of over 64% in the patients with DDR+ tumors who do not undergo cystectomy. Upon initial analysis with a median follow-up of 18.8 months in all patients enrolled (n = 71) and 20.6 months in patients with a DDR mutation and clinical restaging permitting follow-up by surveillance rather than cystectomy, 17 of 26 patients (65%) had urothelial carcinoma recurrence noted including 10 NMIBC, 6 MIBC, and 1 metastatic tumor. Mature follow-up is ongoing.

Utilizing dose-dense cisplatin 35 mg/m^2 intravenously on days 1 and 2 combined with gemcitabine (ddGC) 2,500 mg/m^2 intravenously on day 1 given every 2 weeks with pegfilgrastim growth factor support for six cycles, the Alliance A031701 phase 2 trial (NCT03609216) is also investigating chemotherapy as a bladder-sparing approach. While receiving ddGC, all 271 patients

will have their tumor tested for DDR mutations on a broader panel of candidate DDR genes (*ERCC2, ERCC5, BRCA1, BRCA2, RECQL4, RAD51C, ATM, ATR, FANCC*). Patients with deleterious DDR+ mutations with no tumor, CIS, or Ta disease will be offered a bladder-sparing option consisting of close surveillance or intravesical BCG therapy as appropriate based on post-chemotherapy restaging findings. Patients with DDR- tumors and patients with DDR+ tumors with ≥ T1 residual tumors post-chemotherapy will be offered cystectomy or chemoradiation. The study is aiming to demonstrate an 80% 3-year RFS rate in the DDR+ patients who opt for bladder-sparing surveillance after completion of their ddGC chemotherapy.

Building on the advantages demonstrated by combining chemotherapy with CPI therapy in other tumor types, investigators in the HCRN GU16-257 trial (NCT03558087) will test the safety and potential benefit of combining traditional intravenous cisplatin 70 mg/m^2 on day 1 plus gemcitabine 1000 mg/m^2 on days 1 and 8 with nivolumab 360 mg on day 1 given every 3 weeks. Up to four cycles will be administered to all patients (n = 63) followed by clinical restaging by imaging, cystoscopy, and TURBT. Patients with greater than Ta tumors present on restaging will proceed to cystectomy, while those with restaging T0 or Ta tumors will be offered the choice of proceeding to cystectomy or continuing on nivolumab monotherapy for eight cycles under close surveillance.

Conclusions

As evidenced by the number, size, and novelty of the MIBC trials summarized in this chapter, we are clearly in a new age of bladder cancer clinical investigations. Never before have we had so many effective metastatic treatments and innovative surgical and diagnostic approaches worthy of investigation in MIBC patients as a means to increase cure rates. Our challenge and hope is to complete these critical trials and demonstrate true benefits for MIBC patients throughout the world.

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Clinical Trials in Metastatic Urothelial Carcinoma

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Introduction

Although significant advances have been made in the treatment of metastatic urothelial carcinoma (mUC), it remains an incurable disease. Consequently, consideration of clinical trials plays a very important role in the management of these patients and the development of new regimens. In this chapter, we review a few examples of relevant clinical trials in mUC that may impact treatment options in the future. For ease of reference, discussion is subdivided based on prior therapy exposure and relevant treatment setting. Notably, this review is not meant to be an exhaustive list of clinical trials but rather a practical guide how to think about novel therapeutics in mUC. Readers are also encouraged to review a comprehensive relevant educational review presented at the 2019 Annual ASCO Meeting along with materials from the 2020 ASCO meeting and other evolving more current literature [1].

First Line, Cisplatin-Eligible

For patients with mUC who are treatment-naïve, several large phase III clinical trials that randomize participants to receive either combination of platinum-based chemotherapy and immune checkpoint inhibitor or either treatment alone are ongoing. These trials generally allow prior cisplatin-based treatment in the neoadjuvant or adjuvant setting as long as this treatment was completed >12 months prior to development of metastatic disease. IMVIGOR 130 randomized patients to atezolizumab plus platinum-based chemotherapy (arm A), atezolizumab alone (arm B), or placebo plus platinum-based chemotherapy (arm C) [2]. This trial reported results at the 2019 ESMO Meeting and was recently published, suggesting PFS advantage for arm A over arm C, although OS data was still immature and needs longer follow-up [3]. There was no significant OS difference between arm B and arm C. A similar trial is the KEYNOTE 361, which randomized patients to receive either pembrolizumab, pembrolizumab and platinum-based chemotherapy, or platinum-based chemotherapy alone [4]. A press release recently announced that this trial did not meet its prespecified primary endpoints

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of overall survival (OS) or progression-free survival (PFS), although the data have not yet been presented. Another large phase III trial is the Checkmate-901, which randomized previously untreated patients in a 1:1 fashion to receive combination of nivolumab/ipilimumab or standard-of-care cisplatin or carboplatin-based chemotherapy (based on cisplatin eligibility); this trial includes also another arm treated with gemcitabine/cisplatin/nivolumab which will be compared to gemcitabine/cisplatin alone. The DANUBE trial randomized patients 1:1:1 to receive either durvalumab monotherapy, durvalumab/tremelimumab (anti-PD-L1 and anti-CTLA-4), or standard of care platinum-based chemotherapy (cisplatin or carboplatin based) [5], and recently also had a press release with negative results. The NILE trial is randomizing patients to durvalumab in combination with platinum-based chemotherapy, durvalumab/tremelimumab combination with chemotherapy, or platinum-based chemotherapy alone (cisplatin or carboplatin based on cisplatin eligibility). All the above trials are well designed and may potentially alter the treatment landscape in advanced urothelial cancer; however, statistical design (e.g., hierarchical), selection of (co-) primary endpoints, sample size, follow-up time and exposure to salvage therapies, are all very relevant for final result interpretation. It is also important to note the presence of a few similar key stratification factors across those trials. Overall, the concurrent combination of chemotherapy plus immune checkpoint inhibitor has not led to meaningful outcome improvement so far based on the available data.

There are additionally several smaller studies that are hypothesis generating and support further investigation in this setting and a number of these studies are exploring novel targeted agents. A very promising agent is enfortumab vedotin (EV), an antibody–drug conjugate (ADC) composed of an anti-nectin-4 monoclonal antibody attached to a microtubule-disrupting agent, monomethyl auristatin E (MMAE), that was recently granted FDA approval in the treatment-refractory setting. EV-103 is a phase Ib/II clinical trial for patients with mUC in the first line setting currently accruing patients into various combination cohorts with EV backbone, including cisplatin/EV and cisplatin/EV/pembrolizumab for cisplatin-eligible patients (NCT 03288545). A large phase III trial, EV-302, investigating enfortumab vedotin and pembrolizumab combination versus chemotherapy alone, recently started enrolling patients (NCT04223856).

First Line, Cisplatin-Ineligible

Patients who are treatment-naïve yet are cisplatin ineligible comprise a population in urgent need of novel treatment options given relatively poor outcomes with currently available standard-of-care options. This is particularly the case for patients with low-tumor tissue PD-L1 expression given the currently unclear role of immune checkpoint inhibitors in this population. Therefore, patients with mUC who are deemed cisplatin-ineligible should have tumor tissue tested for PD-L1 expression using FDA-approved companion diagnostic assay before standard-of-care pembrolizumab or atezolizumab (FDA guidelines released in summer 2018 based on preliminary results from IMVIGOR 130 and KEYNOTE 361 mentioned above). If patients are also ineligible for carboplatin, there is no mandate for PD-L1 testing in the US, based on FDA label for those two immune checkpoint inhibitors in this setting. However, all patients should be strongly considered for available clinical trials, regardless of the PD-L1 status. The large, randomized phase III clinical trials mentioned above in the cisplatin-eligible setting allow the inclusion of cisplatin-ineligible patients.

A number of clinical trials are currently enrolling patients and evaluate several immunotherapy combinations. One such trial is the phase II PIVOT-10 trial, which is investigating the combination of nivolumab with NKTR-214, which is a pegylated form of IL-2 (NCT03785925). This trial accepts patients independent of PD-L1 status but the primary endpoint will be assessed in the population of patients with PD-L1 low tumors. This combination has shown robust early activity in the PIVOT-02 phase I trial of solid tumors that included mUC. A phase II clini-

cal trial is evaluating CV301, a vaccine against tumor-associated antigens, CEA and MUC-1 (widely expressed in mUC cells) in combination with atezolizumab (NCT03628716). Another trial is testing the combination of atezolizumab with the cytokine IL-7 (NCT03513952). Overall, moderate-sized phase II studies in this setting usually rely on overall response rate (ORR) as the primary endpoint to make a quick "go" or "no go" decision of whether or not to investigate a particular regimen further. Single-arm studies compare to a historical ORR benchmark, such as with carboplatin/gemcitabine or anti-PD(L)1 agent, while randomized studies use an active comparator. Another relevant discussion point is whether PD-L1 testing is required for eligibility in those trials; frequently this may depend on the study design. For instance, combination regimens in a single-arm study may not necessarily need PD-L1 testing for eligibility (but important to include as correlative endpoint). On the other hand, randomized trials involving an arm with anti-PD(L)1 as a single agent would require following the standard practice with those agents for cisplatin-ineligible patients in the front-line setting. The inclusion of patients who are ineligible for both cisplatin and carboplatin is another relevant consideration if they otherwise meet trial eligibility criteria.

Trials combining anti-PD(L)1 and antiangiogenic agents provide relevant frontline options in cisplatin-ineligible patients and are supported by robust scientific rationale and preclinical data, for example, NCT03898180, NCT03170960, NCT03534804, NCT03472560, among others. Numerous other trials in the cisplatin-ineligible space share the similarity of combining a checkpoint inhibitor with a targeted agent, such as the BAYOU trial combining durvalumab with the PARP inhibitor olaparib (NCT03459846). In patients with tumors harboring FGFR alterations, several phase I/II trials are investigating combinations of an FGFR inhibitor with anti-PD-(L)1. Examples include the combination of erdafitinib/cetrelimab (phase II NORSE trial, NCT03473743), rogaratinib/atezolizumab (FORT-2 trial, NCT03473756), and pemigatinib/pembrolizumab versus pemigatinib monotherapy versus standard-of-care chemotherapy (FIGHT-205 trial, NCT04003610), among others. There is significant interest in such combinations, supported by strong mechanistic rationale and preclinical data [6, 7]; ORR is usually the "metric" for a "go"/"no go" decision in such trials, while biomarker-driven patient selection methods can differ and therefore can impact outcomes.

The EV-103 trial mentioned above also includes a cohort of cisplatin-ineligible patients whose data was presented at the 2019 ESMO meeting. This cohort included patients who were treatment-naïve in the metastatic setting and were treated with combination of pembrolizumab and enfortumab vedotin. Among 45 treated patients, ORR was 73% (16% CRs) with a clinical benefit rate (response and stable disease) of 93% [8]. Despite being a small study with short follow-up and possible selection bias, these promising results support a larger trial of PD(L)1 and ADC combination. Another combination that can be tested in this trial can be the combination of carboplatin/EV/pembrolizumab. Other trials of cisplatin-ineligible patients are including anti-PD(L)1 combinations with radiotherapy, such as NCT03486197, combining pembrolizumab with neutron radiation, aiming to release neoantigens and potentiate immune response.

Post-Platinum

Patients whose disease has progressed following prior platinum-based therapy represent unique challenges for trial accrual as this is generally a sicker population with more advanced disease and worse performance status. A very important niche in the post-platinum treatment space is occupied by "switch maintenance" therapy trials. Switch maintenance is a strategy of initiating a new agent immediately after completion of first-line treatment before progression that is distinct from continuation maintenance of an agent that was already given as part of a first-line regimen [9]. Switch maintenance trials are reserved for patients who completed platinum-based chemotherapy for metastatic disease and

had either response to treatment (CR or PR) or stable disease. In lieu of waiting for progression to start salvage therapy, these trials are using switch maintenance therapy by initiating immune checkpoint inhibitors soon after completion of front-line chemotherapy without waiting for progression. This strategy is used to both deepen responses to chemotherapy and extend progression-free and overall survival. A trial of switch maintenance pembrolizumab randomized against placebo reported improved PFS in patients with mUC completing first-line platinum-based chemotherapy [10]. Importantly, a large randomized phase III switch maintenance trial of avelumab plus best supportive care versus best supportive care alone (NCT02603432) recently reported a significant overall survival benefit (median 21.4 vs. 14.3 months, HR 0.69, $p < 0.001$) for avelumab regardless of PD-L1 expression, that led to FDA approval and inclusion at both NCCN and European guidelines [11].

Although immune checkpoint inhibitors have been FDA-approved for platinum-refractory mUC since 2016, much work remains to be done to increase response rates and prolong survival. Consequently, numerous trials of combination therapies are being pursued in this space, mostly combining an anti-PD-(L)1 agent with other therapies. As the understanding of the heterogeneity that underlies mUC grows, biomarker-driven clinical trials are increasingly emerging in this space. Patients with mUC should have tumor tissue tested for genomic alterations using either commercially available next-generation sequencing platforms, or, where available, institutional platforms. Recently, there is data suggesting a possibly complementary role of cell-free circulating tumor (ct) DNA next-generation sequencing in mUC [12–14]. Tumor genomic sequencing may ideally be done at the time of initial diagnosis of metastatic disease, so results can be readily available to inform either clinical trials or standard therapy with erdafitinib, which received accelerated FDA approval in tumors harboring FGFR2 or FGFR3 activating mutation or fusion [15].

Several of the currently accruing trials in the post-platinum treatment space enroll patients based on the results of tumor sequencing. An example of such a trial is the BISCAY trial, a phase Ib biomarker-directed multidrug "umbrella" trial with an adaptive design in patients with mUC. In this trial, tumor samples were evaluated using next-generation sequencing and patients were assigned to treatment modules based on the results. Patients without "targetable alterations" were initially allocated to durvalumab monotherapy, whereas those whose tumors had specific alterations received combination of durvalumab with a targeted agent. Results of this trial presented at the 2019 ESMO meeting showed that although no treatment module reached the prespecified high ORR threshold to trigger further evaluation, it generated very interesting hypotheses [16]. A similar approach is used in NCI-MATCH "basket" study that enrolled patients across the spectrum of previously treated solid tumors and lymphomas. This study also included multiple arms to which patients were allocated based on tumor somatic genomic testing. Presence of arms targeting molecular alterations that are enriched in mUC, such as in ERBB2, EGFR, FGFR, PIK3CA/AKT/mTOR pathway, among others, allowed for enrollment of patients with mUC; however, dedicated studies in mUC are warranted. MORPHEUS is another phase Ib/II multi-arm randomized umbrella study with an adaptive design investigating multiple combination treatment arms in patients with mUC who progressed on/after platinum-based therapy (NCT03869190). The study includes multiple combinations of atezolizumab with different agents, allowing comparison of several treatment arms with a single control of atezolizumab monotherapy. The study moreover has an adaptive design, allowing for early closure of ineffective combination arms and expansion of arms where activity is noted, while patients are also eligible to enroll into a different combination arm if they experience loss of benefit or unacceptable toxicity on prior treatment.

Novel studies are also targeting several other pathways implicated in the pathophysiology of

mUC. These include FGFR inhibitors, PARP inhibitors and HER2-targeting agents, among others. FGFR inhibitor trials are enrolling across the spectrum of mUC including in earlier stage disease. Thus far, impressive activity has been observed in the platinum refractory space, most notably with erdafitinib which received FDA accelerated approval in April 2019 based on a phase II trial [15]. This accelerated approval is contingent upon data from a confirmatory trial, the currently ongoing phase III THOR trial comparing erdafitinib to either chemotherapy or pembrolizumab in patients with FGFR2/3 genomic alterations. A similar phase II/III trial (FORT-1) compared rogaratinib to chemotherapy in patients with FGFR 1–3 mRNA overexpression who progressed on prior platinum-based chemotherapy. Recently presented trial results reported ORR to be similar in the two groups at around 19%, but with potentially more favorable responses to rogaratinib in a subset of patients with FGFR3 DNA alterations [17]. As FGFR alterations appear to be enriched in patients with upper tract urothelial cancer, special interest is being paid to this subset across trials. Other representative trials include FUZE trial with Debio-1347 which is a "basket" trial in patients with FGFR fusions across solid tumors, including mUC (NCT03834220). Vofatamab, a monoclonal antibody, against FGFR is being tested in the FIERCE-22 clinical trial in combination with pembrolizumab for platinum-refractory patients with both wild-type and mutated FGFR with preliminary results presented at the 2019 ASCO Meeting [18]. There are numerous additional trials, such as Cosmic-021 of atezolizumab/cabozantinib combination and a trial combining pembrolizumab with ramucirumab which have recently reported preliminary results [19, 20]. A similar phase I dose expansion trial combining nivolumab with cabozantinib or nivolumab and ipilimumab with cabozantinib is ongoing and has reported preliminary findings [21]. A trial of cabozantinib monotherapy in platinum-refractory patients has also recently published its findings showing an ORR 19% [22].

The prevalence of homologous recombination deficiency (HRD) in bladder tumors has also generated significant interest in the use of poly(ADP-ribose) polymerase inhibitors (PARPis) in this space. ATLAS trial evaluated the PARP inhibitor rucaparib as single agent in patients with mUC previously treated with platinum-based chemotherapy and/or checkpoint inhibitors and reported no confirmed responses at the 2020 ASCO GU Symposium [23]. A similar trial of another PARP inhibitor, olaparib, in patients with mUC and DNA damage response gene defects is also currently accruing patients. Patient selection (biomarker-driven vs. all comers) is a key parameter in the above trials. ORR is generally used as the primary endpoint in phase II trials, with OS and PFS being the main metrics in large phase III trials. An important point is the emerging presence of adaptive designs, as well as umbrella (one tumor type with multiple alterations) and basket (many tumor types with a specific alteration) type trials based on specific biomarkers.

ADC comprise a particularly exciting class of agents currently in development in mUC and trials of enfortumab vedotin (EV) were described in the treatment-naïve space above. In the platinum-refractory and also PD-(L)1 refractory space, EV is the new standard therapy based on recent accelerated FDA approval (see section below). Patients with mUC refractory to prior platinum-based chemotherapy were treated in the EV-101 study with single agent enfortumab-vedotin with an impressive ORR [24]. Another ADC being investigated in clinical trials of platinum-refractory disease is sacituzumab govitecan (IMMU-132), which targets Trop-2, combined with pembrolizumab in this setting (Trophy U-01, cohort 3). Similarly for patients with HER2 positive mUC, RC48-ADC has demonstrated promising activity with ORR 60.5% in a phase II study of pretreated patients [25]. There are other promising HER2 targeting agents in clinical trials that include DS8201a (ADC) and PRS-343 (bispecific fusion protein) among others.

Post-Immune Checkpoint Inhibitor

The treatment of patients with mUC who progress on both platinum-based chemotherapy and then checkpoint inhibitors still represents an area of need despite the recent approval of enfortumab vedotin in this space based on an impressive ORR and durable responses, subsequently confirmed by the results of EV-301 clinical trial. Still, patients in this space should always be considered for clinical trials. In addition to enfortumab vedotin, erdafitinib can also be used as the standard of care in patients with selected FGFR2 or FGFR3 alterations. Many clinical trials described in the platinum-refractory space above also have cohorts available in this space and include several targeted agents and ADCs. Impressive results from the EV-201 trial investigating enfortumab vedotin in post-platinum and post-checkpoint inhibitor space led to an ongoing confirmatory phase III trial (EV-301) as well as accelerated FDA approval of this agent [26]. EV-301 is a phase III trial that randomized patients who have previously progressed on platinum-based chemotherapy and immune checkpoint inhibitor to receive either enfortumab vedotin or chemotherapy with either taxane or vinflunine, and did show an overall survival benefit of enfortumab relative to chemotherapy. Another trial of patients with mUC progressing on both chemotherapy and immune checkpoint inhibitor is Trophy U-01 (Cohort 1), investigating another ADC, sacituzumab govitecan (IMMU-132), in this space. Results from the initial 35 patients that were presented at 2019 ESMO Meeting showed a promising ORR 29%; this trial is still ongoing and also includes another cohort [2] of patients with mUC who had received prior checkpoint inhibitor but not platinum-based chemotherapy in the advanced disease setting and whose results with ORR 29% were presented at ASCO 2020 [27, 28]. This too has led to the accelerated approval of sacituzumab govitecan for mUC patients previously treated with platinum-based therapy and anti-PD-(L)1 agents. There is plan for a phase III trial comparing sacituzumab govitecan to salvage chemotherapy in this setting. Of note, the "bar" for accelerated approval might possibly be lower in this setting based on the unmet need and could potentially be approached via a single-phase II trial providing impressive ORR and durability of response, coupled with a favorable toxicity profile as was done with EV-201 for enfortumab vedotin. However, full regulatory approval would still require phase III randomized trials.

Additional Considerations

There is a plethora of ongoing clinical trials in mUC, and it is important to keep in mind that the above is just a conceptual framework and not a comprehensive list. There are several important factors to keep in mind about clinical trial designs. One is the importance of biomarkers that can impact trial results. For instance, tumor tissue PD-L1 expression was a significant point of discussion in the IMvigor 211 phase III trial that did not meet its primary endpoint in the subset of patients whose tumors had high PD-L1 expression. Several ongoing trials may use tumor tissue PD-L1 expression or other biomarkers as a stratification factor. Moreover, there is significant variability in the assays, timepoints, and other logistics of biomarkers across trials. This can enable discovery but may impede robust validation of clinical utility. Additional biomarkers, based on next-generation sequencing, have been implemented in new trials impacting patient eligibility and stratification. It is worth highlighting the important distinction between predictive and prognostic biomarkers that usually requires a randomized trial to discern the difference between these two categories.

Oncologists should always be aware of clinical trials available both at their own and other institutions to provide relevant therapeutic options to their patients. This is especially important in a dynamically changing treatment space with a high clinical need. It is likewise important to utilize next-generation sequencing of tumors for all patients at the time of diagnosis of mUC, which may provide additional clinical trial options in addition to assessment of erdafitinib use. Maintaining continued awareness of potential future trials and those that are closed to accrual but whose results have not been reported is important for the understanding of potential future treatment options and the changing treat-

ment landscape. It should be noted that clinically fit patients with mUC who have progressed on multiple treatments and have a good performance status should also be considered for phase I trials; referral to and communication with centers with open trials should therefore be considered as part of routine practice.

Petros Grivas (unrelated to this chapter in the last 3 years): Consulting for AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Driver, Dyania Health, EMD Serono, Exelixis, Foundation Medicine, GlaxoSmithKline, Genentech, Genzyme, Heron Therapeutics, Immunomedics, Janssen, Merck, Mirati Therapeutics, Pfizer, Roche, Seattle Genetics, QED Therapeutics; participation in educational program for Bristol-Myers Squibb; and institutional research funding from AstraZeneca, Bavarian Nordic, Bayer, Bristol-Myers Squibb, Clovis Oncology, Debiopharm, Genentech, GlaxoSmithKline, Immunomedics, Kure It Cancer Research, Merck, Mirati Therapeutics, Oncogenex, Pfizer, QED Therapeutics.

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PG: see link below (last 2 years).

https://coi.asco.org/share/AM6-Y2LD/Petros%20Grivas

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Clinical Trials in Upper Tract Urothelial Carcinoma

32

A. H. Mostafid

Specific Issues Relevant to Upper Tract Urothelial Cancer

Upper tract urothelial carcinoma (UTUC) makes up 5–10% of all urothelial cancers [1]. While non-metastatic UTUC shares some similarities with non-metastatic urothelial carcinoma of the bladder (UCB) such as histological grading and staging, there are important practical issues specific to UTUC:

- In UTUC, due to problems with access and instrumentation of the upper tract, biopsy is often suboptimal which can lead to problems with accurate histological staging.
- Radiological staging may under (or over) estimate the extent of the disease.
- Due to problems with access to the upper tract, topical therapy for UTUC (e.g., mitomycin or BCG) is difficult to administer and will usually require anesthesia.
- Even with minimally invasive surgical approaches, the postoperative recovery time following nephroureterectomy (N-U) is significant and may impact the optimal timing of adjuvant therapies.
- The loss of one renal unit can often result in a significant reduction in renal function limiting the patient's ability to have adjuvant chemotherapy.

These factors will all need to be taken into consideration when planning clinical trials in UTUC.

General Comments on UTUC Trial Design

- Due to the relative rarity of UTUC, randomized trials in this area have been hard to carry out and have therefore usually been underpowered.
- Neoadjuvant trials will invariably depend on suboptimal staging for the reasons outlined above.
- Adjuvant trials will be affected by postoperative recovery times and postoperative changes in renal function.
- Recently randomized trials such as POUT [2] have shown that national or even international collaboration is essential in developing high-quality trial in UTUC. This will hopefully

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pave the way for similar collaborations to answer other issues in UTUC (see below).
- The success of POUT has shown that randomized trials are possible in UTUC and should now be the preferred trial design rather than single-arm phase II trials.
- Important inclusion/exclusion and primary and secondary endpoints will depend on whether the trial is surgical or oncological and are discussed below.

UTUC Surgical Trials

For the reasons outlined above, there are relatively few randomised surgical trials in UTUC. Two prospective randomised trials have demonstrated that a single postoperative dose of intravesical chemotherapy (mitomycin C, pirarubicin) soon after surgery (between 2 and 10 days) reduces the risk of bladder tumor recurrence within the first year post-RNU [3, 4]. These are summarized in Table 32.1.

A systematic review and metanalysis found a 41% decrease in the odds of recurrence with intravesical chemotherapy [5]. More recently the outcomes of early ureteral ligation at N-U on prevention of intravesical recurrence was reported in a single-arm prospective trial using a historical control group [6]. The authors found lower rates of intravesical recurrence after early ureteral ligation in patients with renal pelvis tumors but not ureteral tumors. A prospective single-arm trial (the OLYMPUS trial) assessing the efficacy of a gel containing mitomycin instilled retrogradely for low-grade UTUC is in progress.

There remains a number of important but unanswered questions in the surgical management UTUC that would be ideal candidates for well-conducted randomized trials:

- Endourological treatment of UTUC versus standard N-U
- The optimal method of excision of the distal ureter is unknown – "Rip and pluck" versus formal surgical excision with or without formal opening of the bladder
- The role of lymphadenectomy for UTUC

UTUC Nonmetastatic Medical Oncology Trials

The majority of historical chemotherapy trials for UTUC are retrospective and focus on the role of adjuvant chemotherapy. The success of the POUT trial (Table 32.2) has demonstrated that a randomized trial of adjuvant therapy following N-U is feasible [2] and adjuvant chemotherapy following N-U should now be considered the standard of care in this area when planning future trials.

As with surgical UTUC trials, there remains a number important but unanswered questions, which should be answered by well-conducted randomized trials:

- Neoadjuvant versus adjuvant chemotherapy for UTUC

Table 32.1 Important UTUC surgical trials

	Population	Experimental arm	Control arm	Primary endpoint	*N*	Outcome
Odmit C (O'Brien, Eur Urol 2011)	Patients undergoing N-U	40 mg intravesical Mitomycin-C	Standard care	Bladder cancer in the first 12 months following N_U	284	16% recurred in MMC group 27% in control arm ($p = 0.03$)
Pirarubicin (THP) monotherapy study group (Ito, JCO 2013	Patients undergoing N-U	30 mg intravesical Pirarubicin (THP)	Standard care	Bladder cancer in the first 24 months following N-U	72	17% in THP group 42.2% in control arm ($p = 0.025$)

Table 32.2 Important UTUC medical oncology trials

	Population	Experimental arm	Control arm	Primary endpoint	*N*	Outcome
POUT	Patients undergoing N-U	4 cycles of gemcitabine–cisplatin	Surveillance with subsequent chemotherapy if required	Disease-free survival	248	2-year DFS: 70% for chemotherapy 51% for surveillance

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Part II

Upper Tract Urothelial Carcinoma

33 Patient Evaluation and Diagnosis – Screening, Evaluation, and Workup

Roger Li

Abbreviations

UTUC	Upper tract urothelial carcinoma
AUA	American Urologic Association
SEER	Surveillance, Epidemiology, and End Results
HNPCC	Hereditary Nonpolyposis Colorectal Carcinoma
EAU	European Association of Urology
DW-MRI	Diffusion-Weighted MRI
DETECT I	Detecting Bladder Cancer Using the UroMark Test
UC	Urothelial Carcinoma
RCC	Renal Cell Carcinoma
FISH	Fluorescent In Situ Hybridization

Epidemiology

Upper tract urothelial carcinoma (UTUC) is a rare disease, accounting for only 5–10% of all urothelial carcinoma [1]. It is found in 0.1–0.7% of all patients undergoing hematuria workup [2, 3]. In recent years, the AUA's mandate for workup in all patients with visible hematuria and those ≥35 years with microscopic hematuria has led to an increase in incidence and earlier-stage migration upon diagnosis. A National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database study found annual rates to have risen from 1.88 cases per 100,000 people in 1973 to 2.06 in 2005 [4]. Nonetheless, a majority of the patients (up to 60%) continues to be diagnosed in the advanced muscle invasive stages, compared to only 15–25% in bladder tumors [5]. Five-year disease-specific survival was found to be 75% overall, and 95%, 88.9%, 62.5%, and 16.5% for in situ, localized, regional, and distant disease, respectively [5].

Similar to urothelial cancer of the bladder, UTUC has a 3:1 predilection for men, with incidence peaking in individuals aged 70–90 years [6]. Risk factors for developing UTUC include tobacco exposure, occupational exposure to carcinogenic aromatic amines, ingestion of aristolochic acid and arsenic, and chronic inflammation. Tobacco exposure increases the risk of UTUC in a dose-dependent manner: by twofold in those with 20 pack-year history or less and up to 6.2-fold for those with 60 pack-year history or more [7]. Fortunately, smoking cessation can help reduce UTUC risk from 4.4- to 2.3-fold [8]. Moreover, heavy smoking history and smoking status at the time of surgery has been associated with an increased risk of disease recurrence and cancer-specific mortality in patients treated with radical nephroureterectomy [9]. Occupational hazards such as exposure to benzidine and

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β-naphthalene also increase the risk of UTUC. Though these substances have been banned since the 1960s, tumors can occur at long intervals following exposure [7].

The carcinogen aristolochic acid, found in *Aristolochia fangchi* and *Aristolochia clematis* plants, induces mutations at codon 139 in the *p53* gene, leading to the development of UTUC in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy [7]. Similarly, inorganic arsenic found in the drinking water from artesian wells has also been associated with mutagenesis and increased risk of UTUC. A particularly high incidence of UTUC found in the population residing along the southwest coast of Taiwan is thought to be associated with ingestion of both of these agents. Finally, chronic inflammation related to bacterial infection and urinary stone/obstruction have been linked to the development of squamous cell carcinoma of the upper urinary tract [10].

Hereditary UTUC is associated with hereditary nonpolyposis colorectal carcinoma (HNPCC), or Lynch Syndrome [11]. These patients have germline mutations in four DNA mismatch repair genes, leading to microsatellite instability. HNPCC patients have a 6% lifetime risk for developing UTUC, a staggering 14–22 times higher than the general population [12]. While no guidelines exist on screening for UTUC in HNPCC patients, methods of HNPCC screening have been proposed in patients at risk for hereditary UTUC. These patients tend to have earlier disease onset (mean age 55 years) and are more likely to be female [13]. Audenet et al. recommended HNPCC screening in UTUC patients younger than 60, with previous history of HNPCC-related cancer, with one first-degree relative with HNPCC-related cancer diagnosed before 50 years of age, or two first-degree relatives with HNPCC-related cancer [13]. In another study, point-of-care screening utilizing the Amsterdam Criteria II and tumor immunohistochemistry for mismatch repair proteins were performed, with at-risk patients identified for genetic counseling. This point-of-care method identified 13.9% of all UTUC patients to be at risk, of whom 37.5% were confirmed to have HNPCC [14]. Currently, no specific protocol has been adopted into any of the guidelines for HNPCC screening [15].

Diagnosis

The most common symptom associated with UTUC is hematuria, occurring in 70–80% of the patients. Interestingly, in a contemporary observational study of 3556 patients undergoing workup for hematuria, UTUC was diagnosed exclusively in those who presented with gross hematuria [3]. Others with locally advanced disease may present with flank pain (20%) and lumbar mass (10%) [15]. Systemic symptoms such as anorexia, weight loss, malaise, fatigue, fever, or night sweats portend worse prognosis and should prompt a more rigorous metastatic evaluation.

CT Urography

CT urography is a relatively new diagnostic imaging technique which produces high-resolution images through the rapid acquisition of thin sections during helical tomographic imaging. It is the most accurate imaging modality for the diagnosis of UTUC. Sensitivity range between 67% and 100% and specificity between 93% and 99% [16, 17]. In a recent meta-analysis of five studies comprised of over 1000 patients, pooled sensitivity and specificity were 96% and 99%, respectively [18]. Due to its wide availability and proven efficacy in the detection, staging, and surveillance of UTUC, CT urography has been recommended as the imaging modality of choice by the EAU and other guideline committees [15].

Although standard protocols exist, nuances in adjunctive procedures such as pre-imaging urinary tract distention, method of contrast injection, timing and number of post-contrast imaging, and dual energy techniques can significantly impact the quality of the scan. Diagnostic accuracy is predicated on optimal contrast opacification of a distended intrarenal collecting system and ureter. Hydration with either intra-

venous infusion or oral intake has been shown to adequately dilate the collecting system in preparation of the scan. In addition, the use of diuretics (furosemide 10–20 mg) in conjunction with IV infusion may further enhance image quality, especially for visualization of the mid- to distal segments of the ureter [19]. Whether these enhanced images will translate into clinical benefit is unknown, as non-opacified ureteral segments are unlikely to harbor undiagnosed UTUC in the absence of any secondary findings. In fact, chasing un-opacified ureteral segments with additional imaging in attempt to achieve complete visualization of the entire length of the ureter will only lead to higher radiation exposure [20].

Two strategies may be employed for comprehensive visualization of the renal parenchyma and collecting system (Fig. 33.1). Following non-contrast scan, the entire contrast bolus can be injected, with images taken during parenchymal enhancement, and again after a delay to image the excretory phase. Alternatively, contrast bolus can be split, with 30% injected at first, followed by a delay of 8 minutes prior to injecting the remainder [21]. Thereafter, a single scan is obtained to concomitantly assess the parenchymal enhancement (from the second contrast bolus) and excretory (from the first contrast bolus) phases. Advantages of the single contrast bolus technique include optimal visualization of parenchymal enhancement phase, ability to evaluate urothelial enhancement, and improved collecting system distention and opacification given the higher initial volume of contrast injection. On the other hand, this technique confers higher cumulative radiation exposure owing to the need for three separate scans. In comparison, the split-bolus technique reduces the radiation dose by 15–40%, and is recommended for young patients with tumors with low risk features [21].

MRI

There are several disadvantages associated with using the MRI for detecting UTUC. Unlike the non-contrast CT scan, diagnosis of non-

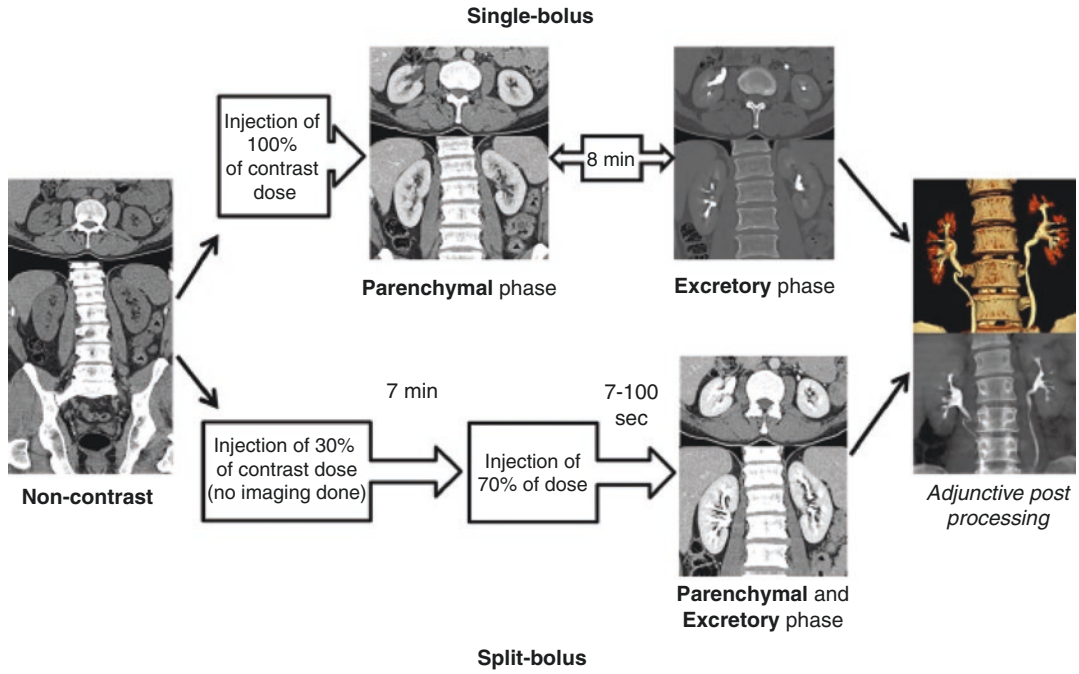

Fig. 33.1 Schematic of single-bolus versus split-bolus imaging protocol. The split-bolus technique is shown approximating the 30/70 dosage division and both with ~min timing of excretory phase. (Adapted from Froemming et al., *Eur J of Radiol*, 2018)

obstructing urinary calculi can be difficult to make, thus making the diagnosis of UTUC based on the presence of filling defect difficult. Moreover, MR images have significantly lower spatial resolution than CT urography, and are more prone to motion artifacts. Image acquisition times are much longer and MRI is approximately three times more expensive than CT. For all these reasons, MRI is generally reserved only for patients who cannot undergo CT due to contraindications for radiation or iodinated contrast.

On the other hand, MR imaging enhances soft tissue resolution in the absence of ionizing radiation. As a result, repeat scanning can be performed for areas with suboptimal image quality on initial scanning. It is also associated with lower risk profile with contrast administration, mainly due to the lower doses required. In the largest study to date, consisting of 91 MR urography exams, sensitivity and specificity for the detection of UTUC were found to be 69% and 97%, respectively [22].

Excretory MR urography may be performed using the 1.5-T or 3.0-T systems in patients with adequate renal function. The protocol for this study is similar to that of CT urography, in which images are obtained during the parenchymal enhancement and excretory phases following injection of contrast material. Intravenous (IV) hydration (250 mL normal saline) and/or diuretics (10 mg furosemide) are used to dilute the gadolinium excreted within the renal collecting system, thereby minimizing problematic imaging artifacts. In patients with contraindications to IV contrast, MR hydrography can be performed. Albeit less sensitive than MR urography, this modality takes advantage of the high T2 signal intensity associated with the urine within the upper urinary tract to contour any filling defects caused by UTUC.

More recently, the performance of diffusion-weighted MRI (DW-MRI) in detecting UTUC has been evaluated. In a retrospective study of 102 high-risk patients, sensitivity and specificity were found to be 92% and 91%, respectively. The addition of DW-MRI to CT urography was demonstrated to bolster the diagnostic accuracy of both mass-forming and wall-thickening lesions [23]. The authors suggested that DW-MRI has the potential to replace selective urine cytology as an adjunctive test for the definitive diagnosis of UTUC in the setting of equivocal CT findings. Taken together, despite having a clear role in the diagnosis of UTUC, MRI is unlikely to supplant CT as the imaging modality of choice.

Plane Film Urography

The use of IV urography to evaluate the upper urinary tract has gradually diminished with the adoption of CT urography since the late 1990s. In a turn of events, resurgence in the use of IV urography has been seen in the surveillance of younger patients with low-risk disease in order to reduce radiation exposure and healthcare cost. Although less accurate than CT urography, retrograde/antegrade pyelography is indicated when findings on cross-sectional imaging are inconclusive or contrast-enhanced CT/MRI cannot be performed due to renal insufficiency or allergies to contrast. Additionally, a well-performed retrograde pyelogram not only accentuates the area(s) of concern, but also serves as a guide for ureteroscopic renal pelvic mapping.

Renal/Bladder Ultrasound

Several efforts have also been made to assess the accuracy of renal/bladder ultrasound for the diagnosis of UTUC in attempt to reduce radiation exposure. These studies, however, consistently proved ultrasound to be inferior to CT urography in the detection of UTUC [2, 18]. Diagnosis of UTUC is often made only on secondary workup prompted by the finding of hydronephrosis on ultrasound. As such, ureteral tumors too small to cause luminal occlusion and hydronephrosis can easily be missed. Additionally, the operator-dependent nature of ultrasound images may also lead to misdiagnosis.

More recently, Tan et al. retrospectively analyzed the detection rates using renal/bladder ultrasound versus CT urography in a cohort of hematuria patients enrolled in a prospective

observational study (DETECT I). They confirmed ultrasound to be less sensitive (14.3%) than CT urography. However, as no case of UTUC was found among 2311 patients undergoing workup for microscopic hematuria, the authors suggested ultrasound to be a reasonable study for evaluating the upper urinary tract in this setting [24].

Imaging Appearance

UTUC can take on many different forms on imaging: papillary lesion, focal wall thickening, focal enhancement, or as an infiltrative lesion. The most commonly reported presentations differ, depending on the imaging modality used and the patient population studied. Large papillary lesions or wall thickening may visibly enhance on parenchymal phase. They can more easily be identified on excretory phase, with the filling defect accentuated by the surrounding contrast-opacified urine. To prevent overshadowing of the filling defect by the extreme high density of the excreted contrast, "bone window" setting can be used and subsequently fine-tuned to allow visualization through the excreted contrast (Fig. 33.2). In addition, careful evaluation of the coronal and sagittal images is important, as some subtle filling defects are better depicted on these planes. On the other hand, focal enhancement or infiltrative lesions are most reliably identified on parenchymal phase of the imaging. Thus, it is imperative for high-quality images to be obtained in both the parenchymal and excretory phases to maximize detection rates of UTUC [25].

Polypoid lesions are typically associated with noninvasive UTUC, whereas infiltrative appearance correlates with T3/4 stage disease. High-grade renal collecting system UC's characteristically infiltrate into the sinus fat or renal parenchyma, while preserving the contours of the reniform shape of the kidney. The calyces adjacent to the mass may be dilated, appearing as hydronephrosis or cystic masses. In such cases, the presence of hydronephrosis has been linked to higher T-staging [26] as well as the presence of lymphovascular invasion [27]. In contrast, RCC is centered in the renal cortex and more commonly forms as a discrete mass lesion altering the shape of the kidney. Despite their differences, it is often difficult to diagnose large, infiltrative lesions. The presence of a renal vein thrombus typically points to a diagnosis of RCC, although aggressive UTUC with renal vein invasion has also been described [28] (Fig. 33.3).

Within the ureter, UTUC may present as abnormal thickening, strictures, or focal masses. They are more frequently associated with hydronephrosis. Diffuse thickening throughout the ure-

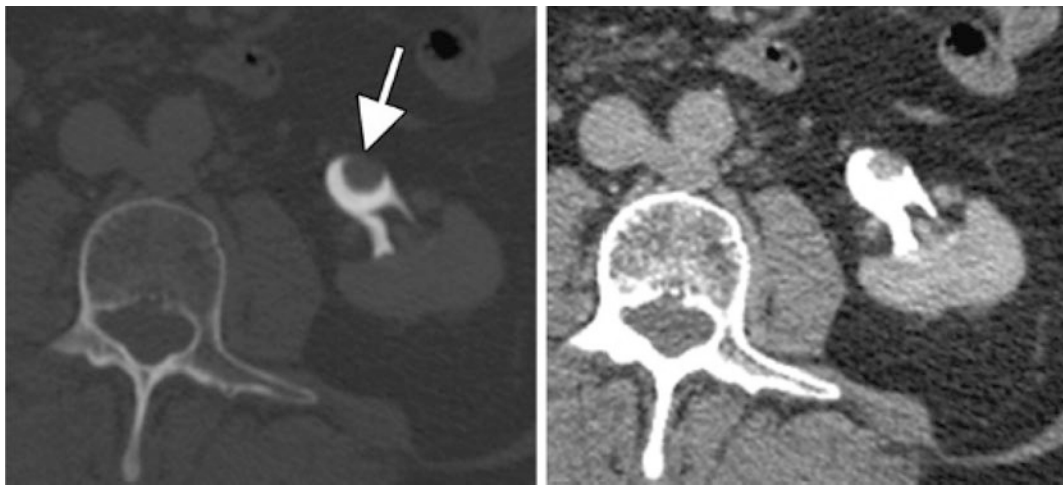

Fig. 33.2 The mass is best visualized in bone window setting on delayed images. Appropriate window/level settings allow the observer to mitigate the overpowering effects of the high density of excreted urine. (Adapted from Zeikus et al., *Magn Reson Imaging Clin N Am*, 2019)

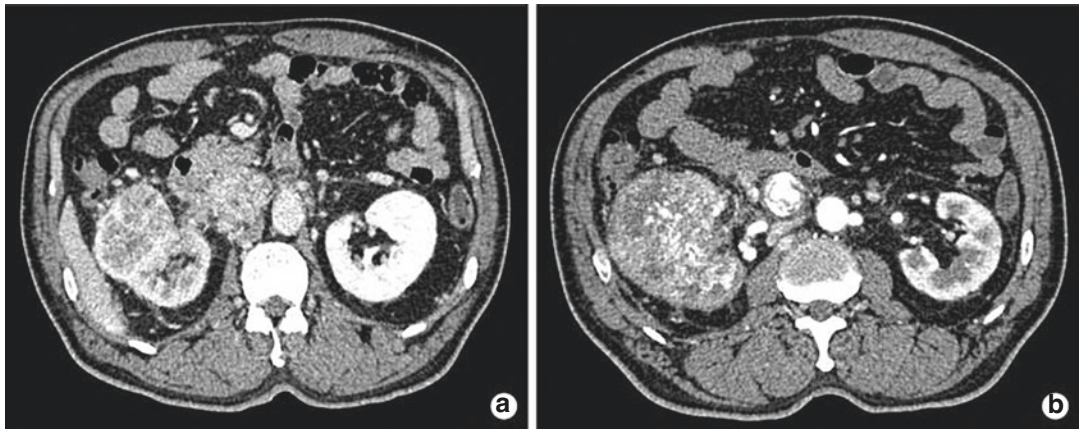

Fig. 33.3 Infiltrative urothelial carcinoma of the renal pelvis with tumor thrombus extending into the inferior vena cava. (Adapted from Diaz et al., *Kor J Urol*, 2014)

ter may indicate inflammation due to chronic ureteral stenting. Careful evaluation using appropriate windows and on multiple planes is imperative for diagnosis.

Urine-Based Studies

Positive cytology in the face of a negative cystoscopic examination may be the first sign of UTUC [29]. However, cytologic examination of voided urine has poor sensitivity in detecting the rare malignant exfoliated cells from UTUC, and is less sensitive for UTUC than for bladder cancer [30]. Furthermore, for low-grade neoplasms, false-positive rates due to instrumentation effects and/or incidental inflammatory processes may be as high as 50% [31]. Site directed collection via endoscopic measures has been shown to increase sensitivity for the detection of both high-grade (HG) (69% sensitivity, 85% PPV) and muscle-invasive UTUC (76% sensitivity, 89% PPV). Nevertheless, cytology alone may not be sufficient to predict pathologic findings of HG or MI UTUC [32].

When performing site-directed collection, urine should be collected from within the renal pelvis or ureteral lumen. If collecting via a previously used instrument, thorough washing using normal saline should be performed prior to specimen collection. Cytology should be obtained prior to the application of a contrast agent for retrograde ureteropyelography, as this may cause deterioration of the cytological specimen [30].

As mentioned, cytology can compensate for nondiagnostic or ambiguous endoscopic biopsy results. Kleinmann *et al.* showed that diagnosis can be made by cytologic evaluation in almost all (91%) patients with nondiagnostic endoscopic biopsies [33]. Furthermore, in patients with grade 2 tumors found on endoscopic biopsy, concomitant positive cytology increased the risk of upgrading [34] and upstaging to MI UTUC [35] on radical nephroureterectomy pathology. In patients managed with ureteroscopic laser ablation, abnormal cytology pretreatment may also predict increased risk of recurrence (94.1% vs. 47.1%, $p = 0.0026$) [36].

Fluorescent *in situ* hybridization (FISH), a urine-based cytogenetic analysis, has also been used to diagnose UTUC. Compared to cytology, FISH consistently demonstrated superior sensitivity (77–100%) while maintaining comparable specificity in detecting UTUC on both voided [37, 38] and site-specific urine specimens [39]. In a multicentered study using site-specific urine, a group from Italy was able to achieve 100% sensitivity in detecting UTUC in 21 patients [39]. Whether FISH can be used to reliably rule out UTUC requires validation in larger studies.

Other efforts have investigated the diagnostic potential of urinary methylation markers for the

diagnosis of UTUC. In a study of 108 cases of UTUC, Guo *et al.* found that a panel of select genes (*CDH1, HSPA2, RASSF1A, TMEFF2, VIM*, and *GDF15*) identified UTUC with a sensitivity of 82% and a specificity of 68%, yielding an AUC of 0.836 (0.782–0.891) [40]. CX bladder, a commercially available urine-based RNA test consisting of five biomarkers (MDK, HOXA13, CDC2, IGFBP5, and CXCR2), was also used to diagnose a case of UTUC in a patient with Lynch syndrome. Importantly, all other urinary tests, including cytology and FISH, were negative.

Conclusion

Due to its rarity, UTUC screening is limited only to the patients presenting with hematuria. The AUA mandate for hematuria workup has led to a rise in UTUC incidence and earlier-stage migration. CT remains the imaging modality of choice for the diagnosis of UTUC, but can be substituted by MRI in patients with contraindications for ionizing radiation or IV contrast. Although urine cytology has fallen out of favor for the detection of UTUC, several experimental urinary diagnostic markers are being investigated.

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34 Risk Stratification of Upper Tract Urothelial Carcinoma for Kidney-Sparing Surgery

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Introduction

Upper tract urothelial carcinoma (UTUC) is a rare tumor with an incidence of two cases per 100,000 persons [1]. This malignancy accounts for 5–10% of all urothelial carcinomas [2]. UTCUs originate from the renal pelvis in two-third of cases and the remaining one-third tumors are found in ureter with the highest frequency being in the distal ureter [3].

Open radical nephroureterectomy (RNU) with bladder cuff excision is the standard treatment in patients with high-risk UTUC [1]. Nevertheless, kidney-sparing modalities, such as segmental resection, endoscopic, and percutaneous approaches, could be used in low-risk and select high-risk UTUC cases with comparable oncological results while maintaining a functional renal unit [1, 4, 5].

Risk stratification for the management of UTUC, therefore, helps urologists together with their patients select the proper therapeutic modality for their tumor at the right time. The technical challenge lies in the assurance of the prognostic risk of each individual tumor.

In this chapter, we provided an overview of the established preoperative predictor factors to risk stratify patients with UTUC for radical surgery versus organ-sparing therapeutic modalities in UTUC. While these factors have prognostic value, their predictive value for the chosen therapy remains to be assessed specifically with the rising evidence of a benefit to perioperative systemic therapy in high-risk UTUC.

Patient-Related Risk Factors

Age and Sex

The prognostic significance of age and sex in patients with UTUC has been investigated in several studies [6–17]. A recent meta-analysis evaluated the prognostic value of demographic factors such as age and sex in UTUC patients treated with RNU [9]. Advanced age was significantly, but weakly, associated with progression-free survival (PFS) (HR: 1.01), cancer-specific survival (CSS)

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(HR: 1.02), and overall survival (OS) (HR: 1.05). Moreover, female sex was significantly associated with a decreased risk of intravesical recurrence (IVR) after RNU (HR: 0.81). Another retrospective study supported the higher IVR rate in UTUC male patients treated with RNU (HR: 1.90, 95% CI: 1.15–3.16, $p = 0.013$) [18]. This is likely due to the higher predisposing risk factors such a smoking rate putting the entire urothelium at risk.

While elder UTUC patients may have worse oncological outcomes compared to their younger counterparts, chronological age should not drive the decision-making regarding curative management, but rather general health status should. Similarly, sex should not be considered as decision factor in the differentiation of treatment strategies in patients with UTUC [1].

Tobacco Consumption

Smoking is a powerful risk factor for UTUC development and progression [18–21]. In a retrospective study of 864 UTUC patients treated with RNU, current smoking status, smoking ≥20 cigarettes per day or ≥ 20 years, and heavy long-term smoking were significantly correlated with advanced disease, higher risk of disease recurrence, and worse CSS [19]. Rink et al. have further shown that smoking cessation over 10 years mitigates the detrimental effect of smoking on oncological outcomes. In a meta-analysis of 2259 patients with UTUC, smoking was demonstrated as a strong prognostic factor for disease recurrence in the operative bed (HR: 1.57, 95% CI: 1.19–1.95) as well as cancer-specific death (CSD) (HR: 1.53, 95% CI: 1.13–1.92) [20]. Today, smoking can be reliably considered not only as the main risk factor for UTUC development but also as the single most preventable prognosticator. Counselling regarding smoking cessation is a must for every smoker. On the other hand, smoking status does not help in the risk stratification of individual patient.

Surgical Delay:

Similarly to other cancers, the surgical waiting time has been proposed as a negative prognostic factor of survival in patients with UTUC. In a retrospective analysis of 3581 UTUC patients treated with RNU, the surgical waiting time of more than 120 days was associated with lower OS in both overall (HR: 1.61, 95% CI: 1.19–2.19) and high-risk cohort groups (HR: 1.56, 95% CI: 1.11–2.20) [22]. Conversely, Sundi et al. demonstrated that surgical treatment delay more than 3 months after UTUC diagnosis did not affect significantly the oncological outcomes including recurrence-free survival (RFS), CSS, and OS [23]. Nevertheless, several other studies confirmed the negative prognostic value of surgical delay in predicting oncological outcomes after RNU in patients with UTUC [24, 25]. Surgical delay can be system inherent or errors in early detection, but most patients who suffer from a delay are multimorbid, creating a risk of competing risks driving the prognosis of the patients. Nevertheless, similarly to bladder cancer, others and we recommend to perform the definitive surgical treatment of high-risk UTIUC patients within the 12 weeks after disease diagnosis [1].

Preoperative Neutrophil-to-Lymphocytes Ratio (NLR)

NLR is a biomarker for systemic inflammation that has recently been proposed as a prognosticator of oncological outcomes in patients with UTUC [26–32]. The ability of preoperative NLR to predict lymph node metastasis, muscle-invasive and non-organ-confined disease was demonstrated in a retrospective study of 2477 UTUC patients treated with RNU ($p < 0.001$). However, the association between this prognosticator and CSS was found only significant in subgroup UTUC patients treated with RNU and lymphadenectomy (HR: 1.43, 95% CI: 1.02–2.00, $p = 0.03$) [32]. In a recent meta-analysis of 4385 UTUC patients, increased pretreatment NLR was associated with OS (pooled HR: 1.64, 95% CI: 1.23–2.17), RFS (pooled HR: 1.60, 95% CI: 1.16–2.20), and CSS (pooled HR: 1.73, 95% CI: 1.23–2.44) [30]. Preoperative NLR, which can be calculated from standard blood tests, could help improve the diagnostic accuracy for advanced disease, thereby adding a marginal additional precision to the clinical decision making.

Ureteroscopy before RNU

The concepts of intraluminal tumor seeding by ureteroscopic manipulation and its impact on oncological outcomes (e.g., IVR and survival) have been investigated in several studies [33–38]. A recent meta-analysis analyzed eight studies evaluating the prognostic effect of ureteroscopy before RNU on oncological outcomes after RNU in 3975 patients with UTUC [36]. Ureteroscopy before RNU was not associated with CSS, OS, RFS, and metastasis-free survival (MFS). However, pre-RNU ureteroscopy leads to a higher IVR rate after RNU (HR: 1.81, $p < 0.00001$). Contrasting results was reported by Lee et al. regarding the impact of ureteroscopy on IVR after RNU [39]. In this single institution retrospective study of 502 patients with UTUC treated with RNU, diagnostic ureteroscopy before radical surgery was not significantly associated with IVR. Future studies may clarify the preventive effect of intravesical single-dose chemotherapy after diagnostic ureteroscopy and its impact on IVR after RNU and in patients treated with kidney-sparing surgery (KSS).

Sarcopenia:

Sarcopenia is a new clinical parameter that represents skeletal muscle wasting; it has been established as a prognostic factor in various malignancies [40]. The prognostic value of sarcopenia in UTUC has been assessed in several studies with different outcomes [41–44]. In a retrospective study of 137 UTUC patients treated with RNU, sarcopenia was associated with shorter RFS, CSS, and OS ($p < 0.0001$) [43]. Conversely, in a retrospective study involving 100 UTUC patients who underwent RNU, sarcopenia was not correlated with RFS or OS. However, in a subgroup of patients, the authors found significant association between sarcopenic obesity (sarcopenia in patients with body mass index >30 kg/m^2) and non-bladder cancer disease relapse ($p = 0.049$) [44]. Although there is controversy regarding the prognostic importance of sarcopenia in UTUC patients, this factor is unlikely to guide clinical decision-making.

The most important studies assessing patients related prognostic factors are summarized in Table 34.1.

Tumor-Related Risk Factors

Tumor Grade

Tumor grade at pathological evaluation represents a powerful prognostic factor for UTUCs [13, 45–48]. In a retrospective study involving 1363 patients treated with RNU for UTUC, high tumor grade was associated with worse RFS (HR: 2.0, $p < 0.001$) and CSS (HR: 1.7, $p = 0.001$) [13]. Similarly, several other retrospective studies confirmed the strong prognostic value of tumor grade [49–51]. A recent systematic review evaluated the prognostic factors and predictive tools of advanced stage, non-organ-confined disease, loco-regional and recurrence, and distant metastatic in patients with UTUC [46]. The authors demonstrated that the presence of high-grade tumor was associated significantly with all of these oncological outcomes.

Indeed, the preoperative diagnostic tools including urine cytology and ureteroscopic-guided biopsy can be used to evaluate UTUC grade. These findings can affect decision-making regarding KSS versus RNU for UTUC. UTUC patients with high-grade cytology or high-grade ureterorenoscopy biopsy should strongly be considered for RNU [1].

Urine Cytology

The role of urine cytology as a prognostic factor in UTUC has been assessed in several studies [52–56]. A positive bladder urinary cytology predicts intravesical urothelial carcinoma recurrence after treatment of UTUC (HR: 1.56, 95% CI: 1.25–1.96, $p < 0.001$) [56]. Moreover, there is a significant relationship between positive urine cytology and high-grade/non-organ-confined UTUC [57, 58]. In a retrospective evaluation of 469 patients with UTUC treated with RNU, combined hydronephrosis, positive cytology, and ureterorenoscopic high-grade biopsy had a positive predictive value of 89% for muscle invasive UTUC [57]. On the other hand, the false-negative rate of cytology was only 50%, partially due to the inaccuracy of this test to detect low-grade UTUC [59].

Table 34.1 Patient-related prognostic factors in patient with upper tract urothelial carcinoma

Prognostic variable	Author	Year	Study design	Patient no.	Treatment type	Survival outcome	Significant correlation (p value <0.05)
Age	Chromecki [6]	2011	Retrospective	1169	RNU	RFS, CSS, OS	Significant correlation with all survival outcomes
	Shariat [11]	2010	Retrospective	1453	RNU	OS, CSS	HR for OS: 1.78 (70–79 vs. ≤50 years), 2.51 (≥80 vs. ≤50 years) HR for CSS: 1.63 (≥80 vs. ≤50 years)
	Yap [12]	2011	Retrospective	12,639	RNU or ureterectomy	OS, DSS	Significant correlation with all survival outcomes (age < 50 vs. ≥50 years)
	Margulis [13]	2009	Retrospective	1363	RNU	DR, CSM	HR: 1.019 for CSM
	Xylinas [14]	2014	Retrospective	1839	RNU	IVR	HR: 1.01
Gender	Hagiwara [18]	2013	Retrospective	245	RNU	IVR	HR: Male gender, 1.90
	Fernández [7]	2009	Retrospective	1363	RNU	DR, DSS	No significant difference between male and female
	Rink [19]	2013	Retrospective	864	RNU	DR, CSM	HR: Female gender, 1.7 for DR and 2 for CSM In heavy long-term smokers
	Shariat [15]	2011	Retrospective	754	RNU	RFS, CSS	No significant difference between male and female
	Li [16]	2008	Retrospective	260	RNU	DR (LR, IVR), CSS	OR: Male gender,1.88 for IVR
	Lughezzani [17]	2010	Retrospective	4850	RNU	CSM, OCM	No significant difference between male and female
Smoking	Rink [19]	2013	Retrospective	864	RNU	DR, CSM	HR: Current vs. never, 1.66 for DR HR: Former vs. never, 1.48 for CSM
	Xylinas [21]	2014	Retrospective	519	RNU	IVR	HR: Current vs. never, 2.55 for IVR[a] HR: Former vs. never, 2.81 for IVR[a]
	Hagiwara [18]	2013	Retrospective	245	RNU	IVR	HR: Former vs. never, 1.77 HR: Current vs. never, 1.58
Surgical delay	Xia [22]	2018	Retrospective	3581	RNU	OS	HR: Surgical waiting time > 120 days, 1.61
	Waldert [25]	2010	Retrospective	187	RNU	DR, CSM	Significant correlation in muscle-invasive disease
	Lee [24]	2014	Retrospective	138	RNU	CSS, RFS	Delay time of >1 month HR: 6.261 for CSS and 4.120 for RFS in ureteral urothelial carcinoma

Prognostic variable	Author	Year	Study design	Patient no.	Treatment type	Survival outcome	Significant correlation (p value <0.05)
Preoperative NLR	Altan [26]	2017	Retrospective	150	RNU	PFS, DFS	Significant worse PFS and DFS in NLR ≥ 2.9 vs. <2.9
	Kohada [27]	2018	Retrospective	148	RNU	CSS, RFS	HR (NLR ≥3.0 vs. <3.0): 3.25 for CSS and 2.13 for RFS
	Dalpiaz [31]	2014	Retrospective	171	RNU or segmental ureterectomy	CSS, OS	HR (NLR ≥1.5 vs. <1.5): 1.16 for CSS and 1.21 for OS
	Vartolomei [32]	2017	Retrospective	2477	RNU	RFS, CSS	HR: 1.43 for CSS in patients treated with RNU + lymphadenectomy
Ureteroscopy before RNU	Liu [33]	2016	Retrospective	664	RNU	IVR	HR: 1.592
	Sung [34]	2015	Retrospective	630	RNU	IVR	HR: 1.558
	Yoo [38]	2017	Retrospective	515	RNU	IVR	HR: 2.06 in renal pelvic tumor
	Lee [39]	2018	Retrospective	502	RNU	OS, DFS, MFS, and IVR	No significant correlation
Sarcopenia	Fukushima [42]	2016	Retrospective	81	RNU	OS, CSS	HR: 6.05 for OS and 8.58 for CSS
	Ishihara [43]	2017	Retrospective	137	RNU	RFS, CSS, OS	HR: 5.18 for RFS, 13.3 for CSS, and 12.1 for OS
	Anno [41]	2018	Retrospective	123	RNU	CSS	No significant correlation

[a] in patients without previous bladder cancer

RNU radical nephroureterectomy, *RFS* recurrence-free survival, *CSS* cancer-specific survival, *OS* overall survival, *HR* hazard ratio, *DSS* disease-specific survival, *DR* disease recurrence, *DFS* disease-free survival, *CSM* cancer-specific mortality, *OR* odds ratio, *LR* local recurrence, *IVR* intravesical recurrence, *OCM* other-cause mortality, *CSM* cancer-specific mortality, *MFS* metastasis-free survival, *NLR* neutrophil-to-lymphocytes ratio

Ureteroscopy and Biopsy

High-grade finding on ureterorenoscopy-guided biopsy is a predictor for advanced pathologic tumor stage [60, 61]. Brien et al. reported that high ureteroscopic grade was associated with muscle invasive UTUC (HR: 4.5, $p < 0.001$) in patients treated with RNU [57]. In a retrospective analysis of 160 patients with UTUC who underwent ureteroscopy before RNU, the diagnostic accuracy of ureteroscopy for cancer detection was 88% [62]. However, there are limitations to the accuracy of ureteroscopic biopsies such as insufficient tissue quality, and crush artifacts [63]. The reliability of small biopsy samples remains a technical and diagnostic challenge.

Stage of Tumor:

Tumor stage is an established prognostic factor in UTUC [49, 64–67]. The 5-year CSS rates vary from >90% in patients with pTa/pT1 organ-confined stage to the less than 20% in patients with T4 UTUC [68]. In a multi-institutional international retrospective study of 858 renal pelvicalyceal tumors treated with RNU, T3 pathological stage defined as macroscopic infiltration of the renal parenchyma and/or infiltration of peripelvic adipose tissue was associated with worse RFS and CSS [49]. In another study, postoperative tumor parameters were evaluated to design a nomogram for RFS after RNU in 2926 patients with high-grade UTUC [67]. The final nomogram included four parameters: age, tumor architecture, pathological tumor, and lymph node stage. All these predictors were significantly associated with RFS.

For diagnostic purposes and pretreatment tumor staging, computed tomography (CT) urography is the modality of choice with an adequate diagnostic accuracy. The sensitivity and specificity of CT urography for UTUC are 67–100% and 93–99%, respectively [69, 70].

Tumor Size, Location, and Multifocality

Several studies evaluated the effect of tumor size on oncological outcomes in patients with UTUC [51, 71–73]. In a retrospective study, Simone et al. investigated the prognostic value of tumor diameter in UTUC patients who underwent RNU [72]. The authors found that tumor size ≥3 cm was associated with worse MFS (HR: 3.92, $p < 0.001$) and disease-free survival (HR: 3.11, $p < 0.001$). Similarly, tumor size was shown in a retrospective study comprising 795 UTUC patients to be predictive of CSS, RFS, and OS after RNU [51]. Tumor multifocality has been shown to affect CSS after RNU [65, 74]. It has been proposed that RNU is a more reasonable treatment in patients with multifocal disease [1, 75]. Although some studies suggested that ureteral disease has worse prognosis in comparison with tumors within renal pelvis, the predictive importance of tumor location remains controversial [68, 76–82]. Conversely, Yafi et al. reported that ureteral urothelial carcinoma is associated with worse RFS (HR: 2.1, $p = 0.006$) and CSS (HR: 2.0, $p = 0.027$) in 637 UTUC patients treated with RNU [77]. Similarly, ureteral tumor was associated with higher risk of surgical bed recurrence in comparison with renal pelvic urothelial carcinoma and adjuvant therapy such as radiotherapy may be consider for this high-risk patients [78]. In a multicentric retrospective study of 1249 patients who underwent RNU and bladder cuff excision for UTUC, the authors found no significant difference between ureteral and renal pelvic tumors after adjusting for the effect of tumor stage in terms of disease recurrence (HR: 1.22; $p = 0.133$) or cancer death (HR: 1.23; $p = 0.25$) [76]. Based on this data both ureteral and pelvicalyceal urothelial carcinomas could be categorized as a single group in TNM staging system. To make a comparison between the oncological outcomes and tumor behaviors and urothelial carcinoma location (UTUC and bladder urothelial carcinoma), 4335 patients with bladder urothelial carcinoma treated with radical cystectomy and bilateral pelvic lymphadenectomy, 877 patients with ureteral UTUC, and 1615 with pelvicalyceal UTUC treated with RNU were analyzed in a retrospective study [83]. In non-muscle-invasive tumor stages, bladder cancer was associated with higher disease recurrence rate and mortality in comparison with renal pelvicalyceal tumor patients ($p < 0.002$) but not ureteral tumors ($p > 0.05$). Conversely, the

authors found that in patients with pT4 ureteral and pelvicalyceal tumors demonstrated more recurrence rate and mortality ($p < 0.004$).

Lymphovascular Invasion (LVI)

Several studies have shown that the presence of LVI in surgical specimens is associated with worse prognosis after RNU for UTUC [84–88]. Moreover, the increased prevalence of LVI has been reported in higher pathological UTUC stage and grade [85]. Godfrey et al. investigated the prognostic value of LVI in pathological report of RNU on OS; they found a significant correlation between LVI and these outcomes. In another study, 4177 UTUC patients were included retrospectively to evaluate the association of LVI and OS after radical surgery for UTUC [84]. In this study, LVI could independently predict worse OS in T3 and T4 disease after RNU. Therefore, it is recommended to record LVI presence in RNU specimen pathological report to prospectively assess the prognostic value in the clinical decision-making (i.e., adjuvant chemotherapy) and patient counselling. Patients with LVI in their primary tumor are not the proper candidate for kidney-sparing management. However, well-designed prospective studies are needed to confirm this conclusion.

Concomitant Carcinoma in Situ (CIS)

CIS is a flat, nonpapillary, and often multifocal high-grade tumor confined to the urothelium that may be found as a pure primary or concomitant lesion with conventional urothelial carcinoma. The prognostic value of concomitant CIS in bladder urothelial carcinoma has been investigated in depth. It has been shown that concomitant CIS in the radical cystectomy specimen is associated with worse RFS and cancer-specific mortality (CSM) in patients with organ-confined bladder cancer treated with radical cystectomy [89]. Nevertheless, the aggressive behavior of CIS for UTUC has not been investigated as widely as for bladder cancer. In a multi-institutional retrospective cohort of 1387 UTUC patients treated with RNU, concomitant CIS was associated with disease recurrence and CSS [90]. Another retrospective study demonstrated the significant prognostic effect of concomitant CIS to predict CSS and RFS in 772 patients treated with RNU [91]. Furthermore, concomitant CIS was found as a predictor of worse CSS when compared with pure CIS in a small retrospective study [92]. It has been accepted that UTUC patients with papillary tumor together with CIS should be categorized in worse prognosis group and might derive more benefit from RNU [1].

Tumor Architecture (Sessile Vs. Papillary)

Ureteroscopy can help assess tumor architecture in patients with UTUC. In a large multi-institutional study, sessile tumor architecture was associated with a higher rate of CSM and disease recurrence (HR: 1.76, $p < 0.001$ for disease recurrence and 1.72, $p = 0.001$ for CSM) [64]. In another study, sessile tumor architecture was presented as a predictor for non-organ-confined disease (HR: 3.274, $p < 0.001$) and high-grade UTUC (HR: 25.192, $p < 0.001$) [93]. Remzi et al. investigated the prognostic effect of UTUC architecture after RNU [45]. The authors found that sessile tumor architecture was an independent predictor of cancer recurrence (HR: 1.5, $p = 0.002$) and CSM (HR: 1.6, $p = 0.001$) and could predict LVI, higher tumor grade and stage, and lymph nodes metastasis. In a recent meta-analysis involving 14,368 UTUC patients in 17 studies, the sessile growth pattern of UTUC was correlated independently with disease recurrence (HR: 1.454) and CSM (HR: 1.416) [94]. Reporting such growth pattern in diagnostic ureteroscopy before treatment may help to select more appropriate therapeutic modality for such high-risk patients.

Surgical Margins

The association between surgical margin status and oncological outcomes after RNU have been reported in [65, 95, 96]. Colin et al. assessed the

prognostic effect of positive surgical status after RNU on survival outcomes in patients with UTUC [95]. In this multicentric retrospective study of 427 UTUC patients treated with open RNU, positive surgical margin was independently associated with worse MFS (HR: 2.7; $p = 0.001$). In another multicenter retrospective study, it was shown that a positive surgical margin after RNU was associated with MFS (HR: 1.46, $p = 0.02$) [97]. Based on these data, the positive surgical margin is a significant prognostic factor to predict metastasis after RNU in patients with UTUC, and is recommended to routinely be recorded in RNU pathological report.

Lymph Node Status

Several studies have been published to propose the prognostic value of lymphadenectomy and lymph node involvement in patients with UTUC [13, 64, 67, 98–104]. In a large multi-institutional retrospective series, Margulis et al. investigated the prognostic factors of UTUC patients treated with RNU [13]. The authors found a significant correlation between lymph node invasion and disease recurrence (HR: 1.8, $p < 0.001$) and CSS (HR: 1.7, $p < 0.001$). Another retrospective study could corroborate these findings [99]. Although an increasing trend of lymphadenectomy concomitant with RNU has been reported, most of UTUC patients do not receive a lymphadenectomy [105].

Moreover, extranodal extension has been suggested to affect the oncological outcomes in UTUC patients. In a retrospective analysis of 222 UTUC patients with lymph node involvement treated with RNU without neoadjuvant therapy, extranodal extension was associated with high disease recurrence rate ($p = 0.01$) and CSM ($p = 0.013$) on multivariable analysis [98]. The authors showed that the extranodal extension can be used as a significant prognostic factor of oncological outcomes in spite of limited clinical value of other lymph node involvement parameters such as lymph node density.

Tumor Necrosis

Tumor necrosis has been proposed as an independent predictor of oncological outcomes in patients with UTUC [106, 107]. In a large multicenter retrospective study involving 1425 patients treated with RNU, extensive tumor necrosis (>10% of the tumor area) was associated significantly with disease recurrence and survival after RNU [107]. The effect of tumor necrosis to predict OS in node-negative UTUC patients treated with RNU was confirmed in another retrospective cohort of 100 UTUC patients [106]. Tumor necrosis could be suggested as a strong prognosticator in patients with UTUC and might be used as an indicator for adjuvant therapies such as chemotherapy after radical surgery.

PD-1 and PD-L1 Expression

Recently, PD-1 and PD-L1 expression has been proposed as prognostic factors in UTUC patients [108–110]. In a cohort study of 423 high-grade UTUC patients treated with extirpative therapy, PD-1 expression was significantly associated with worse CSS and OS. In contrast, PDL-1 expression was demonstrated as a predictor of more favorable RFS and OS [108]. In another retrospective study involving 162 patients with UTUC treated with RNU, PD-L1 expression on tumor cells was defined as a predictor of worse CSS ($p = 0.012$) whereas PD-L1 expression on tumor-infiltrating mononuclear cells was significantly with longer CSS ($p = 0.034$) [110].

The most important studies of tumor-related prognostic factors are summarized in Table 34.2.

Table 34.2 Tumor-related prognostic factors in patient with upper tract urothelial carcinoma

Prognostic variable	Authors	Year	Study design	Patient no.	Treatment type	Outcome	Significant correlation (p value <0.05)
Tumor grade (LG vs. HG)	Remzi [45]	2009	Retrospective	1363	RNU	DR, CSD	HR: 1.91
	Shariat [49]	2012	Retrospective	858	RNU	DR, CSD	HR: 2.027 for DR and 1.819 for CSD
	Raman [76]	2010	Retrospective	1249	RNU	DR, CSD	HR: 2.310 for DR and 1.819 for CSD
	Kamihira [47]	2009	Retrospective	1003	RNU	OS, RFS	HR: 2.95 for OS and 1.92 for RFS
	Inman [48]	2009	Retrospective	168	RNU or NSS	OS, CSS	HR: 3.13 for OS and HR: 5.72 for CSS
	Li [16]	2008	Retrospective	260	RNU	CSS	OR: 2.35
	Kim [50]	2015	Retrospective	445	RNU	OS	HR: 1.85
	Shibing [51]	2016	Retrospective	795	RNU	OS	HR: 1.471
Tumor stage	Margulis [13]	2009	Retrospective	1363	RNU	DR, CSD	RR: 5.059 (PT3) 11.763(PT4) for DR and 5.168 (PT3) 11.040 (PT4) for CSD
	Shibing [51]	2016	Retrospective	795	RNU	CSS, RFS	HR: 3.181 (PT3) 8.108 (PT4) for CSS) and 3.094 (PT3) 6.793 (PT4) for RFS
	Raman [76]	2010	Retrospective	1249	RNU	DR, CSD	HR: 11.733 (PT3) 34.307 (PT4) for DR and 9.827 (PT3) 25.588 (PT4) for CSD
	Li [16]	2008	Retrospective	260	RNU	CSS	OR: 7.83
	Kim [50]	2015	Retrospective	445	RNU	OS	HR: 2.33 in PT3/PT4 vs. PTa/PT1
	Novara [65]	2007	Retrospective	269	RNU	CSS	HR: 3.346
Tumor location	Yafi [77]	2012	Retrospective	637	RNU	DR, CSD	HR: 2.2 for DR and 2.1 for CSD (ureter vs. renal pelvis)
	Ouzzane [80]	2011	Retrospective	609	RNU	CSD, metastasis	HR: 2.09 for CSD and 2.16 for metastasis (ureter only vs. renal pelvis)
	Williams [81]	2013	Retrospective	1029	RNU	DFS, OS, DSS	RR: 1.892 for OS, 1.770 for DFS and 2.490 for DSS (ureter and pelvis vs. pelvis)
	Akdogan [82]	2006	Retrospective	72	RNU	DSS, RFS	HR: DSS for 2.786 RFS for 3.32 (ureter vs. renal pelvis)
	Favaretto [79]	2010	Retrospective	324	RNU	CSS, RFS	No significant correlation (ureter vs. renal pelvis)
	Raman [76]	2010	Retrospective	1249	RNU	CSS, RFS	No significant correlation (ureter vs. renal pelvis)

(continued)

Table 34.2 (continued)

Prognostic variable	Authors	Year	Study design	Patient no.	Treatment type	Outcome	Significant correlation (p value <0.05)
Tumor size	Simone [72]	2009	Retrospective	162	RNU	MFS, DFS	HR: 3.92 for MFS and 3.11 for DFS
	Shibing [51]	2016	Retrospective	795	RNU	CSS, RFS, OS	HR: 2.296 for CSS, 2.193 for RFS, and 2.417 for OS
Tumor multifocality	Novara [65]	2007	Retrospective	269	RNU	CSS	HR: 2.971
	Chromecki [74]	2012	Retrospective	2492	RNU	DP, CSM	HR: 1.43 for DP and 1.46 for CSM in organ-confined disease
Lymphovascular invasion	Danzig [84]	2018	Retrospective	4177	RNU	OS	HR: 1.8 (PT1) to 7.1 (PT4)
	Novara [88]	2010	Retrospective	762	RNU	RFS, CSS	HR: 3.3 for RFS, 5.9 for CSS
	Godfrey [85]	2012	Retrospective	211	RNU	OS	HR: 2.22
	Kikuchi [86]	2009	Retrospective	1453	RNU	DR, CSS	HR: 1.38 for DR and 1.51 for CSS
Concomitant CIS	Wheat [90]	2012	Retrospective	1387	RNU	DR, CSM	HR: 1.25 for DR and 1.34 for CSM in organ-confined disease
	Otto [91]	2011	Retrospective	772	RNU	RFS, CSS	HR: 1.9 for RFS and 1.7 for CSS
Tumor architecture (sessile vs. papillary)	Cha [64]	2012	Retrospective	2244	RNU	DR, CSS	HR: 1.76 for DR and 1.72 for CSM
	Remzi [45]	2009	Retrospective	1363	RNU	CR, CSM	HR: 1.5 for CR and 1.6 for CSM
	Fan [94]	2017	Retrospective	101	RNU	RFS, CSS	HR: 2.648 for RFS and 2.072 for CSS
Surgical margins	Colin [95]	2012	Retrospective	472	RNU	CSS, RFS, MFS	HR: 2.71 for MFS
	Hurel [97]	2013	Retrospective	551	RNU	CSS, MFS	HR 1.46 for MFS
Lymph node status	Novara [65]	2007	Retrospective	269	RNU	CSS	HR: 2.978
	Krabbe [67]	2017	Retrospective	2926	RNU	RFS	HR: 2.50
	Ehdaie [99]	2011	Retrospective	520	RNU	DR, CSD	HR 2.52 for DR and 3.1 for CSD
	Margulis [13]	2009	Retrospective	1363	RNU	DR, CSS	HR: 1.8 for DR and 1.7 for CSS
	Nazzani [100]	2018	Retrospective	2098	RNU	CSM	HR: 3.00
	Lughezzani [103]	2010	Retrospective	2824	RNU	CSM	No significant correlation between pN(x) and pN(0)
	Roscigno [104]	2009	Retrospective	552	RNU	CSM	Number of lymph nodes and CSM in pN0 patients, HR: 0.93
Tumor necrosis	Zigeuner [107]	2010	Retrospective	1425	RNU	DR, CSM	HR: 1.27 for DR and 1.29 for CSM
	Zhang [106]	2015	Retrospective	100	RNU	OS, RFS	HR: 3.46 for OS

Table 34.2 (continued)

Prognostic variable	Authors	Year	Study design	Patient no.	Treatment type	Outcome	Significant correlation (p value <0.05)
PD-1 and PD-L1 expression	Krabbe [108]	2017	Retrospective	423	RNU or ureterectomy	RFS, CSS, OS	PD-1: HR, 1.7 for CSS and 1.5 for OS PD-L1: HR, 0.2 for RFS and 0.3 for OS in organ-confined disease
	Zhang [110]	2017	Retrospective	162	RNU	CSS	PD-L1 expression On tumor cells: HR, 2.572 PD-L1 expression on tumor-infiltrating mononuclear cells: HR, 0.324

LG low grade, *HG* high grade, *CIS* carcinoma in situ, *DP* disease progression, *RNU* radical nephroureterectomy, *NSS* nephron-sparing surgery, *DR* disease recurrence, *CSD* cancer-specific death, *HR* hazard ratio, *OR* odds ratio, *RR* risk ratio, *RFS* recurrence-free survival, *CSS* cancer-specific survival, *OS* overall survival, *CSM* cancer-specific mortality, *CR* cancer recurrence

Conclusion

UTUC risk stratification is essential to select patients for KSS or RNU. Although RNU with bladder cuff excision is the standard of care in patients with UTUC, in the past decades a growing body of literature supports KSS as a safe and effective alternative, indeed KSS preserves renal function without compromising oncological outcomes in selected low-risk patients [1, 111]. Selection of the ideal patient for KSS is difficult as the inclusion criteria remain unclear or even undefined in the literature. Therefore, there has been a search for prognostic factors that could help identify the patients who is most likely to benefit from KSS.

In this chapter, we present the potential patient and tumor-related prognostic factors that help in the risk stratification of UTUC patients. With the precise understanding of the strength of these prognostic factors, KSS could be extended to include more of the right patients.

Although age and gender were identified as prognostic factors in some studies, these factors are no longer considered as inclusion or exclusion factors. Tumor grade and stage together with lymph node status are the strongest prognostic factors predicting oncological outcomes after UTUC treatment. Preoperative tumor stage and grade risk stratification is based on the diagnostic work-up includes imaging modalities (CT urography or magnetic resonance imaging urography), urine cytology (voided or selective), and ureteroscopic evaluation with biopsy. Although these diagnostic modalities are helpful to identify high-risk patients who benefit from radical surgery, these diagnostics have limitations and fail to obtain a perfect negative or positive predictive value. Some of the information obtained through these diagnostic modalities such as tumor size, location, multifocality, and tumor architecture remain controversial as they had to an "excessive" restriction of KSS to very highly selected low-risk patients, thereby with handling KSS to some potential candidates. However, as KSS is a new and still experimental treatment strategy in this field with little evidence-based data, such a risk-averse approach seems the early safe strategy.

Several novel postoperative prognostic factors have been identified that could help staging and improve pretreatment risk stratification of UTUC patients such as information gained from the specimen obtained through ureteroscopic biopsy (e.g., PD-1/PD-L1 expression).

Current guidelines categorize patients into high- and low-risk groups based on the retrospective studies with low level of evidence making a robust recommendation and accurate decision-making difficult. Although, several multicentric

studies have been recently performed to confirm the efficacy of these prognosticators, further external validation and prospective cohort studies are needed to help clarify the prognostic value of these factors.

Recently, several new prognosticators (e.g., preoperative NLR, PD-1/PD-L1 expression, and sarcopenia) have been investigated to strengthen current risk stratification trees through an increase of prognostic accuracy. These novel prognostic factors together with more robust predictive models (e.g., nomograms) may help improve proper decision-making and risk stratifying UTUC patients in order to identify patients who may benefit from kidney-sparing modalities. However, further studies are needed to elucidate the association of these and other new prognostic factors with special focus on biomarkers that capture the biologic and clinical behavior of UTUC tumors in well-designed prospective cohorts.

Key Points

- UTUC is a rare disease with heterogeneous biology and behavior that needs accurate risk assessment to allow the proper therapy for the right tumor, in the right patient, at the right time.
- Current guidelines recommendations regarding the management of UTUC are mostly based on retrospective studies with low level of evidence.
- Patients risk stratification using predictive tools including traditional and novel prognosticators is essential to refine patient selection for RNU versus KSS.
- Future well-designed prospective studies are needed to clarify true prognostic value of novel predictive factors and improve accuracy of current traditional prognostic models.

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35 Ureteroscopic Managment of Upper Tract Urothelial Carcinoma

Etienne Xavier Keller and Olivier Traxer

Indications

Diagnostic Purpose

The entire upper urinary tract can be directly visualized by flexible ureteroscopy. Location, extent, and appearance of suspicious lesions can be recorded. Additionally, enhanced imaging technologies, in situ cytology, and biopsy samples can help to establish final diagnosis [1]. A limitation to this seemingly essential diagnostic approach is the risk of carcinogenic bladder recurrence, which has been repeatedly reported to be higher after diagnostic ureteroscopy, when compared to upfront radical nephroureterectomy [2, 3]. Therefore, diagnostic ureteroscopy should be reserved for well-selected patients. The European Urology Association (EAU) recommends diagnostic ureteroscopy if imaging and cytology are not sufficient for the diagnosis and/or risk stratification of the tumor [4]. Similarly, the French Urology Association (AFU) guidelines recommend diagnostic ureteroscopy only in cases with positive cytology but no evidence for bladder cancer, whenever a benign tumor cannot be ruled out by imagery, or whenever a kidney-sparing conservative treatment may be considered [5].

Therapeutic Purpose

Historically, flexible ureteroscopy was primarily reserved for diagnostic purposes [6]. Owing to technological improvements and refinement of operative techniques, flexible ureteroscopy is nowadays capable of both diagnosis and therapy of UTUC [7–11]. For low-risk disease, kidney-sparing approaches achieve oncological outcomes comparable to radical nephroureterectomy with bladder cuff excision (RNU) [12]. While RNU remains the standard therapy for high-risk disease, a growing body of evidence suggests that endoscopic kidney-sparing approaches are safe in low-risk disease, and a valuable alternative in imperative indications (Table 35.1) [4, 13, 14]. Kidney-sparing surgery should also be considered in patients with Lynch syndrome, considering the comparatively younger age at diagnosis and possibly higher risk for metachronous involvement of the contralateral kidney [15].

Flexible ureteroscopy is also a valid procedure for follow-up surveillance and treatment of recurrent disease after initial treatment [16, 17].

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Table 35.1 Indications for kidney-sparing endoscopic management of UTUC

Indications	Criteria
Low-risk UTUC[a]	Unifocal disease
	Tumor size <2 cm[b]
	Low-grade cytology
	Low-grade biopsy
	No invasive aspect on CT-urography
Imperative indications	Anatomically or functionally solitary kidney
	Severe renal insufficiency
	Bilateral disease
	Lynch syndrome
	Comorbidities or medications impeding RNU
Contraindications	
High-risk UTUC[c]	Hydronephrosis
	Tumor size >2 cm[b]
	High-grade cytology
	High-grade biopsy
	Multifocal disease
	High-grade bladder cancer
	Variant histology
Miscellaneous	Tumor not accessible by endoscopy
	Insufficient surgeon's expertise in flexible ureteroscopy
	Ancillary devices (biopsy forceps, laser generator) not available
	Patient not willing to comply with regular ureteroscopy follow-up controls

UTUC upper tract urothelial carcinoma, *CT* computed tomography, *RNU* radical nephroureterectomy with bladder cuff excision

[a]According to EAU guidelines; all criteria need to be met [4]

[b]Tumor size was not a significant prognostic factor in a recent retrospective review on 92 patients that underwent ureteroscopic management for UTUC [12]

[c]According to EAU guidelines; any criteria needed to classify as high-risk UTUC [4]

Table 35.2 summarizes interval control recommendations.

Patient Preparation

Preoperative workup should include hemostasis and kidney function control, as well as a urine culture that will prompt either antibiotic prophylaxis or therapy ahead of surgery. Patient and family history should be reviewed based on the Amsterdam criteria to identify patients at risk of Lynch disease, which may prompt immunohistochemistry in search of mismatch repair protein expression losses at histology [19, 20]. Anesthesiologic considerations, patient positioning, and organized operative room set-up have been well described earlier and will not be further detailed here [21, 22].

Surgical Technique

Flexible Ureteroscopy: Instrument Characteristics

Characteristics of currently available flexible ureteroscopes are summarized in Table 35.3.

Instrument Miniaturization

Miniaturization of flexible ureteroscopes is particularly relevant to ureteroscopic management of UTUC, since primary instrument insertion in an unprepared ureter is desirable (as discussed later in this chapter under "no-touch ureteroscopy"). Cross-sectional size of a majority of all flexible ureteroscopes is ≤9F (Table 35.3), which remarkably goes in hand with cross-sectional size of native human ureters (≤9F in 96% of all patients, based on a CT-analysis) [23]. Primary ureteral insertion failure rate is <1% for 7.5F flexible ureteroscopes, and up to 37% for 9.0F flexible ureteroscopes, according to a multicentric retrospective study [24]. Similar findings were reported in a more recent study, with an insertion failure rate of 1.4% for 7.5F flexible ureteroscopes [25].

Another advantage of miniaturized ureteroscopes is the improved overall irrigation flow, which is mainly dictated by the free space left between the outer contours of the ureteroscope and the inner wall of the ureter. That space is the only possibility for irrigation to flow out and allow fresh irrigation fluid to flow in. Consequently, at constant intrarenal pressure, the smaller the ureteroscope, the better the overall irrigation flow, and the better the visibility. Good visibility is key for a successful ureteroscopy. Ureteral access sheaths represent another alterna-

Table 35.2 Recommendations for surveillance after kidney-sparing management of UTUC

Investigations	Guidelines	Months after initial treatment								
		1.5 to 2	3	6	12	18	24	Annually after 24	Annually after 60	Annually after 120
Ureteroscopy[a]	EAU (*low-risk*)		x							
	EAU (*high-risk*)		x	x						
	AFU		x	x	x	x	x	x		
	CUA		x	x	x	x	x	x	x	
	Traxer et al. [17]	x	x	x	x	x	x	x	x	x
CT urography	EAU (*low-risk*)		x	x	x		x	x		
	EAU (*high-risk*)[b]		x	x	x		x	x	x	x
	AFU		x	x	x		x	x	x	x
	CUA				x		x	x	x	x
	Traxer et al.				x		x	x	x	x

EAU European Association of Urology [3], *AFU* Association française d'urologie [4]; *CUA* Canadian Urological Association [18]; *CT* computed tomography

[a]Ipsilateral, with cystoscopy and in situ cytology, except for EAU guidelines which recommend cytology only for *high-risk* tumors

[b]EAU guidelines recommend chest CT at 3 and 6 months, in addition to CT urography

tive for increased irrigation outflow [26–28], thus also improving overall irrigation flow and visibility during ureteroscopy. Of note, rising the irrigation pressure to improve overall irrigation flow should be considered hazardous, since pyelovenous backflow or forniceal rupture may occur as a consequence of high intrarenal pressure [29]. In the context of ureteroscopic management of UTUC, these undesirable pressure-associated mechanisms may lead to tumor seeding beyond the renal cavities.

Fiberoptic Versus Digital Ureteroscopes

As the name suggests, the image captured by fiberoptic ureteroscopes is transmitted over a well-orchestrated bundle of glass fibers that travel throughout the entire instrument. The ureteroscopic image can either be viewed by the naked eye at the ureteroscope's eye piece, or alternatively captured by a camera mounted at the eye piece for distant image projection on a display. In digital ureteroscopes, the image is captured by a camera chip at the tip of the instrument and is projected on a display after digital processing. Digital ureteroscopes have superior image quality and may therefore outperform fiberoptic scopes for tumor detection [1, 30, 31], although no study to date evaluated the impact of image quality on oncological outcomes [8]. Figure 35.1 demonstrates the image quality differences between fiberoptic and digital ureteroscopes.

Real-time image enhancement technologies such as narrow-band imaging (NBI) and 1-S technology (formerly named SPIES) have been integrated to some digital ureteroscopes in order to improve the diagnostic yield for detection of UTUC (Table 35.3) [8]. For fiberoptic ureteroscopes, photodynamic diagnosis (PDD), and 1-S technology may be optionally available, although their diagnostic accuracy may arguably be compromised by the overall inferior image quality (high image quality losses and low image resolution), compared to digital ureteroscopes (low image quality losses and high image resolution) [8]. No study to date showed an impact of these technologies on oncological outcomes [32].

Narrow-Band Imaging

NBI was first presented in 1999 [33]. This technology is based on illumination of tissues with two distinctive wavelengths: 415 nm (blue-violet) and 540 nm (green). These two wavelengths are strongly absorbed by hemoglobin [34]. Consequently, highly vascularized tissues appear darker than surrounding tissues (Fig. 35.2).

Table 35.3 Characteristics of currently available flexible ureteroscopes

Brand	Model	Single-use	Type		Cross-section		Cross-section size[a]		Working channel size[a]	Working channel position[a]			Deflection angulation[a] up/downward	Light source[b]		Enhanced imaging		
			Fiber-optic	Digital	Round	Oval	Tip	Shaft		3 o'clock	9 o'clock	Additional		External	Internal	NBI	PDD[c]	Image 1-S[d]
Olympus	URF-P5		x		x		5.3F	8.4F	3.6F		X	–	180°/275°	x			(x)	(x)
	URF-P6		x		x		4.9F	7.95F	3.6F		X	–	275°/275°	x			(x)	(x)
	URF-P7		x		x		4.9F	7.95F	3.6F		X	–	275°/275°	x			(x)	(x)
	URF-V			x	x		8.5F	9.9F	3.6F		X	–	180°/275°	x		x		
	URF-V2			x	x		8.5F	8.4F	3.6F		X	–	275°/275°	x		x		
	URF-V3			x	x		8.5F	8.4F	3.6F		X	–	275°/275°	x		x		
Storz	Flex X2/s		x			x	7.5F	7.5F	3.6F		X	–	270°/270°	x			(x)	(x)
	Flex Xc			x		x	8.5F	8.4F	3.6F	x		–	270°/270°		x			x
Wolf	Viper		x		x		6.0F	8.8F	3.6F	x		–	270°/270°	x			(x)	(x)
	Boa vision			x	x		6.6F	8.7F	3.6F		X	–	270°/270°		x			
	Cobra		x		x		6.0F	9.9F	2x 3.3F	x		12 o'clock	270°/270°	x			(x)	(x)
	Cobra vision			x	x		5.2F	9.9F	2.4F and 3.3F		X	6 o'clock	270°/270°		x			
Boston scientific	Lithovue	x		x	x		7.7F	9.5F	3.6F	x		–	270°/270°		x			
Pusen	Uscope	x		x	x		9.0F	9.5F	3.6F	x		–	270°/270°		x			
OTU Medical	Wiscope	x		x	x		7.4F	8.6F	3.6F		X		275°/275°		x			
Poly-Diagnost	Poly-Scope	(x)	x		x		8F	8F	3.8F	x		–	>250°		x		(x)	(x)

NBI narrow band imaging, *PDD* photodynamic diagnostic, *LED* light emitting diode

[a]As given by manufacturer

[b]External light source is usually a Xenon lamp; Internal light source is usually a LED within the ureteroscope handle

[c]Potentially applicable to any fiberoptic scope by the use of a PDD-able light source and camera

[d]Potentially applicable to any fiberoptic scope by the use of an Image 1-S camera at the eyepiece

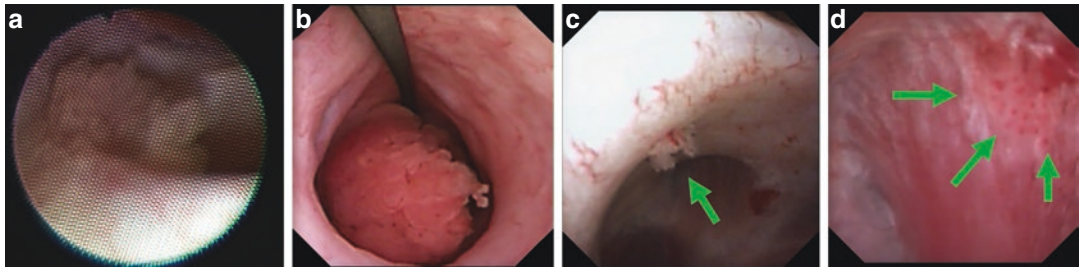

Fig. 35.1 *Ureteroscopic image quality*. (**a**): Caliceal papillary tumor viewed by a fiberoptic flexible ureteroscope. (**b**): Ureteral papillary tumor viewed by a digital flexible ureteroscope. (**c**) and (**d**): Subtle papillary tumors viewed with a digital flexible ureteroscope (green arrows indicated the tumors). All images are histologically confirmed UTUC

Additionally, the 540 nm light propagates deeper into tissues compared to the 415 nm light, which adds to contrasting of highly vascular tissues. In a study including 13 patients with suspected UTUC and 14 patients undergoing follow-up ureteroscopic surveillance of UTUC, NBI was shown to increase tumor detection rate by 22.7% compared to white-light ureteroscopy [35].

1-S Technology

The 1-S technology is based on reprocessing of the image projected on display. This image reprocessing enhances contrast domains that impact on human's eye interpretation of the visualized image. Of the five available reprocessing modalities, the "Clara+Chroma" mode has been shown to reach a significantly better subjective image quality score in a recent in vitro study (Fig. 35.3) [36].

Photodynamic Diagnosis

PDD is based on fluorescent marking of tumor cells (Fig. 35.4). A fluorochrome related to the heme-cycle – typically 5-aminoaevulinic acid (5-ALA) and its derivate hexaminolevulinate (HAL) – needs to be administrated to the patient prior to surgery (typically 60 min before ureteroscopy). Then, tissues need to be illuminated with a distinctive blue-violet light (380–470 nm) to excite the fluorochrome. When relaxation of the fluorochrome occurs, a photon with a red-pink color is emitted and may reveal tumoral tissue by its red-pink fluorescence.

Flexible Ureteroscopy: A Step-by-Step Approach

Cystoscopy

The first step of the endourological approach to UTUC is cystoscopy. The bladder should be carefully inspected, since concomitant bladder cancer may occur in up to 17% of patients, and bladder recurrence may occur in 20–45% of cases in follow-up ureteroscopy controls [37, 38]. Good visibility and high image quality are key for detection of intravesical irregularities. Rigid cystoscopes with a Hopkins rod-lens construct allow inspection of the bladder mucosa with an outstanding image quality (Fig. 35.5a) [39, 40]. Modern digital flexible cystoscopes also provide a high image quality, and additionally allow bladder neck inspection by retroversion (Fig. 35.5b), eventually surpassing diagnostic accuracy of rigid cystoscopes [41].

Bladder cytology shall be withdrawn at the time of cystoscopy. No evidence supports the use of repeated bladder washings [42]. On the contrary, bladder washings may worsen the diagnostic yield of cystoscopy by causing mucosal bleeding. Therefore, we recommend urine collection for cytology immediately after the cystoscope is insert into the bladder, without any bladder washings.

Retrograde Ureteropyelography

Upon retrograde ureteropyelography, UTUC typically appears as a negative contour to the surrounding contrast medium, reminiscent of a

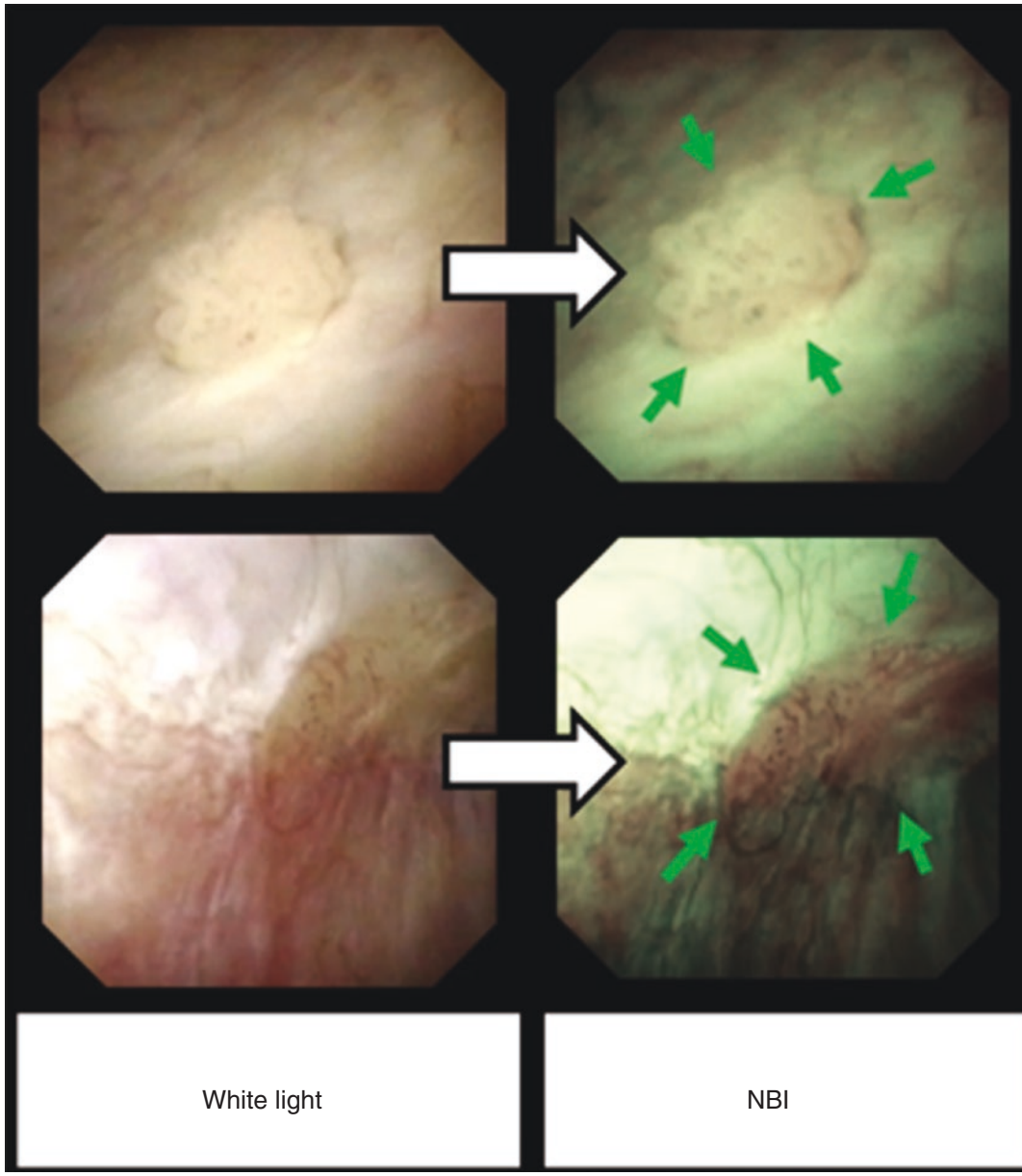

Fig. 35.2 *Narrow-band imaging (NBI).* Comparison of standard ureteroscopic view with white light illumination (left) and activated NBI mode (right), which highlights contours (green arrows) of papillary (first row) or flat lesions (second row). In NBI mode, normal mucosae appear greenish, whereas tumoral tissues appear dark and brown-red. All images are histologically confirmed UTUC

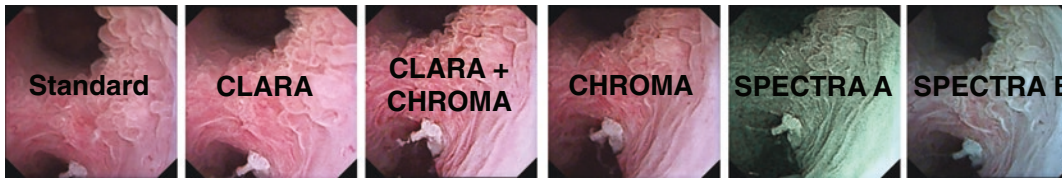

Fig. 35.3 *Image 1-S technology.* Standard mode, as well as the five reprocessing modes

bitten apple (Fig. 35.6). We recommend to perform retrograde ureteropyelography selectively. It has a low added value to the intervention, at the costs of many disadvantages: low sensitivity and specificity for small tumors, potential hazards and complications of over-pressurized retrograde injection, potential negative impact on cytology, temporary worsening of endoscopic visibility, additional operative time, additional radiation exposure, and additional material costs.

If needed, retrograde ureteropyelography can be reasonably used for the following indications: obstructive intraluminal tumor (Fig. 35.6b and c), unusual anatomy (ureteral duplication (Fig. 35.6c), horseshoe kidney, etc.) or when a perforation is suspected.

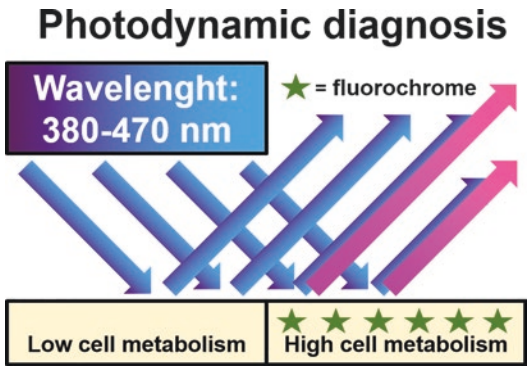

Fig. 35.4 *Photodynamic diagnosis.* A fluorochrome is integrated highly metabolic cells (typically tumor cells). These cells are then revealed by a red-pink fluorescence upon illumination with a blue-violet light

"No-Touch" Ureteroscopy

Wireless and sheathless "no-touch" flexible ureteroscopy was first presented by Grasso et al. in 2006 [43]. This important and challenging technique was developed in the context of a growing interest in kidney-sparing ureteroscopic management of low-grade UTUC. The authors emphasize on the need to prevent any artifacts caused by guidewires or ureteral access sheaths, in order to warrant pristine conditions for the evaluation of the upper urinary tract. A "no-touch" approach should be considered in any retrograde approach to UTUC. This technique shall be reserved for diagnostic purposes only, and therefore does not reject the principle of a "safety guidewire" *per se* [44]. On the contrary, we recommend the use of a safety guidewire whenever further therapeutic steps are required after diagnostic ureteroscopy.

Figure 35.7 illustrates the most important steps of "no-touch" ureteroscopy. To succeed and master this technique, we recommend to manipulate the shaft of the flexible ureteroscope at the urethral meatus with the nondominant hand. In men, this is best achieved by stabilizing the Glans penis between the little and ring finger, leaving the thumb and the index free for pushing the ureteroscope into the urethra.

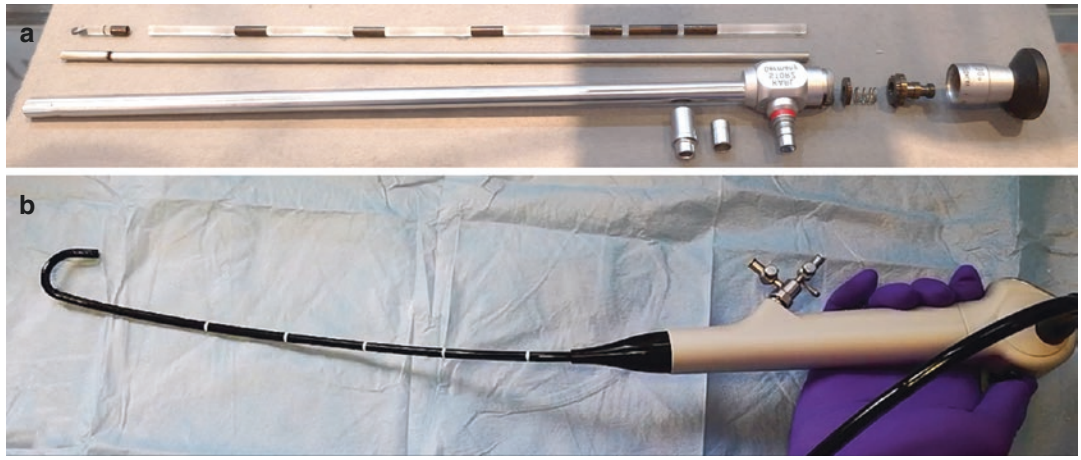

Fig. 35.5 *Cystoscopes.* (**a**) Rigid cystoscope with a Hopkins rod-lens construct (dismantled for demonstration purposes). (**b**) Flexible digital cystoscope with a deflected tip for bladder neck inspection by retroversion

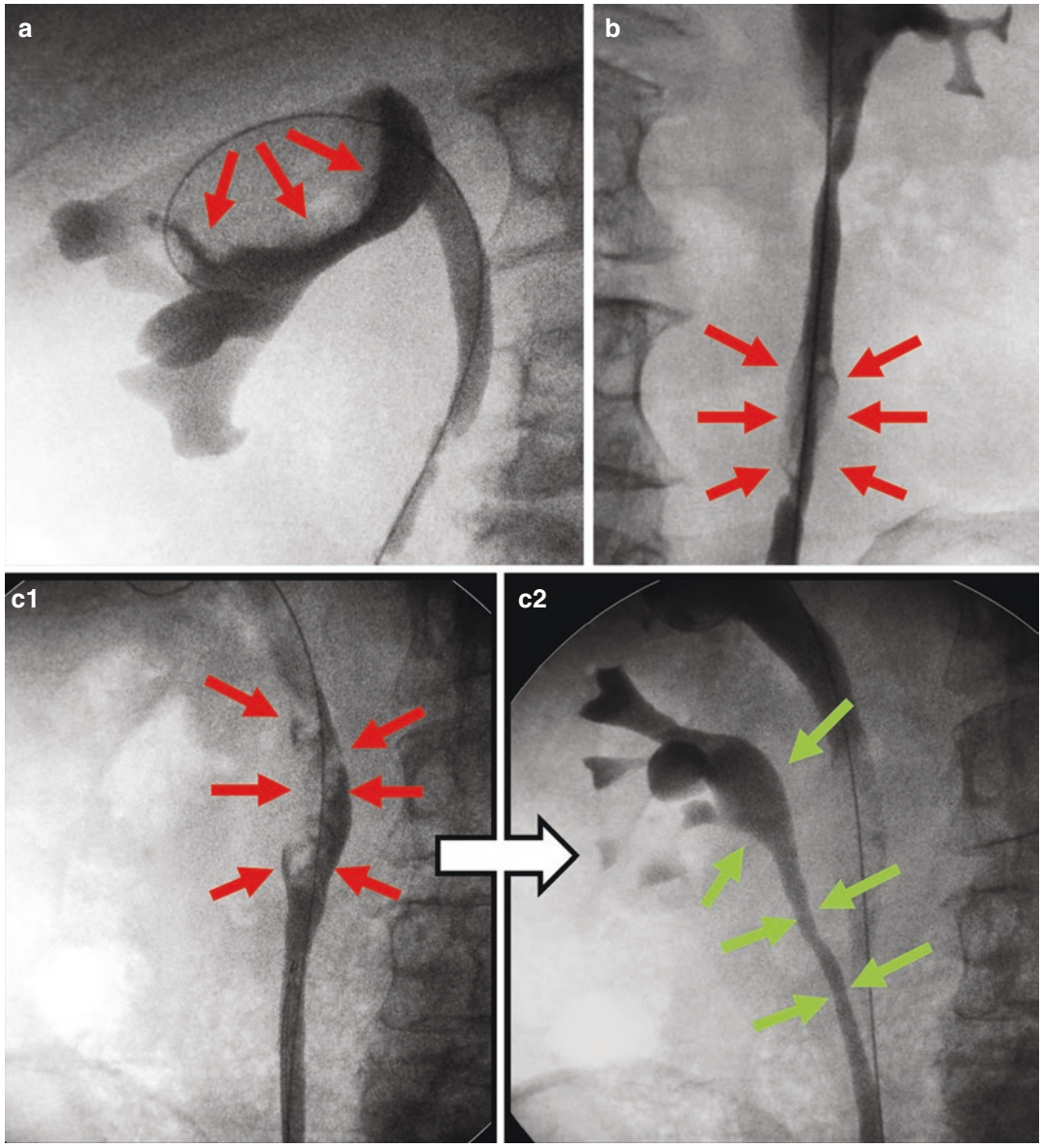

Fig. 35.6 *Retrograde ureteropyelography.* (**a**) Large pyelocaliceal tumor appearing as a negative contour to the surrounding contrast medium, reminiscent of a bitten apple (red arrows). (**b**) Obstructive ureteral tumor (red arrows). C1–2: Obstructive ureteral tumor (red arrows) involving the superior system in a patient with ureteral duplication (green arrows show the tumor-free lower system)

If access cannot be achieved because of a narrow ureteral orifice, the flexible ureteroscope may be backloaded over a guidewire. Ideally, the guidewire should not be inserted any further cranially than the distal ureter, in order to minimize guidewire-inducted artifacts to the mucosa.

If access can still not be achieved, we recommend ureteral stenting and postponement of ureteroscopy. In our opinion, ureteral dilation should not be performed in the setting of UTUC, since disruption of the ureteral wall confinements may put patients at risk of tumor seeding within

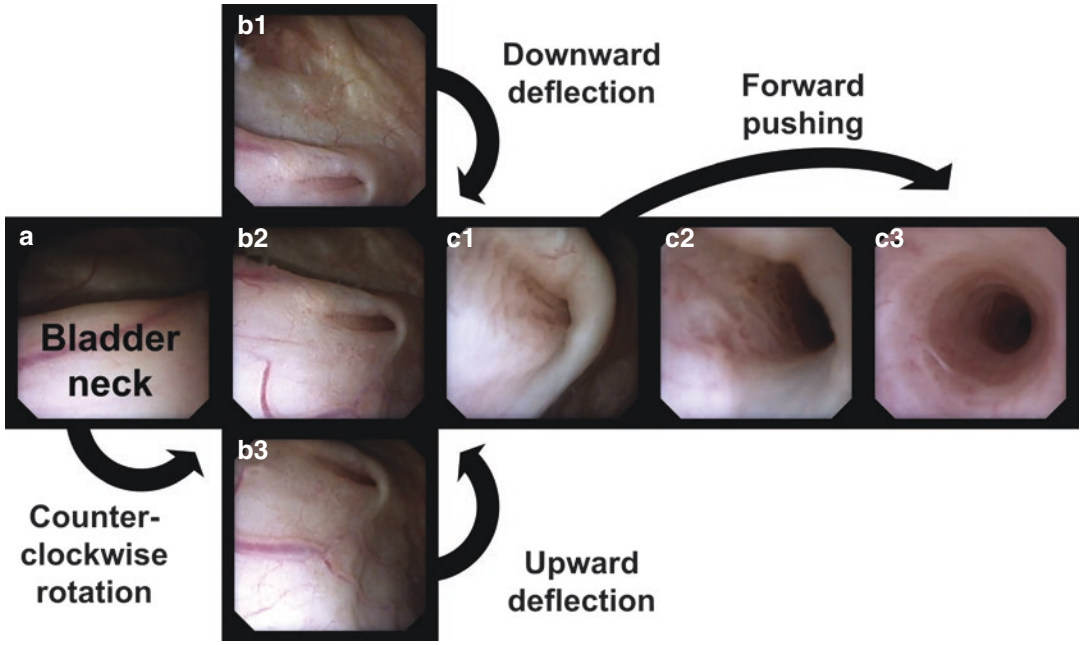

Fig. 35.7 *"No-touch" ureteroscopy*. A: The tip of the flexible ureteroscope is positioned in a straight position at the bladder neck. B1–3: A counterclockwise rotation followed by a deflection shall bring the left ureteral orifice in the field of view. C1–3: Once centered on the ureteral orifice, the ureteroscope is pushed forward with slight rotational and deflection movements to keep the ureteral lumen centered on the image. If available, an irrigation handpump can help opening the ureteral orifice by intermittently increasing irrigation flow rate through the scope.

deeper anatomical layers. This hypothetical risk needs to be evaluated in dedicated studies, but theoretically would also apply to the use of ureteral access sheaths, which may act as dilators during insertion.

Biopsy and Cytology

Biopsy Techniques

Table 35.4 summarizes currently available biopsy devices for flexible ureteroscopes. Conventional cup forceps (Fig. 35.8a) and nitinol baskets (Fig. 35.8c) allow small-sized biopsies to be withdrawn through the working channel of the ureteroscope, arguably preventing tumor spillage along the urinary tract. This strategy also allows to rapidly and sequentially withdraw multiple biopsies from the same region of interest, since the ureteroscope is left in place and samples are withdrawn over the working channel.

The BIGopsy™ is a larger cup forceps (Fig. 35.8b) that has been shown to provide higher quality biopsy samples, compared to conventional biopsy forceps [45]. Another alternative for obtaining high quality tissue samples is the use of a basket (usually made out of nitinol) to grasp papillary tumors, although samples may suffer from crush artifacts and may be lost during tissue withdrawal.

All the aforementioned biopsy devices seem to be comparable for establishing the diagnosis of UTUC, as well as for grade evaluation [46]. Overall sensitivity of biopsies ranges between 89% and 100% [47, 48]. Unfortunately, stage of the disease is underestimated by ureteroscopic biopsies and therefore better evaluated by computed tomography or magnetic resonance tomography [49].

For ureteral tumors, particular care must be taken to first push, and then secondly pull the biopsy device once the tumor has detached from its pedicle, in order to avoid the hazards of ure-

Table 35.4 Biopsy devices for flexible ureteroscopes

Characteristics	Conventional cup forceps	BIGopsy	Nitinol basket
Maximal tip opening	4 mm	5 mm	8–16 mm
Shaft cross-section	3F	2.4 F	1.7F to 3.0F
Biopsy withdrawal over working channel	Yes	No	Yes
Limitations and safety issues	Very small biopsy samples with 1. limited diagnostic yield for tumor staging and 2. risk of sample loss during histological tissue fixation	Needs to be backloaded on the ureteroscope, which must be inserted over an access sheath. Limited visibility because of 1. low irrigation inflow and 2. large forceps in the field of view	Risk of crush artifacts and sample loss during tissue extraction

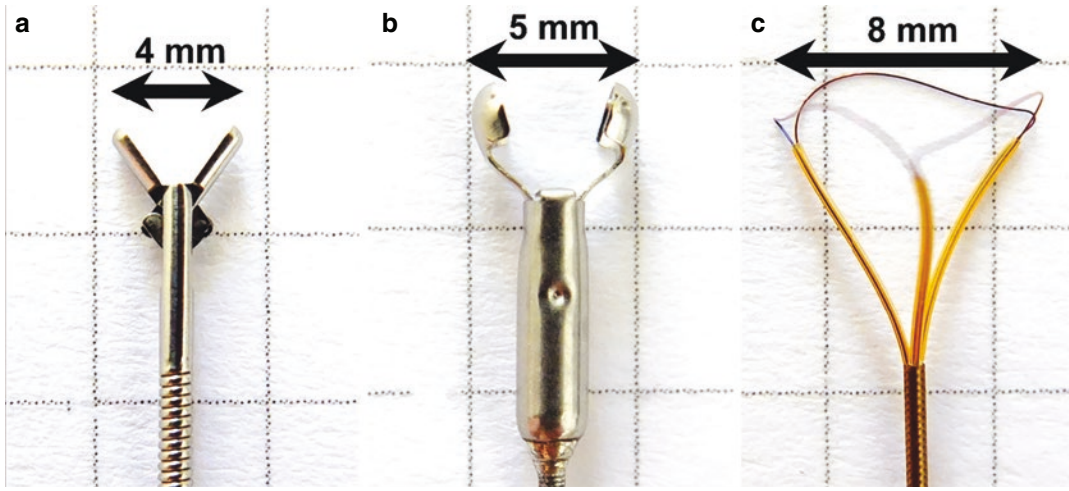

Fig. 35.8 *Biopsy devices for flexible ureteroscopes*. (**a**) Conventional cup forceps (4 mm tip opening). (**b**) BIGopsy™ cup forceps (5 mm tip opening). (**c**) Nitinol basket (8 mm tip opening)

teral avulsion if the tumor would be pulled right away (Fig. 35.9). This technique of ureteral tumor biopsy is valid for any of the aforementioned biopsy devices.

Cytology

The diagnostic yield of combined cytology and biopsy is superior than any of these two alone [50]. Therefore, we recommend *in situ* cytology in every patient with suspected or confirmed UTUC.

Cytology can be aspirated over the working channel of the flexible ureteroscope. In the ureter, cytology aspiration may cause rapid collapse and damage to the ureteral wall by tissue entrapment within the working channel of the scope. Therefore, we recommend to aspirate cytology once the ureteroscope has reached the renal pelvis. Arguably, any tumor cells present in the ureter will flow back to the renal pelvis under the influence of irrigation. Therefore, we do not recommend separate withdrawal from the ureter and pyelocaliceal cavities, but rather recommend to consider only one cytology aspiration for the whole ipsilateral upper urinary tract, ideally withdrawn within the renal cavities.

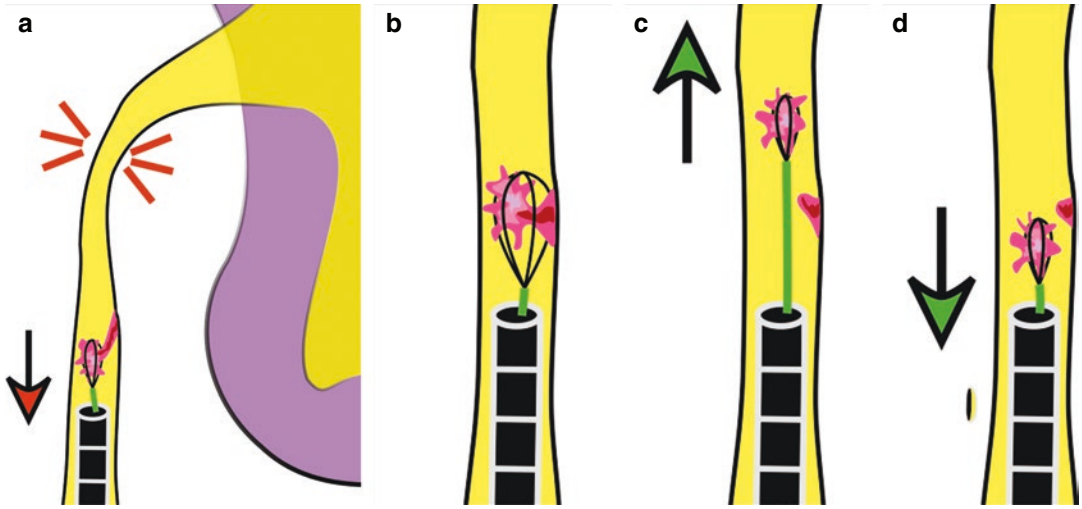

Fig. 35.9 *Technique of ureteral tumor biopsy.* (**a**) Biopsy of a ureteral tumor (pink) entails the risk of ureteral avulsion (red bars at the pyelocaliceal junction) if the tumor is directly pulled caudally (red arrow) toward the flexible ureteroscope. (**b**) The tumor should be first carefully grasped with a biopsy device, ideally as near as possible to its pedicle. (**c**) To avoid ureteral avulsion, the biopsy device should be first pushed cranially (green arrow) until the main body of the tumor has detached from its pedicle. (**d**) Once the tumor has been released from its pedicle, it can be pulled toward the ureteroscope. For demonstration purposes, a nitinol basket has been depicted on this scheme, although this ureteral tumor biopsy technique is valid for any biopsy device

Handling Specimen in OR

We recommend to transfer biopsy specimen directly into a container prefilled with normal saline in order to avoid any alterations or losses of tissue. The saline allows to detach the biopsy specimen after opening the biopsy device without any direct manipulations to the tissue sample.

In cases where only very small tissue samples are available for examination, we recommend performing cytological analysis rather than histological analysis. Even though cytology will be limited to grading of the disease, it will lower the risk of complete loss of tumor sample, which may occur during tissue fixation for histological analysis.

Endoscopic Treatment

Laser Tumor Ablation

Ureteroscopic tumor laser ablation relies on vapo-coagulation of tissues, which is best achieved by infrared lasers such as the Holmium:YAG, Thulium:YAG, or the by the novel Thulium fiber laser (TFL) [51–57]. A short laser tissue penetration depth is desirable to prevent bleeding complications caused by damages to blood vessels lying within the fibro-vascular pedicle of papillary tumors, or by damages to submucosal vessels underlying the urothelium. To that respect, all three laser technologies similarly have a low tissue penetration (generally <2 mm), provided that laser settings are maintained in a low-level range (average power < 10–15 W) [57–63].

Several authors favor the Thulium:YAG over Holmium:YAG for tissue laser ablation, based on the clinical observation of a better tissue coagulation, hemostasis, and hence visibility [51–57]. This assumption has been verified in a recent in vitro study, where the Thulium:YAG revealed a significantly shorter tissue penetration depth and greater coagulation area, compared to the Holmium:YAG [57]. Concerning the TFL, preliminary results revealed this novel technology as a promising new tool for soft tissue laser ablation [59, 60, 64, 65]. Table 35.5 summarizes the most important characteristics of all three laser tech-

Table 35.5 Comparison of laser technologies for ureteroscopic management of UTUC

Technology	Holmium:YAG	Thulium:YAG	Thulium fiber laser
Wavelength	2120 nm	2010 nm	1940 nm
Pulse energy	0.2 to 6.0 J	Continuous wave	0.025 to 6.0 J
Pulse frequency	Up to 120 Hz	Continuous wave	Up to 2000 Hz
Pulse duration	0.05 to 1 ms	Continuous wave	0.05 to 12 ms
Pulse shape	Limited modulation	Continuous wave	Electronically modulable
Smallest laser fiber core	200 µm	200 µm	150 µm
Tissue penetration depth	Low	Very low	Low
Hemostasis proprieties	Medium	Strong	Strong
Tissue blanching	Yes	No	Yes
Limitations	High peak power causing unvoluntary tissue disruption with tissue bleeding in contact mode	Limited versatility, since this laser technology cannot be used for lithotripsy of urinary stones	None
Temperature hazards	Safe within <10–15 W average power and constant irrigation	Safe within <10–15 W average power and constant irrigation	Safe within <10–15 W average power and constant irrigation

nologies currently available for ureteroscopic treatment of UTUC.

We recommend a non-contact laser ablation technique for vapo-coagulation of UTUC lesions. This technique is based on maintaining a working distance (distance between tissue surface and tip of the laser fiber) of approximately 1–3 mm over the mucosa (Fig. 35.10).

The "tissue blanching" associated with the non-contact tissue ablation technique had already been observed in 1992 by Johnson et al. [66]. The favorable coagulation effect of non-contact tissue blanching could be verified in a recent in vitro study, therefore confirming this technique for hemostatic ureteroscopic laser tumor ablation under ideal visibility conditions [59]. Non-contact tissue blanching is best achieved by the Holmium:YAG and TFL (Fig. 35.11). This tissue blanching is the signature of tissue protein denaturation, perceived as a white color by the human eye [67]. Differently, the Thulium:YAG usually causes a more ample brown-dark tissue coagulation necrosis, even in non-contact mode.

Optimal laser parameters for tissue ablation shall be individually adapted to tumor location, size, and configuration, as well as to endoscopic maneuverability and visibility conditions. For the Holmium:YAG and the Thulium fiber laser, we recommend to initiate laser ablation with low pulse energy and low pulse frequency (e.g., 0.1–0.2 J and 5 Hz). After appreciation of the laser effects on tissue, pulse energy and pulse frequency may be gently increased until optimal tissue blanching is observed. If the laser generator allows pulse modulation, we recommend a long-pulse mode. Concerning the Thulium:YAG, we recommend to maintain very low power settings (5–15 W). A non-contact technique is essential for Thulium:YAG tissue ablation, since contact of the laser fiber tip with tissue will cause coagulated tissue to clog at the tip of the fiber, thus profoundly limiting visibility.

The Thulium:YAG operates in a continuous emission mode, whereas the Holmium:YAG and TFL operate in a pulsed mode. This explains why the Holmium:YAG and TFL can reach the high peak power levels needed for lithotripsy of urinary stones, unlike the Thulium:YAG which cannot be used for stone lithotripsy. This advantage of versatility also explains why Holmium:YAG and TFL generators are becoming widely available throughout the world, whereas only few urologic departments dispose of a Thulium:YAG generator.

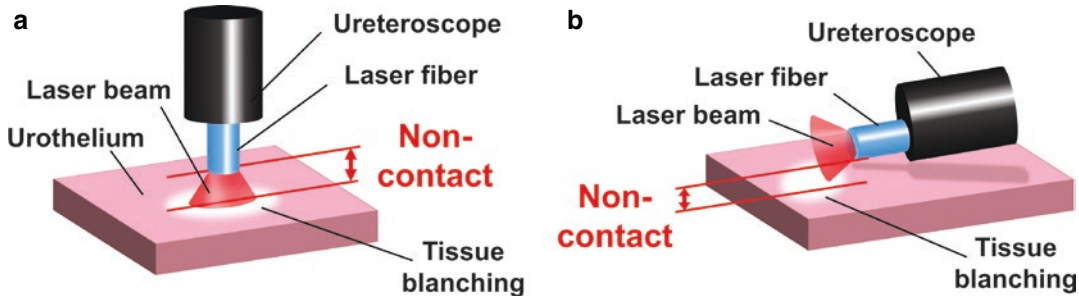

Fig. 35.10 *Non-contact tissue laser ablation.* (**a**) When the ureteroscope is directly facing the tissue surface, a working distance of 1–3 mm should be maintained between the laser fiber tip and tissue surface in order to achieve a proper non-contact tissue blanching. (**b**) When target tissues are lying in a tangential plane to the ureteroscope, the lateral irradiation plane at the tip of the fiber allows safe and gentle tissue blanching with a working distance of about 1–2 mm

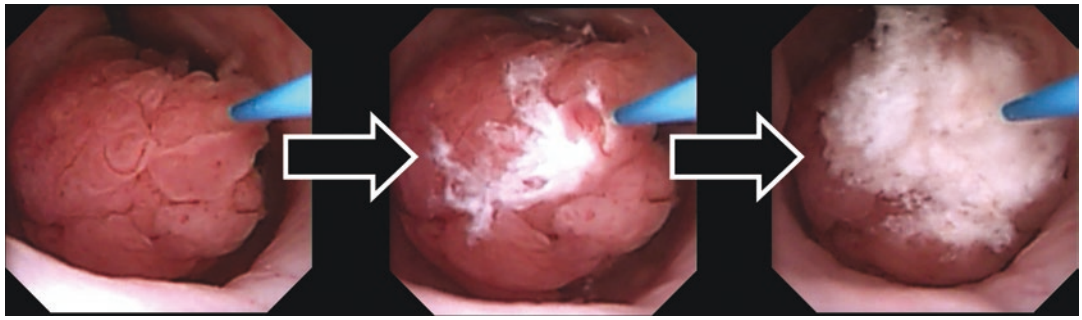

Fig. 35.11 *Tissue blanching.* This ureteral papillary lesion was treated with a Thulium fiber laser using a non-contact tissue laser ablation technique in order to achieved controlled hemostatic tissue blanching under optimal visibility conditions

Monopolar Bugbee

The Bugbee is a flexible 2F monopolar PFTE-coated electrode that can be inserted through the working channel of flexible ureteroscopes and connected to any routinely available electrosurgical generator. The monopolar Bugbee therefore may present as a valuable alternative for tissue vapo-coagulation in case no laser technology is available.

Management of Common Complications

The best strategy to manage complications is to avoid them. Bleeding complications and ureteral wall damages are most relevant to ureteroscopic management of UTUC and will shortly be reviewed above.

Bleeding Complications

Minor, transient bleedings are reported with an incidence of 0.2% to 19.9% after ureteroscopy [68]. In the context of ureteroscopic management of UTUC, bleedings are of particular importance, since they may negatively impact on the diagnostic and therapeutic yield of ureteroscopy because of impaired visibility. Ultimately, even minor bleedings may imply to postpone a session of ureteroscopy.

Bleedings may occur because of direct iatrogenic trauma to the urinary pathways, excessive

intrarenal pressure, tumor biopsy, or because of tumor ablation processes. A common cause of direct iatrogenic trauma is the use of a guidewire or ureteral access sheath, thus justifying the "no-touch" ureteroscopy technique described above. Another common cause of direct iatrogenic trauma is the involuntary aspiration of mucosa during cytology withdrawal (Fig. 35.12a). Also, high intrapelvic pressure (>60–80 cmH20) may cause fornix rupture with consequent bleeding from the forniceal ridge (Fig. 35.12b and c) [29]. Therefore, we recommend to use gravity irrigation system, which easily can warrant a controlled maximal irrigation pressure < 80 cmH20 (Fig. 35.13).

Mostly, minor bleedings can be managed conservatively. Before deciding to postpone an intervention because of impaired visibility, we recommend to irrigate and flush the pelvicalyceal system for 5–10 minutes. In most cases, visibility will spontaneously resolve, possibly allowing to pursue the intervention. If not, we recommend to place a ureteral stent and to postpone the intervention.

Ureteral Wall Damages

In the context of ureteroscopic management of UTUC, it seems of utmost importance to prevent

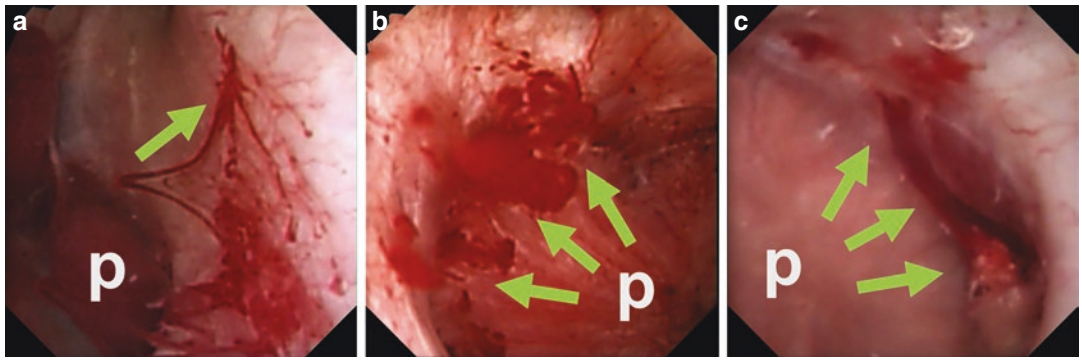

Fig. 35.12 *Minor bleedings*. (**a**) Involuntary aspiration of mucosa into the working channel of the ureteroscope may cause subsequent superficial bleeding (green arrow) (renal papilla (p)). (**b** and **c**) High intrapelvic pressure (>60–80 cmH20) may cause fornix rupture with consequent bleeding from the forniceal ridge (green arrows) (papillae (p) have been marked for orientation)

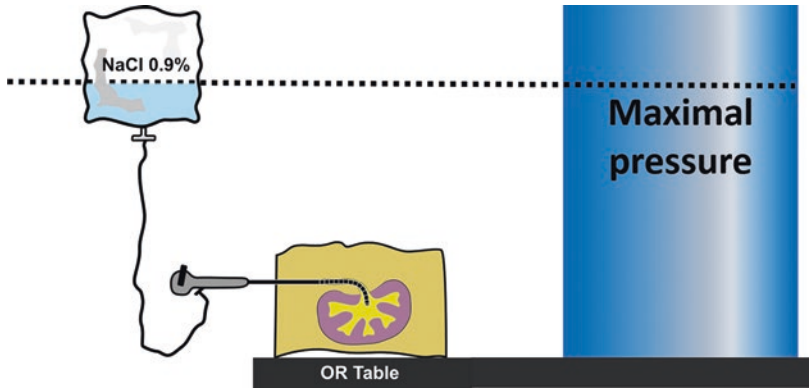

Fig. 35.13 *Gravity pressure irrigation.* Maximal intrarenal pressure can be easily controlled by limiting the height of the column of water connected to the flexible ureteroscope. The distance between the operating room (OR) table and the upper level of the fluid within the irrigation bag directly correlates with intrarenal pressure. Bleeding complications caused by fornix rupture are best avoided by maintaining an intrarenal pressure < 60–80 cmH20

and recognize any breach through the ureteral wall. Indeed, it is conceivable that such event entails the risk of tumor cell spillage beyond the boundaries of the urinary tract, with an according negative oncological impact.

For this reason, we recommend to refrain using any ureteral dilators or ureteral access sheaths in the context of UTUC, since these devices may cause uncontrolled and unrecognized damages to the ureteral wall [28, 68].

Conclusions

Flexible ureteroscopy is an essential diagnostic and therapeutic asset in the urological armamentarium for patients with suspected or confirmed UTUC. Instrument miniaturization, digital image caption, image enhancement technologies, availability of ancillary devices such as Holmium:YAG, Thulium:YAG, or Thulium fiber laser, combined to a complex interplay of technical surgeon's skills are the major determinants for successful flexible ureteroscopy in the context of UTUC.

Kidney-sparing ureteroscopic management of UTUC can be offered to well-selected patients agreeing to undergo repeated ureteroscopic surveillance, provided that criteria for low-risk disease or imperative indications are fulfilled. Because of ongoing novel material requirements and complexity of technical aspects, this challenging procedure shall be reserved to experts in the field.

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Adjuvant Therapy for Upper Tract Urothelial Carcinoma after Endoscopic Management

Morgan Roupret, Thomas Seisen, and Pietro Grande

Introduction

Although radical nephroureterectomy (RNU) remains the standard of care for patients with upper tract urothelial carcinoma (UTUC), kidney-sparing surgery (KSS) has been proposed to preserve the renal unit without compromising oncological outcomes [1]. Traditionally, this approach was utilized only for imperative cases such as individuals with inadequate renal function or other significant comorbidity, as well as those at high-risk of bilateral disease [2, 3]. More recently, advances in endoscopic and other minimally invasive techniques have made KSS safe and feasible in well-selected elective cases such as healthy patients with low-risk disease [2, 3]. Accordingly, the European Association of Urology (EAU) guidelines recommends its use for any individuals with unifocal low-grade tumour not exceeding 2 cm in diameter [1]. However, the risk of disease recurrence following KSS can be as high as 70% [4, 5].

Interestingly, intracavitary instillations of topical agents may provide a better disease control for patients undergoing KSS [2, 3, 6]. Over the past decades, several antegrade and retrograde techniques have been described to deliver either immunomodulatory or chemotherapeutic substances up to the ureter or pelvicaliceal cavities with various efficacy. Thus, we aimed at summarizing current evidence describing topical agents and approaches for intracavitary instillations with their associated oncological outcomes and potential toxicity.

Pretreatment Management

Before considering post-KSS intracavitary instillations, some investigations may help to improve efficacy and safety of such treatment. First, mirroring the bladder cancer setting, the clearance of any macroscopic cancer cell could be confirmed by an ureteroscopic second-look within 6–8 weeks after initial KSS to deliver topical agents in a tumour-free upper urinary tract – except for the treatment of extensive CIS in imperative cases. This has been somewhat suggested by a recent study showing a decreased risk of massive tumour recurrence after ureteroscopic management of UTUC when using such second-look procedure, although the included patients did not receive any intracavitary instillations [7]. Second, given that bacterial sepsis represents a major complication related to the upper urinary tract infusion with both immunomodulatory and chemotherapeutic substances, no bacteriuria should be detected on cytobacteriological examination of urine before starting the treatment.

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Topical Agents

Given that UTUC and bladder cancer have similar histology, treatments are remarkably the same at any stage of the disease. This is also related to the scarcity of UTUC, which makes difficult to conduct any large-scale prospective study – such as randomized controlled trials – for evaluating new drugs to specifically treat these tumours. In particular, as for bladder cancer, BCG and Mitomycin C represent the most important topical agents to consider for intracavitary instillations, depending on the pathological features observed at KSS. Other agents such as Epirubicin [8], Thiotepa [9] and BCG/IFN [10] have also been described to a lesser extent in the current literature.

Efficacy of Intracavitary BCG Instillations

Interestingly, BCG remains the most commonly used topical agents for intracavitary instillations after KSS, given that it has been evaluated for either the eradication of CIS in imperative cases (Table 36.1) or the prevention of disease recurrence in elective cases (Table 36.2).

Since the first experience reported by Studer et al. [11] in 1989, BCG has become a valuable option to treat CIS. Studer used BCG in 10 renal units (RU) (eight patients) with cytological evidence of carcinoma in situ, obtaining in all but one patient a negative post-treatment cytology. In the last three decades, many other descriptive studies reported comparable results, as well by

Table 36.1 Series reporting BCG intracavitary treatment for CIS as curative treatment

Study	Renal units, *n*	Approach	Response	Recurrence rate	Mean follow-up, months
Sharpe et al. [27]	17	Retrograde	76%	18%	49
Yokogi et al. [33]	8	Both	63%	0%	10–46
Nishino et al. [34]	6	Retrograde	100%	0%	22
Nonomura et al. [28]	11	Retrograde	82%	22%	NA
Okubo et al. [35]	14	Retrograde	64%	45%	18–82
Thalman et al. [20]	25	Anterograde	88%	55%	24
Irie et al. [22]	13	Retrograde	100%	11%	36
Miyakeet al [36]	16	Both	81%	19%	30
Hayashida et al. [37]	11	Both	100%	50%	51
Kojima et al. [12]	13	Retrograde	77%	27%	1–76
Giannarini et al. [13]	42	Anterograde	NA	40%	42

Adapted from Audenet et al. [3].

Table 36.2 Instillation of the UT following conservative (kidney sparing) management

Author	Renal units, *n*	Treatment	Instillation approach	Recurrence rate	Follow-up, months
Smith et al.	6	MMC, BCG	Anterograde	17%	9.5
Orihuela et al.	6	BCG	Anterograde	17%	19
Schoenberg et al.	9	BCG	Anterograde	11%	24
Eastham et al.	7	MMC	Retrograde	29%	12
Vasavada et al.	8	BCG	Anterograde	37%	24
Martinez-Pineiro et al.	31	MMC, BCG, Thiotepa, IFN	Both	a	31
Patel et al.	17	BCG	Retrograde	12%	15
Clark et al.	18	BCG	Anterograde	33%	11
Jabbour et al.	13	BCG	Anterograde	23%	59
Thalman et al.	16	BCG	Anterograde	87%	42
Rastinehad et al.	50	BCG	Anterograde	36%	61
Giannarini et al.	22	BCG	Anterograde	59%	42

Adapted from Audenet et al. [3]
a = MMC 14%, BCG 12.5%, Thiotepa 40%

anterograde as by retrograde approach. Taken together all those studies demonstrate that BCG therapy seems to provide cure for at least 50% of treated renal units. However, no study included more than 20 RUs treated. Additionally, the main limitation of these retrospective studies lies on the fact that the initial diagnosis of CIS was usually made by selective urine cytological examinations rather than biopsy. Furthermore, data on recurrence/remission were based on normalization of selective urine cytology rather than ureteroscopy and biopsy. Nonetheless, of the initial responders in these studies, upper urinary tract recurrence occurred in 25% and metastatic disease 10% of these patients. Kojima et al. [12] reported BCG therapy for CIS of the UT to be as effective as RNU in long-term outcomes. They found no significance in 5-years recurrence-free survival (RFS) or 5-year cancer-specific survival (CSS) when they retrospectively analysed the post-treatment course of 17 patients with CIS of the UT who had undergone either RNU (6 patients) or BCG therapy (11 patients).

Conversely, Giannarini et al. [13] reported a recurrence rate of 40% in UT CIS versus 59% in Ta/T1 UTUC after BCG treatment. Greater differences occurred in terms of progression 5% in UT CIS versus 41% in Ta/T1 UTUC. Patients treated with curative intent for CIS had significantly better progression-free survival ($p < 0.01$) and nephroureterectomy-free survival ($p = 0.05$) compared with those treated with adjuvant intent after ablation of Ta/T1 tumours, although the improvement of the recurrence-free survival was not significant.

Intracavitary therapy is currently advisable in patients with CIS and cytology-proven persistence or in patients with indications for renal preservation, most commonly with BCG, although the level of evidence is currently weak [1].

Efficacy of Intracavitary Mitomycin C Instillations

With regard to the use of Mitomycin C, less evidence is available in the current literature. MMC treatment after KSS was firstly reported by van Helsdingen [14]. After this first initial report, MMC was also used by Eastham [15] and Martinez-Pineiro [16]. MMC showed to be safe but no advantages over BCG were found. More recently, Aboumarzouk et al. [17] suggested that MMC following uteroscopic laser ablation of UTUC may be well tolerated, with few side effects and a reduced recurrence rate. Despite this, evidences for MMC are possibly weaker than those for BCG, although this could be a useful alternative for BCG-unfit patients.

Instillation Techniques

It is noteworthy that, as opposed to the bladder, upper urinary tract does not have any reservoir property. Thus, exposure time of the urothelium to the passing topical agents may be limited, which represents a major drawback of the post-KSS intracavitary instillations. Nonetheless, various techniques have been proposed to deliver either BCG or Mitomycin C up to the ureter and pelvicaliceal cavities, including percutaneous nephrostomy for the anterograde approach, and retrograde catheterization or methods exploiting vesicoureteral reflux for the retrograde approach.

Anterograde Intracavitary Instillations

The most reliable method to access the upper urinary tract remains via a large nephrostomy tube (e.g., 10F) left in place after percutaneous resection of UTUC, or placed after any other KSS. This allows reliable and iterative exposure of the urothelium to the topical agent, without the need for further endoscopic procedures, given that the same nephrostomy tube can be reused for each instillation. Some authors have reported that such anterograde approach may optimize contact time of the agent with the upper urinary tract [11]. Despite its advantages, the main criticism of percutaneous intracavitary instillations is the theoretical risk of local tumour recurrence through tract seeding of cancer cells related to the signifi-

cant breach in integrity of the collecting system. However, this remains largely speculative, given that only two cases of tract seeding after percutaneous resection of UTUC without any adjuvant intracavitary instillation, have been reported in the literature [18, 19].

With regards to technical aspects, gravity is used to instil topical agents, which are linked to a manometer. Importantly, intrarenal pressure should be maintained <25 cmH_2O during the intracavitary instillation to avoid systemic absorption and potential sepsis, in particular with BCG [15]. In addition, for the same reasons, unobstructed flow of contrast medium from the renal pelvis to the bladder should be verified to exclude any pyelovenous or pyelolymphatic backflow using fluoroscopy before starting intracavitary instillations of topical agents.

Given that BCG is mostly used after KSS, Thalman et al. recently proposed a safe and reproducible protocol [20]. First, a dose of 360 mg Immun BCG Pasteur or 243 mg Immucyst should be dissolved in 150 mL 0.9% saline, which represents three times the dose and volume but the same concentration than that used in the bladder. Second, the flask should be placed 20 cm above the level of the kidney of the supine patient. Third, a continuous flow of approximately 1 mL per minute should be maintained for 2 hours. Forth, once perfusion is finished, the nephrostomy should be closed. Fifth, patients should receive ampicillin prophylactically and be kept under hospital surveillance for one night; sixth, BCG perfusion should be repeated on a weekly basis for 6 weeks (one treatment course). Finally, if cytology of the retrograde washout remains positive, a further treatment course should be initiated but if not the nephrostomy tube can be removed.

Retrograde Intracavitary Instillations

Given the development of small calibre flexible digital ureteroscopes, allowing easy inspection of the entire ureter and intrarenal collecting system, combined with effective ablative energy sources, the retrograde approach for KSS has received considerable interest in recent years. Thus, using the same retrograde approach, topical agents can be delivered 1) via a transvesical retrograde ureteric catheter or 2) using retrograde reflux from the bladder with an indwelling double-J stent.

Transvesical Retrograde Approach

Transvesical retrograde ureteric catheterization to administer topical agents in the upper urinary tract was first described by Patel et al. [21]. Commonly, a single-J stent can be placed through a retrograde access, with the proximal extremity positioned in the upper calyx. The distal extremity is then secured to the skin of the abdomen. These intracavatiary instillations are completed using gravity to flow topical agents in a retrograde fashion, maintaining a pressure of <20 cmH_2O to minimize pyelorenal reflux of BCG or mitomycin C.

Retrograde instillation of topical agents using a 5F open-ended ureteral catheter placed before each treatment has also been reported by some authors [10]. This may result in an increased risk of ureteral injury and patient discomfort as one cystoscopy per week with placement of a ureteral catheter should be performed each time. Nonetheless, it has shown to be safe and feasible in the outpatient setting.

Vesico-renal Reflux-Based Retrograde Approach

To minimize the risk of intracavitary overpressure, a passive vesico-renal reflux system can be created using an indwelling 6F or 7F double-J stent. This approach allows topical agents to be delivered into the bladder and passively refluxed into the upper urinary tract through the indwelling double-J stent.

With regards to technical aspects, a cystogram is performed while the patient is maintained in the Trendelenbourg position to determine the amount of fluid that is required to inject for clearly visualizing the entire ureter and intrarenal system (range 80–250 mL, median 120 mL) and so achieving

vesico-renal reflux [22]. After intravesical instillation of topical agents, the Trendelenbourg position is commonly held for 15–30 min, and voiding is obtained 30 min to 2 hours later. As for anterograde intracavitary instillations, a course of treatment with BCG involving weekly instillations for 6 weeks has been proposed [22]. After evaluation at the end of the treatment course, the indwelling double-J stent can be removed if cytology remains negative.

Nonetheless, the presence of an indwelling double-J stent does not guarantee vesico-renal reflux, given that only 59% of patients normally show contrast medium into the upper urinary tract after cystography [23]. In addition, the use of such technique for intracavitary instillations of topical agents showed short dwelling time, which may largely impact their efficacy [6]. Other limitations include (1) possible indwelling double-J stent obstruction – with subsequent risks of pyelovenous or pyelolymphatic backflow during instillation, (2) potential chronic injury of the pyelocaliceal mucosa related to the indwelling double-J stent – with subsequent risk of systemic dissemination and (3) difficulties to complete filling of the pyelocaliceal system using the indwelling double-J stent with superior calyx often remaining untreated.

Alternatively, bilateral meatotomies have been proposed to create vesico-renal reflux of topical agents [24]. As for the technique using indwelling double-J stent, vesico-renal reflux is confirmed using a cystography and required volume to fill the upper urinary tract is recorded before starting intracavitary instillations of topical agents. Then, the treatment protocol consists in performing instillations through the bladder for a total of 1 hour of dwelling time.

Comparative Efficacy of Instillation Techniques

Comparison of the efficacy of different instillation techniques is inherently challenging, given the scarcity of UTUC. Nonetheless, Pollard et al. evaluated the extent of upper urinary tract exposure to topical agents in in an *ex vivo* indigo carmine porcine model using the three aforementioned techniques including the antegrade approach with a nephrostomy tube and the retrograde approach with either an open-ended ureteral catheter or an indwelling double-J stent [25]. Overall, the mean percent surface area stained for the nephrostomy tube, double-J stent and open-ended ureteral catheter groups was 65.2%, 66.2% and 83.6%, respectively ($p = 0.002$). Thus, retrograde intracavitary instillations via an open-ended ureteral catheter may be the most efficient technique to deliver BCG o Mitomycin C up to the ureter and pelvicaliceal cavities, as confirmed by a second study published more recently [26].

Toxicity and Post-Instillation Management

Several different complications have been encountered with topical therapy, during both percutaneous and ureteroscopic resection, as well as during drug administration [6].

Post-instillation fever is by far the most common complication, with a reported incidence of up to 67% in percutaneous series.

Minor complications such as fever without infection and the presence of irritative voiding symptoms throughout the treatment period are more common. Colonisation of the nephrostomy tube with skin flora is also frequent.

Other common complications also include transient haematuria and irritative urinary symptoms, usually more frequent in patients receiving therapy by intravesical instillation (retrograde refluent). These symptoms are usually self-limiting, but may take several months to subside [27, 28]. Also common are infections due to *Escherichia coli* and *Candida albicans*, especially in patients with indwelling trans-vesical stents.

Evidences suggest that an overnight hospitalization helps preventing post-instillation complications.

BCG

Because of its mode of action, perfusion of BCG into the upper urinary tract by vesico-ureteral reflux has the potential to cause a strong immune reaction. Indeed, the antitumor effect of BCG occurs primarily through a local immunological reaction. Activation of an immune response is initiated by attachment of the vaccine to the tumour cells or the urothelium and the immune response develops rapidly due to the stimulation of mononuclear cells. It has been reported that the attachment of BCG to tumour cells and stimulation of mononuclear cells could occur within a short timeframe or even by mere contact.

Fever occurring in the post-instillation period is by far the most common adverse event. Although very rare, renal tuberculosis may also occur in patients treated with BCG.

However, fever in this setting does not always require anti-tubercular therapy. Broad-spectrum antibiotics are generally sufficient to resolve the fever.

Severe septicaemia secondary to BCG therapy is a very rare condition, with only four cases described to date. Interestingly, septicaemia was due to BCG in only two cases. In all four cases the anticancer treatment was stopped immediately [29].

MMC

MMC instillations showed reduced side effects compared to BCG. However, Aboumarzuk et al. [17] reported benign ureteric strictures in 3/20 of treated patients (15%) of their series. Those strictures were successfully treated during their ureteroscopic check and have not recurred since. In one case a significant long obstructing benign stricture, which lead to a nephroureterectomy due to the kidney being non-functioning on a renogram was observed. Two of the patients that developed strictures were also seen to have benign calcified debris attached on the wall of upper urinary tract. Patient who didn't tolerate instillation developed a renal stone stuck to the renal pelvis and lower calyx, successfully treated with Holmium: YAG laser 6 months after MMC instillation.

Both

A decrease in renal function and the onset of end-stage renal disease requiring haemodialysis is an infrequent but possible event, especially in patients where a kidney-sparing approach is imperative (impaired bilateral renal function, solitary kidney, etc.).

Keeping the patients in a hospital setting the night after the procedure has been shown to reduce the immediate post-therapy complications.

A cause of possible side effects is the risk of agent extravasation, especially when using an anterograde approach. This is due to the possible creation of uro-vascular fistulas when placing the nephrostomy tube. It is therefore advisable to rule out extravasation prior to the initiation of therapy. It may be advisable to start therapy, not at the same time as nephrostomy placement, but about 1 week later. Although less frequent, this complication may also occur during retrograde instillation, particularly when using transvesical catheters.

One final possible complication is linked to the catheter itself, which may become occluded, especially in the setting of retrograde refluent administration.

Defining and Evaluating Recurrence

The use of intracavitary therapy has routinely failed to give a robust therapeutic response compared to what happens in bladder cancer, irrespective of the agent used. The most robust evidence exists for BCG, particularly in the setting of CIS of the upper tract. However, even then, a lasting response is rare. Given that low-grade Ta tumours are ideal for endoscopic management and that intracavitary adjuvant therapy for papillary tumours appears to have decreased efficacy, it is still debatable whether intracavitary

therapy should be given routinely or not in patients after early recurrence-free resection. Conversely, this approach may be offered to patients with recurrence or in the presence of high-risk disease unwilling to undergo or unfit for radical nephroureterectomy, although the majority of these patients will benefit only from radical nephroureterectomy.

The ability to predict a patient's response to BCG would help in stratifying a patient to surgical or topical therapy management. Nunez-Nateras and colleagues [30] have assessed the immunologic microenvironment of bladder CIS prior to treatment to assess for response potential. Instillation of BCG creates an anti-neoplastic response by inciting a Th1 cytotoxic immune response [31]. A predominant Th1 versus Th2 response were significantly less likely to respond to BCG. Three markers that were able to identify BCG non-responders with a sensitivity of 100% and specificity for BCG responders of 80% were also identified [30]. Unfortunately this work was not replicated in UTUC [32].

Performing follow-up ureterorenoscopy using the same timing than that for cystoscopy in non-muscle invasive bladder cancer may help to detect early recurrence after KSS and intracavitary instillations of topical agents. Nonetheless, inflammation of the upper urinary tract related to the use of BCG or Mitomycin C could largely affect clinical decision making by creating pseudo-tumoral lesion mimicking local recurrence. Thus, additional information from biopsy and intracavitary cytology should be obtained to confirm a potential local recurrence. Interestingly, the introduction of promising technology such as Narrow-Band Imaging (NBI) or intraoperative microscopy (CellVizio®) in current clinical practice may provide even more reliable follow-up information, although the impact of intracavitary instillations of topical agents on their diagnostic performance remains unknown. It is noteworthy that, except for patients with imperative indications of KSS, early recurrence following the infusion of BCG or Mitomycin C in the upper urinary tract should be treated with radical nephroureterectomy [1].

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Novel Adjuvant Therapies for Upper Tract Urothelial Carcinoma After Endoscopic Management

Pranav Sharma and Philippe E. Spiess

Introduction

Upper tract urothelial carcinoma (UTUC) managed endoscopically has a high local recurrence rate of approximately 30–70%, but may be necessary in patients with imperative indications such as a solitary kidney, bilateral disease, significant perioperative risk, genetic predisposition (i.e., Lynch syndrome), or severe renal insufficiency [1]. It may also be considered in compliant patients with low-risk/low-grade UTUC who have a small, unifocal, papillary lesion <2 cm in size with no hydronephrosis or wall invasion seen on cross-sectional imaging as well as no high-grade features on urine cytology or biopsy [2].

Since the 3-year local recurrence rate within the upper urinary tract following endoscopic management is so high, the goal of adjuvant topical therapy is to decrease the risk of local recurrence during follow-up after complete endoscopic ablation/resection [3] (Fig. 37.1). Traditionally, adjuvant topical instillation following endoscopic treatment of UTUC includes Mitomycin C in low-/intermediate-risk disease or bacillus Calmette–Guérin (BCG) for high-risk/high-grade disease [4–6]. Data, however, supporting the heterogeneous application of nontraditional or novel agents as adjuvant therapy for UTUC after endoscopic management is growing and is summarized below.

Epirubicin and Pirarubicin

Older agents such as epirubicin and pirarubicin are both anthracyclines and topoisomerase inhibitors which interfere and inhibit deoxyribonucleic acid (DNA) replication and repair as well as ribonucleic acid (RNA) and protein synthesis [7]. Both may be utilized in an adjuvant setting to prevent recurrences after endoscopic management of UTUC. They can be administered within the upper urinary tract similar to chemotherapy (i.e., Mitomycin C) or BCG in a retrograde fashion with a ureteral stent in place or an antegrade fashion through a percutaneous nephrostomy tube. Both agents are dissolved in 0.9% normal saline (NS) for administration with the typical dose for epirubicin being 50 mg dissolved in 100 mL of saline while the dose for pirarubicin is 30 mg dissolved in 30 mL of saline [8]. Both can also be administered with a similar induction course to BCG (once weekly for 6 weeks) with maintenance given monthly with the medication being retained on average for 30 minutes to 1 hour prior to urinary drainage and/or urination.

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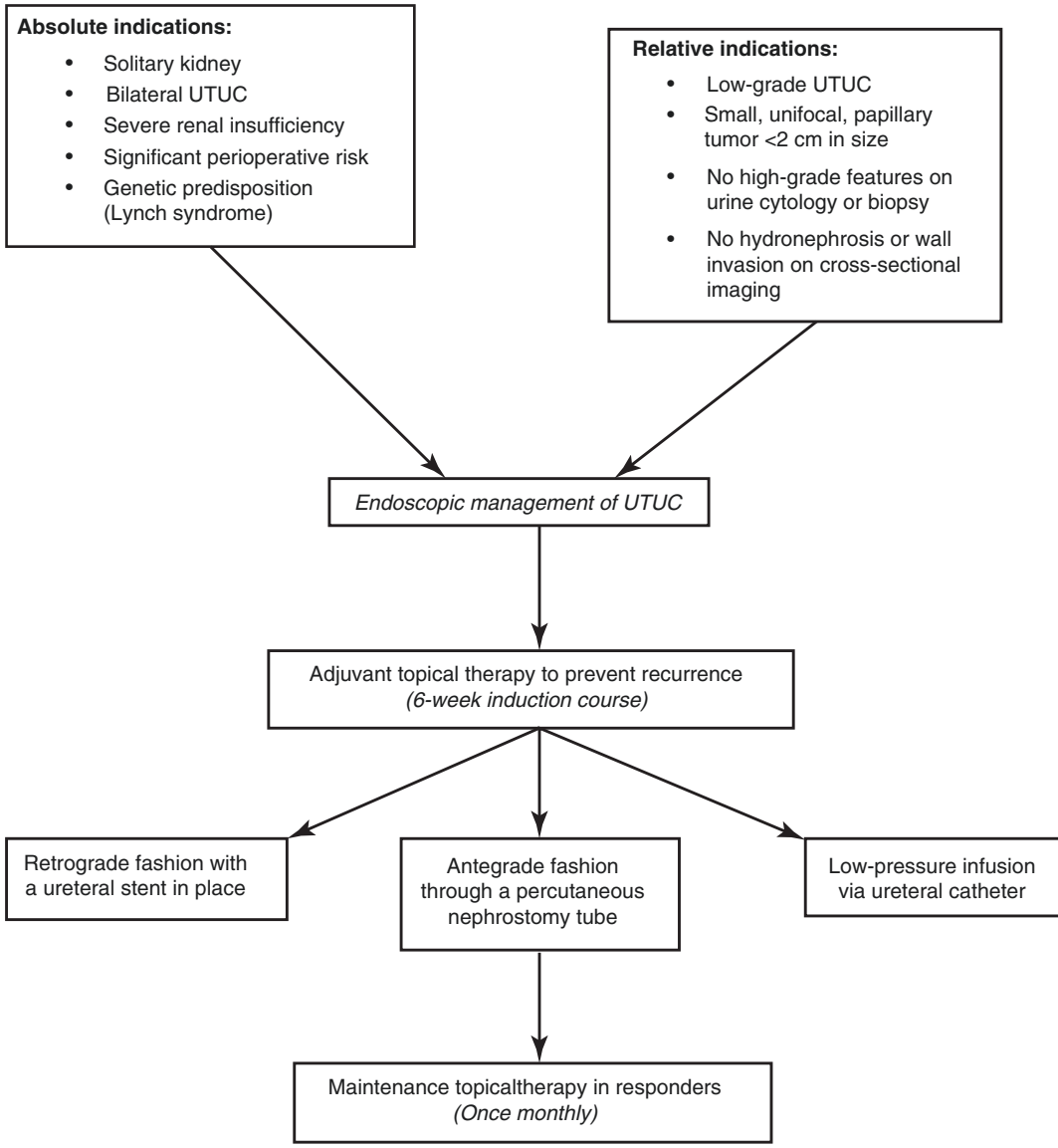

Fig. 37.1 Flow diagram of indications and technique for endoscopic management of UTUC

Toxicity and side effects from epirubicin and pirarubicin are limited and much reduced compared to BCG. The most common treatment-related toxicities include low-grade bladder symptoms such as urinary urgency, frequency, and dysuria, which are typically treated with anticholinergics and bladder analgesics [8]. In randomized trials of Ta or T1 bladder cancer patients reporting toxicity after intravesical therapy, BCG was associated with significantly more drug-induced cystitis [BCG: 54.1% (232/429) vs. epirubicin: 31.7% (140/441)] and hematuria [BCG: 30.8% (132/429) vs. epirubicin: 16.1% (71/440)] compared to epirubicin. Similarly, in studies reporting systemic toxicity, BCG had significantly higher toxicity than epirubicin [34.8% (134/385) vs. 1.3% (5/393), respectively]. In a meta-analysis comparing patients who had treatment delayed or stopped due to side effects, there was no significant difference between BCG and

epirubicin treatments [BCG: 40/431 (9.3%) vs. epirubicin: 33/441 (7.5%); $p = 0.82$]. Huang et al. reported that intravesical instillation of pirarubicin combined with hyaluronic acid after transurethral resection of bladder tumor (TURBT) in non-muscle-invasive bladder cancer patients resulted in more rapid and durable relief of pelvic pain and urinary symptoms such as urinary frequency, urgency, and dysuria with no difference in the observed recurrence rate at 2 years of follow-up [9].

Although there is limited data for both topical epirubicin and pirarubicin in the adjuvant setting to prevent recurrence after endoscopic management of low-grade UTUC or with solitary, low-risk upper tract tumors, both have shown some promise in the adjuvant setting at reducing recurrence rates for non-muscle-invasive urothelial carcinoma of the bladder, including both Ta and T1 lesions. In a Cochrane analysis, Shang et al. demonstrated a 51.4% (289/562) tumor recurrence rate after intravesical epirubicin in patients with Ta or T1 bladder cancer with a progression rate of 10.3% (58/562) and a metastases-free survival rate of 93.7% (464/495) [8]. When compared to intravesical BCG, however, epirubicin was less efficacious in reducing tumor recurrence for Ta and T1 bladder cancer. Rajala et al. and Gudjonsson et al. both studied and analyzed the long-term efficacy of a single, early (within 24 hours), intravesical instillation of epirubicin after TURBT for patients with Ta or T1 non-muscle-invasive bladder cancer [10, 11]. Rajala et al. reported a 6-year recurrence rate of 46% with 100 mg of intravesical epirubicin (compared to 73% with TURBT alone) [11], and Gudjonsoon et al. reported a 62% recurrence rate at median follow-up of 3.9 years with 80 mg of epirubicin in 50 ml of saline intravesically (compared to 77% with TURBT alone) [10]. Early instillation of epirubicin decreased the risk of recurrence by half (hazard ratio [HR] = 0.56), and the most profound recurrence-reducing effect was on patients with primary, solitary tumors compared to multifocal, recurrent tumors. Berrum-Svennung et al. also confirmed that a single instillation of 50 mg epirubicin after TURBT resulted in a 51% long-term recurrence rate, which was better than placebo (62.5%; $p = 0.04$), but only small recurrences are prevented with larger (more than 5 mm) first recurrences more common in the epirubicin arm versus placebo (42.9% vs. 31.5%; $p = 0.12$) [12].

Okamura et al. determined whether a single instillation of pirarubicin immediately after TURBT is beneficial to patients with Ta or T1 bladder cancer and a single, resectable, superficial bladder tumor [13]. Pirarubicin was administered into the bladder within 6 hours after TURBT at a dose of 30 mg in 30 mL of NS. At median follow-up of 40.8 months, the 1-, 2-, and 3-year recurrence-free survival rate in the pirarubicin group was 92.4%, 82.7%, and 78.8%, respectively, compared to 67.0%, 55.7%, and 52.6%, respectively, in the control group ($p = 0.0026$). The recurrence rate per year was significantly lower in the pirarubicin group compared to the control group (0.11 vs. 0.24; $p = 0.007$). Finally, Ito et al. evaluated the efficacy of a single early (within 48 hours) intravesical instillation of pirarubicin in the prevention of bladder tumor recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma in a prospective clinical trial of 77 patients randomly assigned to treatment versus control [14]. Median follow-up was 24.9 months. Significantly fewer patients who received pirarubicin within 48 hours after nephroureterectomy had a bladder tumor recurrence compared with the control group (1-year recurrence rate: 16.9% in the pirarubicin group compared to 31.8% in the control group; 2-year recurrence rate: 16.9% in the pirarubicin group compared to 42.2% in the control group; $p = 0.025$). No significant adverse events were observed in the pirarubicin-treated group, and based on multivariate analysis, postoperative pirarubicin intravesical instillation was independently associated with a reduced incidence of bladder tumor recurrence during follow-up (HR = 0.26; 95% CI: 0.07–0.91; $p = 0.035$). Another phase III clinical trial in this regard is being planned [15].

As can be seen from the literature above, studies are still lacking for epirubicin and pirarubicin in the adjuvant setting to prevent recurrences

after endoscopic management of UTUC, but preliminary results demonstrating efficacy after TURBT for non-muscle-invasive bladder cancer and after nephroureterectomy to prevent bladder tumor recurrence are promising enough to consider testing their use as a topical prophylactic agent in the adjuvant setting to prevent tumor recurrence after endoscopic management of select UTUC patients.

Thiotepa

Another older agent that has limited data in the adjuvant setting to prevent recurrence after endoscopic management of low-risk UTUC but has some preliminary results in the adjuvant setting at reducing recurrence rates for non-muscle-invasive urothelial carcinoma of the bladder is thiotepa. Thiotepa is an alkylating agent that may be used to prevent recurrence and seeding of tumor cells after TURBT or after endoscopic resection/ablation of UTUC [16]. For use within the urinary tract, thiotepa is given in 30 mg doses weekly diluted in 50 ml of saline for a 4–6-week induction course. Similar to other intravesical agents, it may be administered within the upper urinary in a retrograde fashion with a ureteral stent in place or an antegrade fashion through a percutaneous nephrostomy tube. Toxicity is more significant compared to other agents with risk of bone marrow suppression due to systemic absorption of the drug resulting in leukopenia, thrombocytopenia, and anemia. Occasionally, this requires cessation of thiotepa intravesical therapy and possible transfusion of red cells, white cells, or platelets until blood counts can rebound.

The Medical Research Council Working Party on Urological Cancer conducted a multicenter, randomized trial to determine the role of intravesical instillation of thiotepa in the adjuvant setting after resection of newly diagnosed non-muscle-invasive urothelial carcinoma of the bladder [17]. After TURBT, 30 mg thiotepa in 50 ml saline was administered intravesically as a one-time instillation or at 3-monthly intervals for 1 year (for a total of five instillations) compared to placebo in 417 patients with newly diagnosed superficial bladder cancer. At median follow-up of 8.75 years, there was no significant difference between all three groups with respect to time to first recurrence, overall recurrence rate, or progression rate. Thiotepa, therefore, should not be used outside of a clinical trial as a topical agent in the adjuvant setting in the treatment of urothelial carcinoma of the upper or lower urinary tract managed endoscopically to prevent recurrence.

Gemcitabine

Gemcitabine has grown as a desired intravesical agent in the adjuvant setting to minimize recurrences after endoscopic treatment of urothelial carcinoma. The typical dose is 2 gm gemcitabine mixed in 50 or 100 cc NS administered intravesically weekly for a 6-week induction course and then monthly for maintenance. Administration is similar to the other topical agents noted above. It is generally well tolerated with the majority of toxicity being low-grade (grade 1 or 2) related to irritation of the urinary tract (primarily dysuria and urinary frequency). No apparent increase in toxicity is observed with an increased number of treatments with most patients able to complete at least one full induction course. Prasanna et al. in fact reported significantly less AEs with gemcitabine compared to BCG (7% vs. 44%, $p < 0.05$) with improved disease-free survival (HR = 0.49) [18]. A further trial comparing gemcitabine with intravesical mitomycin C reported that the rates of recurrence (28% vs. 39%) and progression (11% vs. 18%) were lower with gemcitabine, and the overall incidence of AEs was significantly less with gemcitabine (38.8% vs. 72.2%) [19].

Although there is limited data for topical gemcitabine in the adjuvant setting to prevent recurrence after endoscopic management of UTUC, it has been extensively tested in the adjuvant setting at reducing recurrence rates for non-muscle-invasive urothelial carcinoma of the bladder, both as an induction and maintenance regimen and as a single postoperative dose after TURBT. A sys-

tematic review by Shelley et al. showed that gemcitabine and BCG were similar with respective recurrence rates of 25% and 30% in untreated patients at intermediate risk of recurrence (primary Ta–T1, no carcinoma in situ [CIS]) but dysuria (12.5% vs. 45%) and frequency (10% vs. 45%) were significantly less with gemcitabine [20]. In untreated, high-risk patients, the recurrence rate was significantly greater with gemcitabine compared with BCG (53.1% vs. 28.1%) and the time to recurrence was significantly shorter with gemcitabine (25.5 vs. 39.4 months). In high-risk patients who had failed previous intravesical BCG therapy, gemcitabine was associated with significantly fewer recurrences (52.5% vs. 87.5%) and a longer time to recurrence (3.9 vs. 3.1 months) compared with BCG with similar progression rates in both groups (33% vs. 37.5%).

In a phase II trial of 58 patients with recurrent non-muscle-invasive bladder cancer stage Tis (CIS), T1, Ta high-grade, or multifocal Ta low-grade who failed at least two prior courses of BCG, the 1-year and 2-year recurrence-free rate after induction and maintenance intravesical gemcitabine was 28% and 21%, respectively [21]. Sternberg et al. reported a CR rate of 39% (27/69) at median follow-up of 3 years in a similar population but no difference in progression-free, cancer-specific, or overall survival (OS) in responders compared to non-responders [22]. Similar results have been seen in other trials using intravesical gemcitabine in combination with mitomycin C or BCG in the pretreated superficial bladder cancer population [23–25]. Finally, Messing et al. conducted a randomized, double-blind clinical trial in patients with suspected low-grade non-muscle-invasive urothelial cancer to receive postoperative intravesical instillation of gemcitabine (2 gm in 100 mL of saline) versus placebo (100 mL of saline) 1 hour immediately following TURBT. The 4-year estimated recurrence rate was 35% in the gemcitabine group compared to 54% in the placebo group, but progression-free and OS were similar [26]. There were no grade 4 or 5 AEs in either group and no significant differences in AEs of grade 3 or lower.

As can be seen from the aforementioned literature, studies are still lacking for gemcitabine in the adjuvant setting to prevent recurrences after endoscopically managed UTUC, but results demonstrating some response at reducing recurrence rates in the treatment-naïve as well as pretreated non-muscle-invasive bladder cancer population are promising enough to consider testing its use as a topical prophylactic agent in the adjuvant setting to prevent tumor recurrence after endoscopic management of select UTUC patients. A clinical trial in this regard would provide further evidence to substantiate its use in the adjuvant setting for UTUC after endoscopic management.

BCG Combination Agents

Combination agents of BCG with interferon are growing as a potential adjuvant agent to prevent recurrence after endoscopically managed UTUC. This is based on prior literature demonstrating preliminary efficacy in the non-muscle-invasive bladder cancer population in the adjuvant setting to prevent recurrence. Hemdan et al. reported a 5-year recurrent-free survival rate of 38%, progression-free survival rate of 78%, and cancer-specific survival (CSS) rate of 90% of combination intravesical BCG with epirubicin and interferon-α2b in the treatment of 250 patients with T1 bladder cancer after complete and restaging TURBT [27]. Tumor size and tumor status at second resection were independent variables associated with recurrence.

Unlike the other agents listed above, combination agents of BCG and interferon have been tested in the adjuvant setting to prevent recurrences after endoscopic management of UTUC with some reported complete response (CR) rates. Katz et al. analyzed 10 patients (11 renal units) between 2000 and 2006 with UTUC who received adjuvant BCG and interferon-α2b after complete or partial endoscopic ablation of all papillary lesions [28]. Half-strength BCG + 50 million units of interferon was infused under low pressure for 1 hour per a 5Fr ureteral catheter placed in the appropriate renal collecting system

in the office. The ureteral catheter was then removed, and patients were instructed to void 1 hour later. Unlike other mechanisms of delivery, including percutaneous administration through a nephrostomy tube or reflux via double pigtail stents, this office-based technique spared the morbidity of a chronically indwelling nephrostomy tube or ureteral stent. A 6-week induction course was completed in all patients with a follow-up ureteroscopy with or without biopsy performed to evaluate response. Complete responders were then placed on a maintenance regimen. At median follow-up of 24 months, eight patients (80%) demonstrated a CR to therapy, and two patients (20%) had a partial response (decrease in tumor size, number, or both) during follow-up. Six patients (60%) with a CR continued on maintenance therapy, and there were no side effects or complications with the instillation therapy.

Shapiro et al. also reported on 11 patients with isolated, biopsy-proven upper tract CIS from September 2003 to January 2012 treated with a 6-week induction course of adjuvant BCG and interferon-α2b [29]. Patients were administered therapy similarly via a 1-hour infusion through an open-ended ureteral catheter and dose was half-strength BCG + 50 million units of interferon. Follow-up at 1 month after completion of intrarenal therapy consisted of flexible ureteroscopy, selective urinary cytology, retrograde pyelography, and rebiopsy of the upper tract. CR was defined as the absence of visualized lesions on ureteroscopy, negative selective cytology results, and absence of clinical progression. Absence of visualized lesions with persistently positive urine cytology results or persistence of lesions after induction therapy was considered no response (NR). New upper-tract lesions after an initial CR were considered recurrences. Patients with a CR were placed on maintenance therapy for 2 years, and surveillance was performed every 3 months with ureteroscopy, selective urine cytology, and imaging. At median follow-up on 13.5 months, eight (73%) patients had an initial CR, while three (27%) initially had NR. Two of the NR patients had negative biopsy results but persistently positive urine cytology results, and both of these patients underwent a second 6-week induction course of BCG and interferon-α2b and achieved a CR. The third NR patient had persistence of lesions after induction therapy and underwent a nephroureterectomy resulting in a total kidney preservation rate of 91% (10/11). There were no treatment-related adverse events to the 6-week induction course of BCG and interferon-α2b.

Although interferon-α2b (IFN-α2b) as an immunoagent is a logical next step for adjuvant therapy to prevent recurrences in endoscopically managed urothelial carcinoma, it is often ineffective due to short exposure to the urothelium. Intravesical IFN-α2b gene delivery offers a novel approach and increases the duration of exposure to IFN-α2b [30]. Recombinant adenovirus (rAd)–IFN-α2b is a replication-deficient adenovirus-based gene transfer vector that encodes the human IFN-α2b gene [31]. Syn3, a polyamide surfactant, is incorporated into the drug formulation (rAd–IFN-α2b/Syn3) to enhance adenoviral transduction of the bladder lining [32]. Dramatic enrichment of rAd–IFN-α2b gene transfer and expression has been shown with Syn3 in both normal urothelium and human urothelial carcinoma that grows in mice [33]. RAd–IFNα-2b gene therapy mimics the physiologic events associated with viral infection, which results in local rather than systemic rAd–IFN-α2b production and subsequent tumor regression.

Based on a phase I study showing a 43% response rate in BCG-refractory, high-grade, non-muscle-invasive urothelial carcinoma of the bladder [34], a phase II study in 43 patients with BCG refractory or relapsed high-grade, non-muscle-invasive urothelial carcinoma of the bladder was conducted with intravesical rAd–IFN-α2b/Syn3 through a urethral catheter with a planned retention time of 1 hour. [35] Low-dose (1×10^{11} viral particles [vp]/mL) or high-dose (3×10^{11} vp/mL) was given. Overall, 35.0% of patients ($n = 14$) remained free of high-grade recurrence at 12 months after the initiation of rAd–IFN-α2b/Syn3 treatment. Median time to recurrence was 6.5 months, which was significantly longer in the high-dose group

(11.73 months) compared to the low-dose group (3.52 months). The majority of patients remained disease-free for close to 24 months with a 30% durable CR for patients with any element of CIS and 50% for patients with papillary disease only at study entry. The most frequently reported drug-related adverse events (AEs) were micturition urgency in 16 patients (40%), dysuria in 16 patients (40%), fatigue in 13 patients (32.5%), pollakiuria in 11 patients (28%), and hematuria and nocturia in 10 patients each (25% each). Notably, for the majority of patients (78%), the AEs were transient and classified as either grade 1 or 2. There was no significant difference in the initial occurrence of AEs in those who received the low dose or high dose of rAd–IFN-α2b/Syn3. Based on these results in the BCG-refractory/relapsing population of patients with superficial bladder cancer, intravesical rAd–IFN-α2b/Syn3 could possibly play a role in the adjuvant setting as a topical agent to prevent recurrences after endoscopic management of UTUC but further trials are needed for confirmation.

As noted from the aforementioned studies of adjuvant BCG combination agents in both non-muscle-invasive bladder cancer and UTUC to prevent recurrence, most of the literature is single-institutional with small sample size of highly selected patients. Few studies have a control group for comparison, especially in the UTUC population. A phase III study is being conducted on intravesical rAd–IFN-α2b/Syn3 in the BCG-refractory, high-grade, non-muscle-invasive bladder cancer population, but adjuvant trials for alternative topical agents to reduce the recurrent rate after endoscopic management of UTUC are limited with most trials focusing on BCG or Mitomycin C chemotherapy (i.e., Mitogel). Immunotherapy, however, will continue to play a prominent role in the future in urothelial carcinoma of the upper tract, especially in combination with BCG to enhance its effects. As drug delivery of immunotherapy improves, further testing of topical BCG combination agents in the adjuvant setting to prevent recurrence after endoscopically managed UTUC will evolve.

Checkpoint Inhibitors

Checkpoint inhibitors have exploded onto the oncology setting in the treatment of locally advanced and metastatic genitourinary malignancies in the chemo-refractory or chemo-ineligible population. Currently approved checkpoint inhibitors block CTLA4 and PD-1 and PD-L1, proteins that stop the immune system (i.e., T cells) from attacking the cancer cells.

Blocking the PD-1 checkpoint or its ligand PD-L1 has revolutionized the management of patients with metastatic urothelial carcinoma. The phase II KEYNOTE-052 trial studied pembrolizumab as first-line treatment for 370 cisplatin-ineligible patients with metastatic urothelial carcinoma with a 24% overall response rate [36]. A PD-L1-expression cutoff of 10% was associated with a higher frequency of response to pembrolizumab. Similar results with pembrolizumab were seen in patients with locally advanced or metastatic urothelial carcinoma who had progressed following treatment with platinum-based chemotherapy [37]. In the phase II IMvigor210 trial, 119 patients with locally advanced or metastatic urothelial cancer who were cisplatin-ineligible received atezolizumab as first-line treatment with a 23% overall response rate and 9% complete response rate at 17.2 months median follow-up [38]. Tumor mutational load was associated with response. Similar results with atezolizumab were seen in patients with locally advanced or metastatic urothelial carcinoma who had progressed following treatment with platinum-based chemotherapy [39]. Finally, in a phase III randomized control trial (IMvigor211) of 931 patients with locally advanced or metastatic urothelial carcinoma who had progressed after platinum-based chemotherapy randomized to atezolizumab or physician's choice chemotherapy, atezolizumab was not associated with significantly longer OS than chemotherapy in patients with platinum-refractory metastatic urothelial carcinoma overexpressing PD-L1 [40]. The safety profile, however, for atezolizumab was more favorable compared with further chemotherapy.

Table 37.1 Clinical outcomes of adjuvant BCG + interferon in endoscopically managed UTUC

Study	N	Dosage	Administration	Follow-up	Complete response rate
Katz et al. [28]	10	Half-strength BCG + 50 million units of interferon	Infused for 1 hour per a 5Fr ureteral catheter (6-week induction course)	24 months	80% (8/10 patients)
Shapiro et al. [29]	11	Half-strength BCG + 50 million units of interferon	Infused for 1 hour per a 5Fr ureteral catheter (6-week induction course)	13.5 months	73% (8/11 patients)

Ipilimumab is an anti-CTLA-4 monoclonal antibody that has been tested in urothelial cancer. Carthon et al. treated 12 patients with localized disease with anti-CTLA-4 therapy prior to undergoing cystectomy with eight patients having a lower stage of disease on their surgical specimen [41]. These data suggest that CTLA-4 blockade leads to a therapeutic effect in urothelial cancer with several ongoing efforts to combine CTLA-4 blockade with PD-1/PD-L1 blockade.

Use of checkpoint blockade has also expanded in urothelial carcinoma to the role of neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma with a complete response rate (i.e., pT0) of 42% (21/50 patients) and downstaging to pT < 2 of 54% (27/50 patients) [42]. Phase II trials of pembrolizumab and atezolizumab in BCG-unresponsive non-muscle-invasive bladder cancer are currently ongoing based on preliminary favorable results in mouse bladder cancer models [43].

Although there is a surplus of recent evidence evaluating checkpoint blockade in cisplatin-ineligible or chemo-refractory locally advanced or metastatic urothelial cancer as well as in the adjuvant setting for BCG-refractory non-muscle-invasive disease, the response rate is not defined for immune checkpoint inhibitors in patients with UTUC, especially in the adjuvant setting to prevent recurrence after endoscopic management of UTUC. Most patients should be considered for treatment with these agents after platinum failure initially, but expansion as a systemic agent to prevent recurrence after endoscopic treatment, especially in a BCG-unresponsive setting after failed topical therapy, is inevitable.

Conclusions

As can be noted from the above alternative "novel" agents and prior literature, most have not been tested in the adjuvant setting after endoscopic management of UTUC except for combination agents of BCG and interferon (Table 37.1). Most of the data is extrapolated from the non-muscle-invasive bladder urothelial carcinoma population that would suggest these agents may be useful for the adjuvant indication in endoscopically managed UTUC. Even the dosing is extrapolated from non-muscle-invasive bladder cancer studies. Futures trials, however, could focus on testing these unique agents as topical therapy to prevent recurrence after endoscopic management of UTUC and would add to the armamentarium in this unique patient cohort for renal preservation.

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Nephroureterectomy for Upper Tract Urothelial Carcinoma: Indications and Technique

Vitaly Margulis, Rashed A. Ghandour, and Nirmish Singla

Introduction

Upper tract urothelial carcinoma (UTUC) comprises 5–10% of urothelial tumors [1, 2]. UTUC tumors are located in the renal pelvis approximately twice as often as in the ureter and are multifocal in 10–20% of cases [3, 4]. Nearly 60% of UTUC tumors are locally invasive at diagnosis, with regional metastases present in 25% of patients [5]. Unfortunately, high-level evidence regarding the management of UTUC is limited given the rarity of this disease [1], and many management principles from studies of urothelial carcinoma of the bladder are applied to UTUC, despite increasing evidence suggesting disparate diseases [6–8].

The current gold standard treatment of UTUC remains radical nephroureterectomy (RNU) with bladder cuff excision [1], though the utilization of partial/distal ureterectomy, endoscopic ablation, and other nephron-sparing approaches has been increasing to minimize morbidity related to renal functional compromise while maintaining oncologic efficacy. In this chapter, we focus specifically on RNU, including indications for RNU, preparation for surgery, intraoperative techniques, management of common complications, and related considerations. We focus largely on our institutional approach and supplement our discussion with relevant contemporary evidence supporting our practice. While we also offer renal-sparing approaches in appropriately selected patients, discussion of such approaches is beyond the scope of the present chapter.

Indications and Preparation for RNU

With diagnostic suspicion for urothelial carcinoma (e.g., hematuria, flank plain, or an incidental renal or ureteral mass), we typically pursue cross-sectional imaging with excretory urography to completely assess the kidneys and ureters. Computed tomography urography (CTU) is our preferred imaging modality given its superior sensitivity and specificity for detecting UTUC [1, 9], though in patients with contraindications to receive intravenous iodinated contrast, magnetic resonance urography (MRU) or retrograde pyelography with non-contrast-enhanced cross-sectional imaging of the urinary tracts is an acceptable alternative. To confirm urothelial carcinoma pathologically, we obtain tissue biopsies preferably via flexible ureteroscopy (which further enables endoscopic evaluation of the bladder to rule out concomitant bladder cancer, present in approximately 20% of UTUC cases [3], and complete visual evaluation of the renal pelvis and ureter), though percutaneous biopsies are

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occasionally utilized. Biopsies provide important pathologic information including tumor grade, architecture, and location, which are critical in selecting patients for presurgical chemotherapy and for nephron-sparing options. Although the sensitivity of urinary cytology is limited for UTUC [10], we often obtain urinary cytology washings from either the suspicious side alone or bilaterally. Once the diagnosis of UTUC is confirmed, we complete the clinical staging work-up with chest CT and laboratory evaluation (comprehensive metabolic profile, complete blood count).

Although the local staging of UTUC tumors endoscopically is notoriously difficult due to limited tissue acquisition and risks of perforation with deeper biopsies, ureteroscopic biopsy grade has relatively better concordance with final pathologic grade [11, 12]. We have developed [13] and recently refined [14] preoperative models to accurately predict high-risk, non-organ-confined disease using multiplex variables. In general, in nonmetastatic patients without precluding medical comorbidities, we offer RNU to patients based on a combination of factors largely driven by tumor location, focality, and grade. While we reserve distal ureterectomy for unifocal/limited involvement of the distal ureter regardless of grade, we resort to RNU if there is involvement of the proximal ureter and/or renal pelvis with high-grade or infiltrative disease, multifocal disease, or high-volume low-risk disease not amenable to endoscopic ablation. While we certainly exercise caution with RNU in patients with functionally solitary kidneys that are affected, the risk of pursuing an oncologically inferior operation must be weighed against renal functional preservation. Prior to pursuing RNU in any patient, the risks of progressive renal function deterioration and possible need for dialysis must be discussed thoroughly, along with the perioperative risks of surgical intervention.

Given the risk of local understaging from biopsy alone and the loss of renal function after RNU that may preclude the adjuvant receipt of nephrotoxic chemotherapy [15–18], we have a low threshold to administer cisplatin-based neoadjuvant chemotherapy (NAC) before RNU in patients with adequate renal function, especially in those with high-risk features (e.g., high-grade tumors on biopsy, hydronephrosis, radiographic infiltration), and we recently presented the results of a phase II trial demonstrating efficacy of NAC before RNU for high-grade UTUC (NCT02412670) [19]. Our preferred NAC regimens include either gemcitabine and cisplatin (GC) or accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (aMVAC), and we generally try to pursue RNU 1 month after completion of NAC to allow sufficient recovery from chemotherapy, with restaging imaging performed prior to surgery. In parallel, should the patient have extensive medical comorbidities or deconditioning, consultation with an appropriate specialist (e.g., cardiology, pulmonology) can be helpful in optimizing the patient's general health in anticipation of surgery. In patients who are not cisplatin-eligible due to poor renal function, we proceed directly to RNU rather than pursue carboplatin-containing regimens, which may unduly delay effective treatment.

Surgical Technique

Approach

Preoperative review of the patient anatomy by the operating surgeon—both physically and radiographically—is critical. Any anomalies or duplications, including duplicated renal vessels or collecting systems, must be anticipated prior to entering the operating theater. Oncologic principles must be followed throughout the operation [5], including avoidance of entry into the urinary tract to prevent tumor seeding, early clipping of the ureter to limit antegrade seeding of tumor cells into the bladder during renal and ureteral manipulation, and removal of the specimen (kidney, ureter, and bladder cuff) *en bloc*.

In the operating room, after anesthetic induction and intubation, it is our practice to instill mitomycin C (MMC) intravesically and clamp the catheter for 1 hour to reduce the risk of intravesical recurrence. This practice is based on randomized prospective evidence demonstrating that a single dose of intravesical chemotherapy (MMC or pirarubicin) within 72 hours of surgery

can significantly reduce the risk of intravesical recurrence within the first year after surgery [20–23]. Despite this data, the actuarial utilization of postoperative MMC is low (51%), however [24]. Although the initial trials investigated the use of the intravesical agents in the postoperative setting, we generally perform the instillation intraoperatively, immediately prior to commencing surgery. We sterilely prepare the catheter into the surgical field and drain the MMC 1 hour into the operation (before making a cystotomy) to prevent escape of MMC into the intraperitoneal space. This approach necessitates the exchange for a fresh catheter at the conclusion of the case.

We have increasingly used minimally invasive (MIS) approaches (conventional laparoscopy or robot-assisted) to RNU, even for invasive or large tumors. Multiple studies, including a randomized control trial of laparoscopic versus open RNU [25], have revealed oncologically similar outcomes between MIS and open approaches, with less morbidity using MIS [25–29]. In very few instances would we opt for an open approach—namely situations in which certain factors would preclude performing MIS safely. A preoperative assessment of a patient's cardiopulmonary reserve to tolerate insufflation in a lateral decubitus position for a prolonged period of time is mandatory. Furthermore, extensive prior surgical history can amount to considerable intraperitoneal scarring or adhesions that may increase the technical difficulty of MIS. When we perform an open RNU, our preference is to position the patient supine and employ a midline approach in order to gain access to both the renal hilum and the ureterovesical junction via a single incision. The specimen can then be extracted through the same incision. For the present chapter, we will largely focus our discussion on our preferred approach using robotic assistance.

In the MIS approach, the patient is positioned in a modified lateral decubitus position with the affected side presented and the ipsilateral arm secured across the chest. Sterile access to the catheter is preferred. The operating table is flexed at the level of the umbilicus. Insufflation to 15 mmHg can be achieved using a Veress needle inserted into the intraperitoneal space via the umbilicus, though in more obese patients, we prefer to insufflate and shift all trocars more laterally. Trocars are inserted with the patient rotated 17 degrees toward the operator to minimize interference from intraperitoneal contents. In the conventional laparoscopic approach, our port sites mimic those used in a standard laparoscopic radical nephrectomy, and distal dissection of the ureter and bladder cuff can be achieved via a Gibson incision. In the robotic approach, we utilize a fourth robotic arm that can be placed either near the anterior superior iliac spine or toward the midline. The use of a second assist port can be helpful for the distal dissection. When operating on the right kidney, we use an additional liver retractor cranially.

We begin by releasing any adhesions and reflect the bowel medially to expose the kidney. We identify the ureter and apply at least two clips to prevent antegrade seeding of tumor cells during manipulation without dividing the ureter. The remainder of the nephrectomy portion proceeds in a fashion typical of minimally invasive radical nephrectomy, with the caveat that the ureter is never divided, and the adrenal gland is spared nearly routinely. We develop the posterior plane of the kidney and use an endovascular stapler to divide the renal hilum. We recommend judicious use of clips around the hilum so as not to impede the stapler. Stapling flush with the great vessels is also important to ensure removal of lymphatic tissue if this is necessary. Following this, the superior and lateral dissections are completed, and the tail of Gerota's fascia is divided (either stapled or cauterized) so the kidney is tethered by only the ureter. We generally perform a templated lymph node dissection (LND) at this stage and submit the ipsilateral retroperitoneal lymph nodes as a separate specimen (refer to section below). We continue our dissection caudally by circumferentially dissecting and tracing the ureter as it enters into the pelvis. During this step (and during the dissection of the lower renal pole, particularly for larger kidneys), it is critical to be wary of the location of the common iliac vessels. As the ureter crosses directly anteriorly to these vessels before entering the pelvis, careless dissection may result in a serious vascular injury.

Once the ureter is dissected as caudally as possible, the robot will usually need to be

undocked, adjusted (rotated), and redocked in order to access the deeper pelvis. One of the benefits of using the Intuitive da Vinci® Xi™ robot for this operation compared to the Si™ robot is the increased range of motion that enables the overhead boom to be simply rotated and reengaged. The Si™ robot, in contrast, typically requires readjustment of the angle at which it contacts the operating table in order to optimize pelvic access. On redocking the robotic arms, the prior trocars may be usable depending on their location and the patient's body habitus; however, if reusing the original trocars amounts to excessive struggle in the pelvis, then we maintain a low threshold to insert an extra trocar if needed. We routinely excise a segment of the bladder cuff together with the ureter and close the cystotomy in two layers (refer to section below for technical considerations). Once the kidney, ureter, and bladder cuff are completely detached *en bloc*, they are immediately placed in a specimen pouch.

For extraction, we often extend one of the caudal trocar incisions in manner akin to a Gibson incision. As postoperative pain may be exacerbated by muscle splitting and as transection of the epigastric vessels is possible with a Gibson incision, we occasionally make a separate low midline incision for extraction, though extension of a lower quadrant port site avoids the need for an extra incision. Following extraction, we close the fascia of the extraction site using a running No. 1 polydioxanone (PDS) suture. The laparoscopic camera is then reinserted and the abdomen reinsufflated to visually ensure that no bowel is tethered to the incision closure and to evaluate the renal fossa and adjacent organs for bleeding. A Jackson–Pratt (JP) drain is positioned in the pelvis near the cystorrhaphy, the trocars are removed under direct visualization, the incisions are reapproximated, and the procedure terminated.

Management of the Bladder Cuff

Excision of the bladder cuff at the time of RNU is considered the gold standard [1], and our institutional series [30] among others [31] has shown a decreased rate of intravesical recurrence with bladder cuff excision at RNU. Thus, our practice is to excise the bladder cuff routinely, and utilization of this practice is increasing according to a recent study of the Surveillance, Epidemiology, and End Results (SEER) database [32]. We recommend dividing the ipsilateral medial umbilical ligament and dropping the ipsilateral side of the bladder to facilitate dissection of the distalmost segment of the ureter. Filling the bladder with saline can also be helpful in delineating anatomy and confirming entry into the bladder. Prior to making a cystotomy, it is important to circumferentially dissect around the distal ureter through the perivesical fat until the detrusor muscle and ureteral hiatus are definitively evident, with a small margin of detrusor cleared of fat to facilitate reconstruction during cystorrhaphy. It is also important to verify that there is no MMC remaining in the bladder. Once the hiatus is clearly demarcated, a cystotomy can be made, ensuring a small margin of bladder mucosa is continuous with the ureteral specimen. Prior to separating the ureter entirely, we find that placing a barbed suture (e.g., 2-0 V-Loc™) at the apex of the cystotomy will help maintain tension for closure. The remainder of the ureter with its bladder cuff is then divided and placed in the specimen collection bag *en bloc* with the kidney. Of note, in cases of distal ureteral tumors, we may consider applying a laparoscopic Satinsky clamp around the bladder cuff and excising distal to the clamp to prevent spillage of tumor from the ureter. The cystorrhaphy is then completed in two layers, with care not to obliterate the contralateral ureteral orifice with the suture. It is also important to visualize and incorporate the bladder mucosa in the inner closure to avoid a leak from the bladder repair. We then test the closure with intravesical instillation of sterile saline (usually 120–180 cc is sufficient) and leave a JP drain in the pelvis at the conclusion of the case. If intravesical MMC was administered at the beginning of the case, as is our routine practice, we also ensure that a new catheter is replaced.

Management of Lymph Nodes

Although the role for routine LND in managing UTUC has not been definitively established [1], we frequently perform concomitant LND during RNU, especially for high-risk disease or poor prognostic features. When performing LND, we prefer a templated approach over a "plucking" approach [33, 34]. The template we use is contingent on tumor location and the presence of lymphadenopathy. Typically for right renal pelvic, proximal, and mid-ureteral tumors, we remove the ipsilateral hilar, paracaval, retrocaval, and inter-aortocaval nodes. For left renal pelvic, proximal, and mid-ureteral tumors, we remove the ipsilateral hilar and para-aortic nodes. For more distal ureteral tumors, we will consider removing the ipsilateral common iliac, external iliac, internal iliac, and obturator nodes. More extensive LND increases the risk of lymphoceles and chylous ascites, especially on the left side given the location of the cisterna chyli; hence, we recommend liberal use of clips and bipolar cautery during LND.

Management of Common Complications

In line with our enhanced recovery after surgery protocol, our routine postoperative management after RNU entails the judicious use of intravenous fluids, minimization of narcotics, early ambulation, and early advancement of diet (clear liquids on postoperative day 0, advanced as tolerated thereafter). Laboratory values, specifically complete blood counts, creatinine, and electrolytes are monitored closely along with differential outputs from the JP drain and the catheter. Creatinine from the JP fluid is usually tested, and if consistent with serum, the drain is removed prior to discharge. Contingencies for discharge include dietary tolerance, return of bowel function, ambulation, adequate pain control, and plateauing of the serum creatinine. The patient must be instructed on home catheter maintenance and generally returns to clinic 1 week postoperatively for catheter removal. Unless there is concern for a urine leak, we typically do not obtain a cystogram prior to removing the catheter.

Undoubtedly, complications may arise during or following RNU, and the surgeon must be adequately prepared to handle potential emergencies. At the beginning of the case, it is prudent to have extra staple loads and 4-0 polypropylene suture available in case of a major vascular injury or uncontrolled bleeding. The surgeon must also be prepared for open conversion either due to uncontrolled bleeding, cardiopulmonary intolerance of insufflation, or other factors. Furthermore, advanced notification of consulting surgical services (general, vascular, or colorectal) may be warranted if difficulties are anticipated based on anatomic considerations or local tumor invasion of adjacent structures.

As discussed previously, the iliac and great vessels may be susceptible to injury during ureteral dissection and LND, respectively, if performed carelessly. Organs adjacent to the kidney that may also be at risk include the stomach, spleen, pancreas, liver, and bowel. For left-sided RNU, we routinely ensure gastric decompression via an orogastric tube and exercise caution during dissection of the upper renal pole to avoid injuring the stomach. Although the majority of splenic injuries can be addressed with modern hemostatic products (e.g., Floseal® and Surgicel® Fibrillar™, which we use in our institution), splenic bleeding can be potentially unforgiving and necessitate a splenectomy if significantly injured. Prospective identification of the splenic hilum and minimizing forceful retraction of the spleen can help prevent such situations. Injuries to the bowel, particularly monopolar thermal injuries, may be more extensive than anticipated and if noted, are best handled intraoperatively with bowel resection and re-anastomosis. For left-sided dissections, identification of the pancreas can help minimize the chance of injury, but in the case of a sizable laceration or crush injury to the pancreas, a distal pancreatectomy may be necessitated, with a separate pancreatic drain left in place at the conclusion of the case and conservative advancement of diet postoperatively. The diaphragm may also be prone to injury, particularly during posterior dissection of the upper

renal pole. Should a diaphragmatic injury be noted, often signified by billowing of the diaphragm, difficulty maintaining pneumoperitoneum, and elevated airway pressures, the injury may be repairable primarily with negative pressure applied to the pleural cavity (e.g., with the assistance of a red rubber catheter), though more sizable defects may require the use of a patch.

Postoperatively, unstable transfusion-unresponsive bleeding noted immediately after surgery requires surgical re-exploration and emergent source control, including evaluation of the renal hilum, great vessels, iliac vessels, and adjacent organs. Aside from standard surgical complications that may arise (poor wound healing, infection, fascial dehiscence, thromboembolic complications, etc.), other postoperative complications specific to RNU to consider include urinary leakage from the cystorrhaphy, prolonged ileus, chylous ascites, or persistently deteriorating renal function. In the case of urinary leakage, usually evident by high JP output, elevated JP creatinine, and sometimes a chemical ileus, conservative management with prolonged JP and catheter drainage until the cystotomy heals is usually sufficient. Eventual cystography may be useful to confirm cystotomy closure prior to drain removal. While a multitude of causes may give rise to ileus, which can often be managed conservatively, a low threshold to pursue imaging (abdominopelvic CT with oral contrast) must be maintained to rule out occult bowel injury, even in the absence of leukocytosis. Extravasation of oral contrast would necessitate surgical exploration to correct, which we recommend performing in conjunction with general surgery colleagues. While acute renal injury can be anticipated due to removal of a functional renal unit, persistently worsening renal function without a plateauing trajectory, especially in the setting of little to no urine output, should raise concern for either an obstructed (e.g., during cystorrhaphy) or nonfunctional contralateral kidney. Once obstruction is ruled out, judicious use of fluids, close monitoring of electrolytes, and consultation with nephrology colleagues may be warranted. Should suspicion for chylous ascites arise, often in the context of progressive painless abdominal distension, we prefer a relatively conservative management strategy, including dietary measures (implementation of a low-fat medium-chain triglyceride diet or, if even more severe, total parenteral nutrition to bypass the bowel) and pharmacologic agents (octreotide). Should these measures be unsuccessful, we tend to pursue therapeutic paracentesis for symptomatic ascites (and repeat as needed) until the lymphatic leak resolves spontaneously. We have not needed to pursue other measures that have been described to date, such as percutaneous embolization, peritoneovenous shunting, transjugular intrahepatic portosystemic shunting, or surgical reintervention [35].

Summary

In this chapter, we have discussed the current gold standard treatment for UTUC, which remains RNU with bladder cuff excision. We review indications and preparation for surgery, including the frequent use of NAC at our institution in cisplatin-eligible patients and routine intraoperative instillation of intravesical MMC to reduce bladder recurrence. We also share intraoperative techniques for RNU, including our institutional practice, which has largely shifted to the use of robotic approaches. Based on contemporary evidence in managing the distal ureter, we routinely excise the bladder cuff to decrease intravesical recurrence, and we tend to perform templated LND, particularly in high-risk patients. Finally, we provide tips to avoid and manage common intraoperative and postoperative complications, including uncontrolled bleeding, injury to visceral organs (spleen, stomach, pancreas, bowel, liver), diaphragmatic injury, urinary leakage, progressive renal function deterioration, and chylous ascites.

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39

Selection, Administration and Description of Neoadjuvant versus Adjuvant Therapy for Upper Tract Urothelial Carcinoma

Rohan Shotton and Alison Birtle

Introduction

Cytotoxic chemotherapy for early-stage upper urinary tract urothelial carcinoma (UTUC) has long been a controversial topic, with a paucity of high-quality evidence to support neoadjuvant or adjuvant chemotherapy. With no established international consensus, clinical practice varies considerably, with an inconsistent approach across different centres. Numerous case series and retrospective studies have variably suggested a progression-free survival (PFS) or overall survival (OS) benefit in selected patients, though other studies suggest that this benefit was of little clinical significance. Use of perioperative chemotherapy remains infrequent; a 2017 registry study reported that adjuvant chemotherapy was given to 11.3% of patients with resected UTUC in 2013, and neoadjuvant chemotherapy was given to 2.1% [1]. The POUT study, the first randomised trial of adjuvant chemotherapy versus surveillance alone, only recently reported results, with a statistically significant PFS advantage observed after adjuvant chemotherapy [2]. OS data are still awaited, though as the only randomised trial of its kind, it is likely to be practice-changing.

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Risk Prediction Tools

A number of preoperative and postoperative risk prediction tools have been published to aid patient selection for systemic therapy (Table 39.1). Most are limited by a lack of external validation and retrospective study design, though Yates (2012) was subsequently validated on an external cohort (Ku 2013 23949152) with discrimination accuracy of 71.6% and 71.8% for 3- and 5-year survival respectively.

Risk Factors for Relapse/Poor Prognosis

Patient Factors

A large number of studies have cited advancing age [14–16], poor performance status [17] and male gender as adverse factors in UTUC, though a large retrospective validation study suggested that age only influenced all-cause mortality, and not recurrence-free survival (RFS) or cancer-specific survival (CSS) if adjusted for ECOG performance status [18]. As with a number of cancers, diabetes mellitus is associated with

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Table 39.1 Risk prediction tools in UTUC

Reference	Pre/post-op	Numbers		Variables	Endpoint
		Development	Validation		
Marguilis 2010 [3]	Pre-op RNU	Total 659 Bootstrap validation on 200		Grade Tumour architecture Tumour location	Non-organ confined disease (76.6% accuracy)
Favaretto 2012 [4]	Pre-op RNU	Total 274		Local invasion on imaging and ureteroscopy	PT2+ (AUC 0.71) or non-organ-confined disease (AUC 0.70)
Petros 2019 [5]	Pre-op RNU	396	170	Pre-op stage Biopsy grade Tumour architecture Haemoglobin	Non-organ-confined disease (82% accuracy, 48% sensitivity, 95% specificity)
Jeldres 2010 [6]	Post-op RNU	2959	2959	Age pT/pN stage Grade	5-year CSS (75.4% accuracy)
Yates 2012 [7]	Post-op RNU	397	270	Age pT/pN stage Grade Location	3- and 5-year CSS (accuracy 78%)
Cha 2012 [8]	Post-op RNU	1273	971	pT/pN stage LVI Tumour architecture Concomitant carcinoma in situ	2- and 5-year RFS (accuracy 76.8%) and CSS (accuracy 81.5%)
Rouprêt 2013 [9]	Post-op RNU	2371	1016	Age pT/pN stage Tumour architecture LVI	CSS (accuracy 80%)
Xylinas 2014 [10]	Post-op RNU	1261	578	Age Male gender Tumour location Laparoscopic surgery Endoscopic distal ureteral management Prior bladder cancer pT/pN stage Concomitant CIS	Intravesical recurrence (concordance index 69%)
Seisen 2014 [11]	Post-op RNU (pT1-3 pN0-x only)	1563	660	Age pT stage Grade Location Tumour architecture LVI	CSS (81% accuracy)
Krabbe 2017 [12]	Post-op RNU (high grade disease)	2926	2088	Age pt/pN stage Tumour architecture	RFS (accuracy 71%)
Zeng 2019 [13]	Post-op RNU	445	227	Age Concurrent bladder cancer Ureteral and renal pelvic tumour LVI Divergent differentiation Grade pT/pN stage	CSS (c-index 0.74)

poorer outcomes in UTUC, though metformin use may be associated with significantly reduced risk of recurrence or death [19]. Similarly, smoking is associated with adverse outcomes, especially in female patients [20]. The radiological presence of preoperative hydronephrosis is an independent adverse risk factor. A retrospective study of 469 patients showed that preoperative hydronephrosis was associated with higher T stage, non-organ-confined disease, and higher tumour grade, and other evidence suggests a link to poorer RFS and CSS [21].

Biochemical Factors

Several inexpensive and readily available preoperative biochemical biomarkers have been associated with adverse outcomes in UTUC. Elevated white cell count (without infection) and more specifically a neutrophil–lymphocyte ratio >3.0 are associated with worse RFS and CSS [21]. Similarly raised preoperative serum C-reactive protein (CRP) may predict more advanced disease, CSS and RFS [22, 23]. In patients with a preoperatively raised level, postoperative normalisation of the CRP may reflect a better prognosis. Other studies have observed associations between poorer prognosis and a raised preoperative AST/ALT ratio [24] and fibrinogen levels [25]. The combination of several raised inflammatory indices may reflect higher risk disease [26].

Macroscopic Pathology Factors

Macroscopic sessile tumour architecture, as opposed to papillary, is observed in around 20% of patients with UTUC, and is associated with biologically more aggressive disease, reflected in higher grade, T/N status, lymphovascular invasion (LVI) and concomitant carcinoma in situ (CIS), and poorer RFS and CSS [27]. Ureteral tumours with length >5 cm and with disease both in the ureter and renal pelvis have been linked to an increased risk of intravesical disease recurrence [15, 28].

Microscopic Pathology Factors

In addition to the common oncological predictors of high-risk disease such as higher T/N status [14, 29–31] and the presence of LVI [30, 32, 33], several other adverse microscopic features have been reported. Multifocal tumours and those with concomitant areas of carcinoma in situ are associated with worse RFS and CSS [34, 35]. The presence of extensive tumour necrosis is associated with higher tumour grade, stage, the presence of LVI and CIS, disease recurrence and survival [36].

Overall, 9–25% of patients with UTUC have tumours which exhibit variant histology (rather than pure UTUC), a trait which is associated with biologically aggressive disease and worse CSS and OS [37–39]. In particular, micropapillary histological variant tumours tend to display aggressive behaviour, with more advanced disease and limited responsiveness to neoadjuvant or adjuvant chemotherapy reported [40, 41].

Positive preoperative–voided urine cytology is associated with higher tumour T status, grade and the presence of LVI [42] and also with intravesical disease recurrence [43].

Molecular Markers

Several molecular markers of higher risk UTUC have been identified. Programmed cell death 1 (PD-1) may be expressed in around a third of UTUC cases, and may predict worse clinical outcome [44, 45]. Similarly, greater than moderate expression of p21-activated kinase 1 is associated with higher tumour grade, T stage, LVI and extravesical recurrence, and also disease-specific survival [46]. Increased expression of nuclear factor E2–related factor 2 (Nrf2) is associated with poorly differentiated disease, local invasion, nodal involvement and shorter OS [47]. Heightened cytoplasmic expression of HuR protein predicts worse CSS and metastasis free survival [48]. Loss of immunohistochemistry expression of the GATA3 transcription factor is associated with lower RFS and CSS [49].

Evidence for Perioperative Chemotherapy

There has historically been a paucity of data on chemotherapy in UTUC. Reported treatment regimens have generally been platinum based, most commonly given in three-weekly cycles of gemcitabine with carboplatin or cisplatin. Until recently, all data has been retrospective in origin, or based on registry series, and results have been inconsistent. For example, three meta-analyses have found significant OS, CSS and DFS improvements in patients treated with chemotherapy [50–52], but other results have been inconsistent. The most recent of these compared outcomes in 1170 patients given perioperative (neoadjuvant or adjuvant) systemic therapy with 3472 controls and reported improved OS, DFS and CSS with hazard ratios of 0.75, 0.54 and 0.69, respectively [50]. Although the vast majority of retrospective studies report improved outcomes in patients receiving adjuvant chemotherapy, this is far from ubiquitous. A multicentre 2018 study, for example, compared 312 patients given chemotherapy with 1232 undergoing observation alone, and reported no improvement in OS [53].

Exactly which patients benefit most from perioperative chemotherapy appears to depend on a large number of factors, as described above. Regardless of how high risk an individual is judged as being, though, there is evidence that certain subtypes of UTUC respond less or more favourably to chemotherapy than others. Some studies have found UTUC with variant histology to be less responsive to chemotherapy, though others have disputed this [54, 55]. Patients with hereditary-like UTUC may derive greater benefit more from adjuvant chemotherapy than patients with sporadic tumours, with 5-year OS reported as 48.2% versus 32% respectively [56].

Recent Developments in the Adjuvant Setting

Prior to the POUT study [2], there were no randomised, prospective trials of adjuvant chemotherapy in UTUC. A number of retrospective studies observed improved survival among patients treated with adjuvant chemotherapy, particularly in high-risk patients, though some studies found no evidence of benefit of treatment. POUT randomised patients with resected non-metastatic pT2-pT4pN0 or pT1-4pN1-3 UTUC and good performance status to either four cycles of gemcitabine with platinum chemotherapy or surveillance. Chemotherapy regimen was stratified according to glomerular filtration rate (GFR) only, with significantly more permissive cut-off ranges employed compared to other studies. A GFR cut-off of ≥50 ml/min was used for cisplatin, and 30–49 ml/min for carboplatin. A total of 124 patients received adjuvant chemotherapy, and 126 were kept under surveillance. Recruitment was stopped early due to efficacy in favour of chemotherapy. Improvements in DFS and MFS were seen in both chemotherapy regimens (2-year hazard ratio 0.47 for both DFS and MFS) and across all stages of eligible patients in pre-planned subgroup analyses. Grade 3–4 adverse events were reported in 62.1% of the chemotherapy group and 24.8% of the surveillance group. Quality of life data showed a decline at pre-cycle 3 and post-cycle 4 checkpoints, followed by return to normal by 6 months. Although overall survival data are yet to be reported, publication of mature data from the POUT study is likely to define future treatment recommendations.

Neoadjuvant Evidence

Neoadjuvant chemotherapy has been shown to improve DFS and OS in muscle-invasive bladder cancer, though ironically its real-world use is somewhat limited. UTUC may represent a different disease entity with increased incidence of microsatellite instability and differential chemotherapy responses, and evidence for neoadjuvant chemotherapy in UTUC is limited to a number of retrospective studies [57–60]. A 2019 meta-analysis of 318 patients reported absolute improvements in OS, CSS and PFS by 11%, 18% and 13%, respectively, in patients treated with neoadjuvant chemotherapy for locally advanced UTUC [61]. Unlike in the adjuvant setting, there

is little randomised prospective evidence for neoadjuvant chemotherapy, and there is no evidence to support a greater survival advantage either of preoperative over postoperative chemotherapy, or vice versa.

In addition to the possible survival benefits suggested by retrospective studies, neoadjuvant chemotherapy has been shown to have a benefit in pathological downstaging of UTUC [62]. A large registry review of 260 patients treated with neoadjuvant chemotherapy compared with 5194 controls observed pathological response in 25.2% in the chemotherapy group, with a complete pathological response reported in 6.1% [63]. Both partial and complete pathological response may be useful tools in predicting OS in order to guide postoperative follow-up [64]. The only prospective neoadjuvant UTUC data currently presented is from the ECOG-ACRIN 8141 trial, examining pathological complete response (pCR) rates, following four cycles of accelerated methotrexate, vinblastine, doxorubicin and cisplatin (aMVAC) or gemcitabine/carboplatin chemotherapy [65]. Though the gemcitabine/carboplatin arm closed early due to poor accrual, pCR was reported in 14% of the 30 patients treated with aMVAC.

An aspect of chemotherapy decision-making unique to malignancies of the urinary tract is the expected significant decline in renal function following nephrectomy. This is particularly pertinent to platinum-based chemotherapy, in which renal excretion of cytotoxic drugs is essential. Renal function was observed to decline by a median of 32% post-operatively in patients with previously normal eGFR, with no significant improvement over time [66]. Significantly fewer patients may be eligible for platinum-based chemotherapy following nephroureterectomy [67]. Factors such as increasing age, preoperative eGFR, smaller contralateral kidney, renal pelvis tumour location, absence of ipsilateral hydronephrosis and higher BMI have been identified as associated with larger postoperative decline in GFR [68–70]. In the POUT study, however, choice of chemotherapy regime was stratified by renal function, and patients with permissively lower GFRs were safely and effectively treated postoperatively with carboplatin, rather than cisplatin.

Why Not Use Neoadjuvant Treatment?

It is established that survival of patients with pT1 tumours is significantly better than those with pT2 disease. Even in the best of hands, however, the sensitivity and specificity of preoperative imaging, biopsy and urine cytology may be as low as around 75%. A review of 39 patients with no preoperative histology found that 12.8% had no UTUC in surgical specimens, with four containing only benign changes and one containing renal cell carcinoma [71]. Without the benefit of the full pathological staging afforded by the adjuvant setting, there is therefore a risk of significant overtreatment of patients with low-risk, pT1 disease if routinely treated preoperatively.

So What Should We Recommend?

While the POUT study has demonstrated a survival advantage to adjuvant chemotherapy, preoperative chemotherapy in UTUC remains a controversial practice and risks overtreatment of low-risk patients. Patients with lower GFRs postoperatively may be safely treated with carboplatin, rather than cisplatin.

Adjuvant chemotherapy	Neoadjuvant chemotherapy	No chemotherapy
High-quality evidence Benefit of pathological staging Avoids overtreating low risk disease	Low-quality evidence Pathological downstaging as a useful biomarker Chemotherapy not prohibited by reduced GFR post-op	Comorbidity Inadequate renal function Poor performance status Histology with poor chemo-sensitivity Patient choice

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40 Oncologic Monitoring After Radical Nephroureterectomy

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Intravesical Recurrence

Intravesical recurrence (IVR) after radical nephroureterectomy (RNU) is relatively common—with most reported estimates varying between 13% and 47%—and is predominantly characterized by non-muscle-invasive intravesical disease [1–9]. IVR generally occurs within 2 years after RNU. In a systematic review and meta-analysis of 18 studies and over 8000 patients by Seisen et al. (2015), 2402 (29%) developed IVR within a median of 22.2 months postoperatively [10].

In an effort to reduce the occurrence of post-RNU IVR, a number of trials have sought to evaluate the impact of perioperative intravesical chemotherapy. A recent meta-analysis examined five clinical trials that used various intravesical agents (most commonly mitomycin C [MMC]) within 1–2 weeks after RNU [11]. The analysis demonstrated a significant reduction in IVR among patients who received prophylactic intravesical chemotherapy compared to patients who did not receive prophylactic treatment (20.5% vs. 36.7%, respectively, odds ratio [OR] = 0.48, 95% CI: 0.33–0.69, $p = 0.0001$), with a relative risk reduction of 41% [11]. Although some patients experienced mild irritative bladder symptoms, none experienced serious adverse events [11]. Furthermore, in another recent study, patients who received intravesical MMC intraoperatively prior to bladder cuff excision had significantly lower rates of IVR within the first postoperative year than patients who received intravesical MMC 1–3 days after RNU (adjusted hazard ratio [aHR] = 0.113, 95% CI: 0.28–0.63, $p = 0.01$) [12]. Additionally, in our series (unpublished data), patients with high-grade upper tract urothelial cell carcinoma (UTUCC) who received neoadjuvant chemotherapy (NAC) without any adjuvant intravesical treatment had reduced rates of IVR at 1 year post-RNU compared to patients who did not receive NAC (21% vs. 40%, respectively) and had significantly longer bladder recurrence-free survival (BRFS) compared to patients who did not receive chemotherapy (median BRFS not reached at 39 months vs. median BRFS = 23 months, respectively).

Several studies have also examined patient and tumor characteristics associated with IVR in an effort to identify patients who may benefit most from close monitoring or prophylactic intravesical therapy. In developing a nomogram to predict the probability of IVR after RNU, Xylinas et al. (2014) examined data from 1839 patients undergoing RNU for UTUCC at 15 centers across Europe and North America. With an

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overall IVR rate of 31% at a median follow-up of 45 months, they identified older age, male gender, a prior history of non-muscle-invasive bladder cancer (NMIBC), ureteral tumor location, presence of concomitant CIS, higher stage, lymph node involvement, laparoscopic surgical approach, and endoscopic distal ureteral management as significant predictors of IVR [13]. Seisen et al. (2015) additionally identified preoperative CKD, positive preoperative urine cytology, tumor multifocality, tumor necrosis, positive surgical margins, and extravesical bladder cuff removal as significant predictors of IVR, while concomitant CIS, lymphovascular invasion, and endoscopic bladder cuff removal were not significant predictors [10].

Given the prevalence of IVR, we recommend intravesical treatment at the time of RNU for all patients (including both low- and high-grade upper tract tumors). Intravesical treatment strategies most often employ cytotoxic therapy (i.e., MMC, gemcitabine) although continuous bladder irrigation is a reasonable option for patients with a contraindication to chemotherapy [14, 15]. Currently, our practice involves intraoperative or perioperative cytotoxic therapy (gemcitabine) either at the time of RNU or within 48 hours after a negative cystogram. However, a variety of strategies including different agents, timing of therapy, and timing of catheter can be employed. It should be noted that the European Association of Urology (EAU) recommends a single postoperative dose of intravesical chemotherapy after RNU [16].

Furthermore, although the EAU guidelines recommend cystoscopy at 3 months after RNU and then yearly thereafter for at least 5 years (Grade C recommendation), we recommend more frequent monitoring with cystoscopy and prompt treatment of any intravesical recurrences as follows: every 3–4 months during the first postoperative year, every 6 months during postoperative years 2–3, annually during years 4–5, and then every 1–2 years for postoperative years 5–10 [16]. Beyond the tenth postoperative year, we recommend cystoscopy for patients with high-risk disease (stage ≥2 or positive lymph nodes) at the patient's discretion.

Contralateral Upper Urinary Tract Recurrence

Metachronous contralateral upper urinary tract tumors after RNU are rare, with reported rates of 0.8–6.9% [2, 5, 17–22]. Although contralateral recurrences may be symptomatic, some relapses have a more insidious onset and require regular monitoring for early detection. Reported predictors of contralateral recurrence include female gender, a history of renal transplantation, preoperative renal insufficiency, and no preceding IVR [17, 20, 22]. In a multi-institutional European study of 234 patients with a median follow-up of 34 months, 14 (6.0%) developed contralateral recurrence after RNU, and a prior history of bladder cancer was the only significant predictor [21]. The reported 5-year probability of being free from contralateral recurrence was 96.6% for patients without a history of bladder cancer, 91.1% for patients with a history of NMIBC, and 55.3% for patients with a history of muscle-invasive bladder cancer (MIBC) prior to RNU [21].

Given the potentially serious consequences of contralateral recurrence after RNU, we recommend urine cytology at every follow-up cystoscopy (see above). Any abnormal cytology in the setting of normal surveillance cystoscopy should warrant evaluation of the remaining upper tract with retrograde pyelogram and selective cytology. We prefer blue light cystoscopy of the bladder with selective cytology of the upper tract and, in order to minimize iatrogenic injury to a solitary renal unit, reserve ureteroscopy only for patients with a visible abnormality on retrograde pyelogram (or axial imaging) or selective cytology suspicious for malignancy.

Regarding follow-up imaging post-RNU, the EAU recommends an annual CT for patients with noninvasive tumors for at least 5 years and CT urography every 6 months for 2 years and then yearly for patients with invasive tumors [16]. We recommend more regular imaging as follows: low-risk patients (stage 0 or 1) should have a contrast-enhanced, multiphasic CT (including urogram) of the abdomen and pelvis at 6 and 12 months during the first postoperative year, annually during postoperative years 2–5, and at

the patient's discretion after the fifth postoperative year. For high-risk patients, we recommend a CT every 3–4 months during the first postoperative year, every 6 months during postoperative years 2–3, annually during postoperative years 4–10, and at the patient's discretion after the tenth postoperative year. For patients with high-risk disease, it should be noted that the above-mentioned CT scans of the abdomen and pelvis with contrast suffices for both metastatic survey and evaluation of the contralateral renal unit. For patients who undergo transurethral resection of bladder tumor (TURBT), retrograde pyelograms can replace axial imaging; however, we recommend at least one multiphasic axial imaging annually in all patients.

Systemic Recurrence

Rates of systemic (loco-regional or distant) recurrence vary depending on the cohort, with some estimates nearing 31% [23–29]. In a systematic review of 33 studies assessing outcomes after RNU, the mean rate of recurrence in the retroperitoneum or pelvis was 4.6% (range 0–12%), and the mean rate of distant recurrence was 16.4% (range 8–28%) [30]. In a recent study, Locke et al. (2018) examined post-RNU recurrence patterns in a multi-institutional retrospective review [24]. Among 1029 patients, the overall rate of loco-regional and distant recurrences was nearly 24%, the mean time to recurrence was approximately 8 months, 50% of recurrences were detected during the first postoperative year, and 93% were detected within 5 years [24]. The most common sites were lung (26%), nephrectomy bed (26%), liver (21%), bone (18%), and retroperitoneal lymph nodes (8%) [24]. In our unpublished series of 248 patients who underwent RNU without NAC or adjuvant chemotherapy, 50 (20%) developed a systemic recurrence, with a median time to recurrence of 12.5 months (IQR 4–24). The most common individual sites of recurrence were lung (28%), bone (14%), liver (12%), and lymph nodes (12%). Overall, 80% of patients with systemic recurrence died, with a median time to death of 10 months (IQR 4.5–15 months). Compared to recurrence in the lymph nodes, recurrences in the liver and bone were associated with an increased risk of death (liver: HR 6.3, 95% CI: 1.7–23.8, $p = 0.007$; bone: HR 4.9, 95% CI: 1.3–18.8, $p = 0.02$), with liver recurrences portending the worse prognosis.

A number of predictors of loco-regional and distant recurrence have been reported, including female gender, advanced age, higher stage, high grade, multifocality, ureteral tumor location, positive nodal status, and positive surgical margins [23–25, 29, 31]. In a retrospective review that highlighted the poor prognosis of systemic recurrences, Kluth et al. (2014) reported that 185 of 242 patients with systemic recurrence died from UTUCC, and the estimated cancer-specific survival at 12 months was 37% [32].

Perioperative chemotherapy is indicated to reduce the risk of systemic recurrence. In a meta-analysis of retrospective studies evaluating the role of perioperative chemotherapy, patients who received adjuvant chemotherapy had significantly improved disease-free survival compared to controls (HR 0.54, 95% CI: 0.32–0.92, $p = 0.02$), and patients who received NAC had significantly improved overall survival compared to controls (HR 0.36, 95% CI: 0.19–0.69, $p = 0.002$) [33]. While most data about the efficacy of perioperative chemotherapy is retrospective, the maturing POUT phase III randomized trial (NCT01993979) demonstrated that adjuvant chemotherapy improved disease-free survival [34]. This trial enrolled patients who had pT2-T4 N0-3 M0 UTUCC and had undergone RNU within 90 days to either four cycles of adjuvant chemotherapy (gemcitabine/cisplatin or gemcitabine/carboplatin) or surveillance followed by chemotherapy if required [34]. The interim analysis included 125 patients in the treatment group, 123 patients in the surveillance group, and a median follow-up of 17.6 months (IQR 7.5–33.6) [34]. Patients who received adjuvant therapy had improved disease-free survival (HR 0.47, 95% CI: 0.29–0.74, $p = 0.0009$) and progression-free survival (HR 0.49, 95% CI: 0.30–0.79, $p = 0.003$) [34]. Recruitment for the trial was closed early due to these results.

While adjuvant chemotherapy improves disease-free survival, chemotherapy in the neoadjuvant setting may be preferable due to post-RNU renal dysfunction. A recent phase II trial (ECOG-ACRIN 8141) included patients with high-grade UTUCC who received four cycles of NAC prior to RNU, with the interim analysis focusing on 30 patients who received aMVAC [35]. Among these patients, 14% achieved pathologic complete response (ypT0N0/x) at the time of RNU, and no patients progressed while on chemotherapy [35]. Therefore, we recommend NAC to all patients with high-grade UTUCC and a visible lesion on axial imaging. For patients not receiving NAC, we recommend adjuvant therapy based on adverse pathological features, including pT3 or greater or any patient with positive lymph nodes.

To monitor for loco-regional and distant recurrence, we recommend the same follow-up imaging schedule outlined above for the assessment of contralateral upper urinary tract recurrence. For low-risk patients, we recommend a contrast-enhanced CT abdomen/pelvis at 6 and 12 months during the first postoperative year, annually during postoperative years 2–5, and at the patient's discretion after the fifth postoperative year. For high-risk patients, we recommend a CT abdomen/pelvis every 3–4 months during the first postoperative year, every 6 months during postoperative years 2–3, annually during postoperative years 4–10, and at the patient's discretion after the tenth postoperative year.

Additionally, we recommend a chest X-ray (CXR) every 6 months during the first postoperative year for all patients. For low-risk patients, we recommend an annual CXR for postoperative years 2–5, and then at the patient's discretion thereafter. For high-risk patients, we recommend a CXR every 6 months during postoperative years 2–3, followed by an annual CXR during postoperative years 4–10, and then at the patient's discretion thereafter. Chest CT should reflexively be ordered in any patient with an abnormality on CXR or in patients at highest risk for pulmonary metastases (i.e., node positive disease). Bone scan, brain scan, and PET imaging should only be ordered based on symptoms or abnormality on axial imaging – they should not be considered routine imaging for UTUCC surveillance (Fig. 40.1).

Low-risk upper tract urothelial cell carcinoma					
	Time after surgery				
	Year 1	Years 2–3	Year s4–5	Years 5–10	>10 years
Cystoscopy + urine cytology	Every 3–4 months	Every 6 months	Annually	Every 1–2 years	No data to support/refute*
CT abdomen/pelvis	Every 6 months	Annually	Annually	No data to support/refute.*	No data to support/refute*
CXR	Every 6 months	Annually	Annually	No data to support/refute.*	No data to support/refute*
High-risk upper tract urothelial cell carcinoma					
	Time after surgery				
	Year 1	Years 2–3	Years 4–5	Years 5–10	>10 years
Cystoscopy + urine cytology	Every 3–4 months	Every 6 months	Annually	Every 1–2 years	No data to support/refute*
CT abdomen/pelvis	Every 3–4 months	Every 6 months	Annually	Annually	No data to support/refute*
CXR	Every 6 months	Every 6 months	Annually	Annually	No data to support/refute*

CXR=chest x-ray
*Follow-up based on individualized patient risk.

Fig. 40.1 Recommendations for oncologic monitoring after radical nephroureterectomy

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