Bladder Neoplasms: Muscle Invasive Bladder Cancer

Editors:

Solomon Woldu, MD

Authors:

Neil Desai, MD; Robert Svatek, MD, MSC; Parminder Singh, MD; Sia Daneshmand, MD

Last Updated:

Tuesday, March 14, 2023

Keywords:

Muscle Invasive Bladder Cancer, bladder cancer staging, Cystectomy, Neoadjuvant chemotherapy, checkpoint inhibitors, urinary diversion, urothelial carcinoma

1. Introduction

In the United States, urothelial carcinoma of the bladder is the second most common malignancy of the genitourinary tract, and the second most common cause of death of all genitourinary tumors. An estimated 81,180 new cases of bladder cancer and approximately 17,100 deaths from bladder cancer were expected in 2022 in the United States[1]. Most patients will be diagnosed after developing microscopic or gross hematuria. Approximately three-fourths of patients present with non-muscle-invasive tumors, while **20% to 40% will either present with or progress to high-grade, muscle-invasive bladder cancer (MIBC)**. These cancers are highly lethal and are the cause of death in the majority of patients within two years of diagnosis without aggressive treatment.[2] **Approximately 70% of patients present with localized disease, while 33% have regional spread and 5% have distant metastasis at the time of diagnosis. Radical cystectomy and thorough, meticulous pelvic lymph node dissection is considered standard therapy for high-grade, muscle-invasive bladder cancer and high-grade non-muscle-invasive cancers deemed to be at high risk for progression**[3] **Peri-operative cisplatin-based chemotherapy** can be used to improve survival. Evaluation begins with abdominopelvic cross-sectional imaging (CT or MRI, contrast-enhanced whenever possible), staging of the chest and transurethral resection of the bladder tumor (TURBT) with careful attention to histopathologic details such as the depth of invasion (staging), the presence of carcinoma in-situ, lymphovascular invasion, and/or histologic variants as well as a bimanual exam under anesthesia. Subsequent management heavily relies on findings at initial and/or repeat TURBT.

Improvements in anesthesia, surgical technique, and perioperative management have led to a decrease in perioperative morbidity and mortality from surgery. Nevertheless, radical cystectomy with pelvic lymphadenectomy and urinary diversion remains a complex operation with significant early and late complications. **Enhanced recovery protocols** have substantially decreased the hospital length of stay and improved the patient experience. The choice of urinary diversion relies heavily on patient factors, surgeon and/or institutional experience and practice. Orthotopic diversion offers excellent functional outcomes for both men and women in experienced centers in carefully selected and well-counseled patients. **Bladder preservation protocols such as trimodality therapy (complete TURBT followed by concurrent chemoradiation) are an appropriate option for selected patients and those who refuse or are not suitable candidates for radical cystectomy** . Partial cystectomy is an option in very select cases such as isolated disease in the dome of the bladder or tumor in a bladder diverticulum but very few patients qualify. Other **palliative bladder sparing protocols include 'radical TURBT' which should only be used in patients who refuse or are not candidates for standard definitive treatment options. At this time chemotherapy or radiation alone should not be recommended for patients with MIBC unless for palliation if no other options are available** .

Metastatic bladder cancer carries a poor prognosis and is treated with first-line cisplatin-based combination chemotherapy. Patients who progress following front-line chemotherapy or who are not eligible for platinum-based chemotherapy are candidates for either immune checkpoint blockade therapy, non-platinum-based combination or single agent chemotherapy, or novel targeted therapies. Consolidation of locally advanced disease with radical cystectomy or chemoradiation after response to neoadjuvant chemotherapy should be considered on an individual basis and for ongoing clinical trial.

2. Histopathology

The cells lining the urothelium of the bladder are traditionally known as transitional cells. Bladder malignancy can form from these cells or from the mesenchymal cells beneath the urothelial cell layer. **Worldwide, urothelial (formerly transitional cell) carcinoma of the bladder is the most common subtype of bladder cancer**. The majority of this core curriculum will be focused on muscle invasive urothelial cancer. Immunohistochemistry can be used to confirm urothelial differentiation, distinguish atypia from dysplasia, in the work-up of spindle cell lesions and for prognosis. Commonly used markers in bladder cancer include GATA-3, p63, and cytokeratin 7, cytokeratin 5/6. GATA-3 is a nuclear transcription factor expressed in 67-90% of urothelial tumors but also stains for lymphocytes and some other tumors such as breast and squamous cell carcinoma. Immunohistochemistry is helpful for confirmation of neuroendocrine differentiation (see 2.1 Variant Histology).

2.1 Variant Histology

Histologic variants are identified in up to a third of radical cystectomy specimens[4] and include **variants of urothelial cancer** (e.g. micropapillary, nested, plasmacytoid, sarcomatoid, lymphoepithelioma-like), **diverging histologies** (e.g. squamous cell carcinoma or squamous differentiation, glandular differentiation), or **non-urothelial tumors** (e.g. adenocarcinoma, neuroendocrine / small cell tumors, carcinosarcoma). Urothelial carcinoma can be composed partially or completely of these variant histologic types. Other rare **non-epithelial tumors** of the bladder include neurofibroma, pheochromocytoma, lymphoma, sarcomas.[5]

There is limited data regarding clinical outcomes in patients with variant histology tumors of the bladder as these tumors are typically excluded from clinical trials, and there is lack of consensus on guideline panels regarding management. Consideration should be given in this context for genomic profiling to assess for actionable alterations in the advanced state. In general, variant histology tumors are aggressive and often under-staged.[6] Regarding variant histology, the **2017 AUA guidelines** on non-muscle invasive bladder cancer recommend:[7]

1. **An experienced genitourinary pathologist should review the pathology of a patient when variant histology is suspected or if muscle invasion is equivocal (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, extensive squamous or glandular differentiation). (Clinical Principle)**
2. **If a bladder sparing approach is being considered in a patient with variant histology, then a clinician should perform a restaging TURBT within four to six weeks of the initial TURBT. (Expert Opinion)**
3. **Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy (Expert Opinion)**
4. **In a high-risk patient who is fit for surgery with persistent high-grade T1 disease on repeat resection, or T1 tumors with associated CIS, LVI, or variant histologies, a clinician should consider offering initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)**

The diagnosis of pure squamous or pure adenocarcinoma should be made only when the entire tumor is composed of squamous or adenocarcinoma cells, respectively.[8]

Micropapillary urothelial cancer is histologically similar to ovarian papillary serous carcinoma. There is no clear evidence that neoadjuvant chemotherapy improves oncologic outcomes, although there does appear to be an association with pathologic downstaging at the time of radical cystectomy. It is not clear if micropapillary variant

histology confers worse survival outcomes after radical cystectomy, when adjusted for pathologic staging[9,10]

Nested variant of urothelial cancer is characterized by confluent small nests and abortive tubules and despite a relatively bland histologic appearance (often mistakenly as low-grade disease), it has an aggressive behavior[11] Patients are typically managed with radical cystectomy –there are limited reports on efficacy of neoadjuvant or adjuvant therapy.[12]

Plasmacytoid urothelial cancer is a rare (1-3% of invasive bladder cancers) and very aggressive malignancy characterized by eccentric nuclei and abundant cytoplasm resembling plasma cells with similar morphology to signet ring cancers. It is characterized by frequent CHD1 (encoding E-cadherin) loss of function.[13] Due to sheet-like spread into the peritoneum and soft tissues, it is associated with **higher rates of positive surgical margins, a propensity to develop peritoneal carcinomatosis** and is consequently associated with worse cancer-specific survival outcomes compared to conventional urothelial cancer.[14,15] No consensus exists on the comparative efficacy of neoadjuvant chemotherapy, cystectomy alone, or adjuvant therapy, although a **multimodal approach** is common.[16]

Squamous cell carcinoma accounts for 3-7% of bladder cancers in the U.S. is associated with chronic inflammatory conditions such as **bladder stones, bladder diverticuli, chronic bladder infections, chronic indwelling catheters, or bilharziasis** .[17] Histologically, squamous cell carcinoma is composed of keratinized islands that contain concentric aggregates of cells and keratin called squamous pearls.[8] Squamous malignancy can represent divergent differentiation of urothelial cancer or be pure squamous cell carcinoma. **Radical cystectomy is the mainstay of treatment. Neoadjuvant chemotherapy has not consistently shown to benefit patients with SCC**[18] although various regimens including epirubicin,[19] ifosfamide/paclitaxel/cisplatin,[20] and gemcitabine/cisplatin have been reported to have significant rates of response at the time of cystectomy. Radiation, both in the neoadjuvant and adjuvant setting, may have a role in decreasing loco-regional recurrence, which is otherwise common in squamous cell cancer of the bladder – however this must be balanced with toxicity risk associated with perioperative radiation[21]

Both **squamous differentiation** and **glandular differentiation** of urothelial cancer are associated with more advanced disease at presentation. Although there is some suggestion that these variants are less responsive to treatment, outcomes are generally considered similar to conventional urothelial cancer when accounting for stage. Treatment is similar to conventional urothelial carcinoma. [22]

Adenocarcinoma of the bladder accounts for <2% of bladder cancers in the U.S., often arises from the dome of the **bladder**[8] and is morphologically similar to colon adenocarcinoma with glandular cells with atypical cytoplasm, mucin production, poor differentiation and mitotic figures.[8] These tumors are often difficult to distinguish from urachal adenocarcinoma which arises from the vestigial urachal epithelium.[23] **Management of localized adenocarcinoma typically involves partial cystectomy (i.e. urachal adenocarcinomas) or radical cystectomy with pelvic lymph node dissection**. While neoadjuvant chemotherapy is commonplace for adenocarcinomas of the colon, it is not recommended for bladder adenocarcinomas due to lower response rates.[24] There may be a role for adjuvant radiotherapy, similar to that in urothelial cancer.[25]

Neuroendocrine carcinomas of the bladder are rare and include **small cell carcinoma (most common)**, large cell carcinoma, and mixed patterns. The immunohistochemical findings, such as **tendency to stain positive for neuron-specific enolase, neurofilament, epithelial membrane antigen, synaptophysin, chromogranin, or serotonin** , are typical of small cell carcinomas originating from other sites. Frequent genomic alterations include loss of *RB1* and *TP53*.[26] These tumors tend to be advanced, commonly present with synchronous metastases, and are associated with an aggressive clinical course. As such, these cancers should be managed with **multi-modal therapy, generally starting with up-front chemotherapy**. Commonly used chemotherapy regimens include cisplatin/etoposide, etoposide alone, or ifosfamide/doxorubicin).[8,27] Given the high competing risk of distant relapse, consideration for triple modality therapy (TURBT & chemoradiation) should be given, abstracting from limited data and small cell lung cancer[28]

3. Natural History and Patterns of Spread

3.1 Origin of Urothelial Cancer

Urothelial carcinoma is considered a **field change defect** disease, which describes a biologic process in which all cells in a region of tissue undergo genetic alterations, often related to prolonged carcinogen exposure (e.g. tobacco, environmental exposures, radiation). As a result, the urothelial cells spanning the renal pelvis to the urethra suffer widespread genetic damage of varying degrees and are at risk for development of tumors at variable times and variable sites. De-novo bladder tumors can arise many years after the original cancer was diagnosed. Bladder tumors can derive from a polyclonal origin or, in some cases, multiple tumors can derive from a single cell clone that disseminated or spread to other sites of the urinary tract.

3.2 Patterns of Dissemination of Bladder Cancer

Bladder cancer is considered to develop principally in urothelial cells. During malignant transformation, the urothelial cells can acquire the ability to penetrate the basement membrane into the **lamina propria (T1 or 'invasive disease'), also described as subepithelial connective tissue**.[17] Tumors can subsequently invade further into the bladder wall to include the **muscularis propria (T2 or 'muscle invasive disease')**, the **perivesical fat (T3), or neighboring organs (T4a) and/or the pelvic sidewall (T4b). Malignant cells entering the lamina propria and to a greater extent the muscularis propria, have access to lymphatic and vascular channels** which can result in lymphatic or hematogenous metastasis. This process requires a variety of biologic processes to include epithelial-to-mesenchymal transitioning, neovascularization (angiogenesis), proteolysis, increased cellular motility, proliferation and escape from local immune surveillance.[17] Local invasion of bladder cancer can occur through *en bloc* spread, characterized by cancer cells invading directly beneath the mucosal surface.[29] **Approximately 5% of patients with well-differentiated or moderately differentiated NMIBC will develop vascular or lymphatic spread, while 20% of patients with high-grade NMIBC will progress to metastasis**.[29]

Lymphatic metastasis of bladder cancer can occur independent of hematogenous spread.[29] Lymphatic spread is directly **correlated with the extent of the local tumor** as assessed by tumor stage and other adverse pathologic features such as the presence of **lymphovascular invasion**. The most common site of metastasis in bladder cancer are the pelvic lymph nodes, including **perivesical nodes (16%), obturator nodes (74%), external iliac nodes (65%), presacral nodes and internal iliac nodes (25%).** The principal sites of non-lymphatic, hematogenousbladder cancer metastases include the **liver (38%), lung (36%), and bone**. Metastatic bladder cancer is associated with limited response to therapies, and limited survival.[17,29]

4. Clinical and Pathologic Staging System

4.1 Clinical Staging

Prior to management and treatment considerations, a full history and physical exam should be performed, including an exam under anesthesia (**bimanual examination**) at the time of TUR for a suspected invasive cancer. In addition, proper management of MIBC is dependent on accurate pre-operative staging, including **imaging of the chest** (CT or 2-view chest x-ray to rule out intrathoracic metastases) and **cross-sectional imaging of the abdomen and pelvis (CT or MRI) with intravenous contrast** if not contraindicated. Laboratory evaluation for staging should include a **comprehensive metabolic panel** (complete blood count, liver function tests, alkaline phosphatase, albumin, and renal function).

MIBC can be staged clinically (i.e., prior to cystectomy) and pathologically (i.e., based on the cystectomy specimen). Clinical stage T3 disease is defined as a palpable mass on bimanual examination performed **following** complete resection of the intravesical tumor. **It is imperative that the muscle is included in the histologic specimen obtained from TUR for accurate staging of disease**. Despite technical advances, there is a significant risk of radiographic under-staging owing to the difficulties in determining extravesical extension on cross sectional imaging. **The reported rate of post-surgical upstaging to extravesical disease is as high as 40%**.[30,31,32] **The presence of hydronephrosis is a strong predictor of upstaging to extravesical disease and is an independent predictor of a worse prognosis**.[31,32]

While CT is the most common cross-sectional imaging technique employed in bladder cancer staging, there is recent interest in the use multi-parametric MRI for bladder cancer. Advantages of MR imaging include absence of ionizing radiation, high degree of soft tissue contrast and multi-planar imaging capability. However, MR imaging of the bladder is more technical and subject to variations such as motion artifact and bladder filling. Similar to PI-RADS for prostate cancer, a VI-RADS protocol has been developed and appears to show promise in distinguishing muscle-invasive disease before TURBT and residual disease [33,34] after resection, although the schema remains to be validated. Other concerns regarding the VI-RADS system include the risk of interobserver variability which is associated with both technique and the experience of the interpreter, as well as low sensitivity for detecting nodal metastases.[35]

Bone scans are <u>not</u> recommended in the routine work-up of bladder cancer unless the patient has an elevated alkaline phosphatase or the patient suffers from signs or symptoms of bone involvement, such as new onset bone pain.[36] Routine brain/head imaging is also not recommended as metastasis to the brain is rare in bladder cancer.

Positron emission tomography (PET) with ^{18}F-Fluoro-D-Glucose (18-FDG) is currently not recommended in initial bladder cancer staging due to excretion of the tracer into the urinary tract. In the evaluation of metastatic disease, PET has not demonstrated sufficient accuracy to be used routinely[37] however, PET may be used when considering surgical resection of oligometastatic disease to assess for metastatic burden.[37] **Lymph node staging with PET has an accuracy of ~80%, which may not appreciably outperform CT**.[38]

Table 1: VIRADS system for Bladder tumors

	Findings	Probability of muscle invasion
VIRADS 1	Uninterrupted low Signal Intensity line with muscularis integrity. <1.0 cm size	muscle invasion highly unlikely
VIRADS 2	Uninterrupted low Signal Intensity line with muscularis integrity. >1.0 cm size	muscle-invasion unlikely
VIRADS 3	Disappearance of category 2 findings, but no clear disruption of low signal intensity muscularis layer	muscle-invasion equivocal
VIRADS 4	interruption of low signal intensity line suggesting extension into muscularis layer	muscle-invasion likely
VIRADS 5	Extension of intermediate signal intensity tumor to extra-vesical fat	invasion beyond bladder is very likely

4.2 Pathologic Staging

Bladder cancer is staged according to the tumor, nodes, and metastases (TNM) staging classification system (**Table 2**). **Other prognostic factors include the presence of variant histology, lymphovascular invasion**,[39] **the number of lymph nodes involved**,[40] **the presence of extranodal extension, and size of the largest tumor deposit in the lymph nodes**.[41] Muscle-invasive urothelial carcinomas are generally high-grade and extend through the lamina propria into the deep muscle bundles (i.e., muscularis propria).[41] Patients with **bladder tumors that invade through the bladder wall directly into the prostatic stroma are staged T4a and are associated with a poorer prognosis** .[42] Non-invasive extension of urothelial carcinoma as an in-situ component into prostatic glands and ducts or even extension into the seminal vesicles via mucosal/epithelial extension without stromal invasion is considered **Tis**. Finally, **urothelial carcinoma arising from the prostatic urethra alone** (without spread from the bladder) are staged according to the urethral cancer staging system, wherein prostatic stromal invasion would be staged as **pT2**.[43] Urethral tumors can arise directly from the urethra (i.e., primary) or through direct extension from the bladder (i.e., secondary). The 8th Edition of the AJCC Cancer staging manual does not specify the stage of urothelial carcinoma invading the seminal vesicle however it is associated with a grim prognosis.[44] Importantly, nodal involvement superior to the common iliac chain is now considered M1a disease and any non-lymphatic metastasis is M1b.

Table 2: TNM Staging system
AJCC prognostic groups (TNM staging system for bladder cancer 8th ed. 2017)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall
Regional Lymph Nodes (N)	
Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.	
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastases limited to lymph nodes beyond the common iliacs
M1b	Non-Lymph -- node distant metastases

AJCC prognostic groups (TNM staging system for bladder cancer 8th ed. 2017)			
Stage	T	N	M
0a	Ta	N0	M0
is	Tis	N0	M0
I	T1	N0	M0
II	T2a T2b	N0 N0	M0 M0
IIIA	T3a T3b T4a T1-T4a	N0 N0 N0 N1	M0 Mo M0 M0
IIIB	T1-T4a	N2,N3	M0
IVA	T4b Any T	Any N Any N	M0 M1a
IVB	Any T	Any N	M1b

5. Management

For patients with newly-diagnosed MIBC, curative treatment options should be discussed before determining a plan of therapy that considers patient comorbidity, functional status, as well as tumor characteristics. **The 2020 AUA guidelines** recommend **a multidisciplinary approach** to treatment planning. **Prior to treatment, clinicians should counsel patients regarding the risk of treatment-associated complications and the implications of treatment on quality of life** (e.g., impact on continence, sexual function, fertility, bowel dysfunction, metabolic problems). **Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (M0) MIBC**. Careful selection and multi-disciplinary evaluation is important for those considering bladder preservation alternatives.

5.1 Radical cystectomy

Radical cystoprostatectomy in the male patient includes removal of the bladder, the perivesical fat, the prostate, the seminal vesicles and the prostatic urethra. Some groups advocate the use of prostate or prostate capsule-sparing techniques to improve erectile function recovery and continence preservation, however **caution should be applied since there is a high risk of cancer involvement of the prostate** (either urothelial carcinoma or adenocarcinoma of the prostate).[45-46] Nerve-sparing techniques in the male are identical to those with prostate cancer surgery and include preservation of the neurovascular bundles lateral to the prostatic capsule.[47] **Total urethrectomy is rarely performed concomitantly for primary cancer of the bladder in the male since in the vast majority of cases a negative urethral margin can be achieved**. Patients with **a positive urethral margin on final pathology may undergo delayed urethrectomy**.

In females, the term **anterior pelvic exenteration incorporates removal of the uterus, cervix, fallopian tubes, ovaries and the anterior vagina in addition to the bladder and perivesical fat with or without total urethrectomy**. The female reproductive organs are traditionally removed at the time of radical cystectomy although **risk of involvement in female patients who undergo anterior pelvic exenteration for urothelial carcinoma of the bladder is less than 10%** with the vagina the most commonly involved site.[48-49] **Patients with low stage disease or those with anteriorly located disease can be considered for vaginal-sparing techniques, which can offer preservation of sexual function,** and potentially improve outcomes of orthotopic diversion. Consideration may be given to **complete female organ preserving** or ovary-sparing surgery following shared decision-making, in which the ovaries are divided from the fibriae due to potential endocrine benefits from retaining the ovaries, even in post-menopausal females). Furthermore, evidence suggests that removal of the fallopian tubes alone may decrease the risk of ovarian cancer without impacting hormonal function.[50-51] (**Figure 1**)

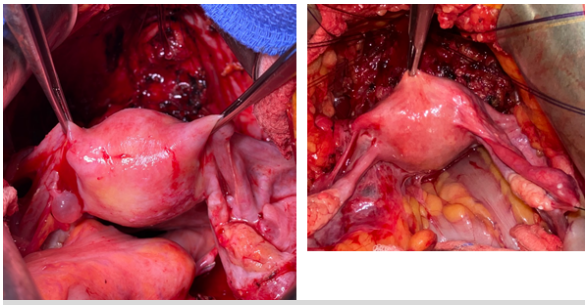

Figure 1: Complete female organ preserving radical cystectomy. The endopelvic fascia and the peri-urethral tissues have been preserved for an orthotopic neobladder

In both male and female patients, bilateral distal ureteral margins are sometimes sent for frozen section to ensure the absence of dysplasia or frank carcinoma although its relation to outcome is controversial.[52-53] The management of positive ureteral margins is controversial. There is an increased risk of upper tract disease with CIS noted at the ureteral margin, but subsequent diagnosis of upper tract disease is NOT inevitable in these circumstances.

A radical cystectomy may be approached through an open approach or laparoscopically (**including robotic-assisted laparoscopic radical cystectomy**). Potential advantages of robotic-assisted laparoscopic surgery include decreased blood loss, increased magnification, and decreased transfusion rates.[54-55-56] Disadvantages include lack of tactile feedback, increased technical demand, increased operative time, and increased surgical costs. Early experience with robotic cystectomy is associated with a low but not negligible rate of post-operative carcinomatosis and other atypical recurrences. However, publication bias and retrospective design of most studies reporting on these events to date preclude definitive conclusions comparing results of the different approaches.[57] Current trends indicate increased utilization of robotic-assisted approach for radical cystectomy, however the majority of radical cystectomies are still performed with an open approach in the U.S and Europe and the majority of urinary diversions are completed in an open fashion.[58] **Two randomized trials have shown no difference in rate of overall complications with the robotic vs. open approaches**.[56-58] **The RAZOR trial found that robotic cystectomy was non-inferior to open cystectomy for recurrence, 3-year progression-free survival or overall survival**.[59] There were also no differences in quality-of-life outcomes between patients undergoing the open vs. robotic approach.[60]

5.2 Role of Lymphadenectomy in Bladder Cancer

5.2.1 Rationale for Lymphadenectomy

It is imperative that a meticulous and thorough pelvic lymph node dissection be performed at the time of cystectomy. The rationale for lymphadenectomy in bladder cancer is to provide accurate nodal staging. In addition, **although lacking level I evidence, there is substantial data indicating that a meticulously performed lymph node dissection can optimize disease control and survival in patients undergoing cystectomy**[61-62] **Several observational cohort studies have shown improved survival with thorough lymph node dissection, however the extent of the dissection required remains controversial** .[63]

The **AUA guidelines recommend that clinicians should remove, at a minimum, the external and internal iliac and obturator lymph nodes (standard lymphadenectomy)** Other groups advocate an extended lymph node dissection up to the aortic bifurcation or inferior mesenteric artery, with inclusion of the presacral lymph nodes given the substantial percentage of patients with lymph node involvement above the common iliac bifurcation.

A prospective, multicenter, phase-III trial patients with resectable high grade pT1 or MIBC (T2-T4aM0) included 401 patients who were randomized to limited vs. extended lymphadenectomy at time of cystectomy.[64] The median number of dissected nodes was 19 in the limited and 31 in the extended arm. The extended lymphadenectomy detected metastases in 11% more patients and 2% had skip metastases. While median overall survival was 52.2 months for the limited lymphadenectomy versus 70.6 months for the extended lymphadenectomy, differences were not statistically significant for RFS (5-yr RFS 65% vs 59%; hazard ratio [HR]=0.84 ; p=0.36), CSS (5-yr CSS 76% vs 65%; HR=0.70; p=0.10), or OS (5-yr OS 59% vs 50%; HR=0.78; p=0.12). Notably, there were more Clavien grade ≥3 lymphoceles reported in the extended lymphadenectomy group. Results regarding the utility of extended lymphadenectomy are anticipated from the SWOG S1011 study of patients with ≥T2 MIBC which allows for neoadjuvant chemotherapy.

Current imaging modalities such as CT scan, MRI, and PET scan are insufficient for proper staging for nodal metastasis in bladder cancer due to inability to detect micrometastasis or early lymph node metastases. Sentinel lymph node biopsy, which is used in some malignancies, does not have a role in bladder cancer due to

the unpredictable nodal drainage pattern of bladder tumors and the potential for skip metastasis (positive nodes in higher echelon nodes despite no involvement in nodes closer to the bladder).

5.2.2 Anatomy of Lymphatic Drainage of the Bladder

The anatomic lymph node drainage of the bladder starts in microvascular lymphatic channels within the bladder wall beneath the basement membrane, followed by the perivesical lymphatic tissue which drains to the internal and external iliac lymphatic chains, common iliac, aortic bifurcation and presacral nodal region and then further proximal to the inferior mesenteric artery (IMA). Nodal disease can then spread proximal, to the IMA, to the retroperitoneal and renal hilar lymph nodes, and beyond.[61,62]

5.2.3 Technique, Boundaries and Complications of Lymphadenectomy for Bladder Cancer

The boundaries for a standard lymph node dissection are listed in **Table 3**. The extended lymph node dissection includes the standard template and extends the dissection up to the aortic bifurcation (with some templates extending to the IMA to include the para-aortic and paracaval nodes. The extended template also includes the pre-sacral lymph nodes, common iliac lymph nodes and the **triangle of Marcille** (defined as the area bounded by the medial border of the psoas major, the lateral margin of the vertebral column, and the iliolumbar ligament below; the obturator nerve traverses through it).[65] (**Figure 2**, **Figure 3**).

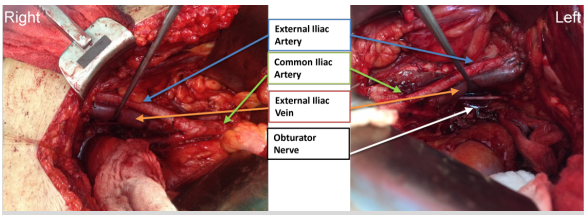

Figure 2: Boundaries of Lymphadenectomy for MIBC

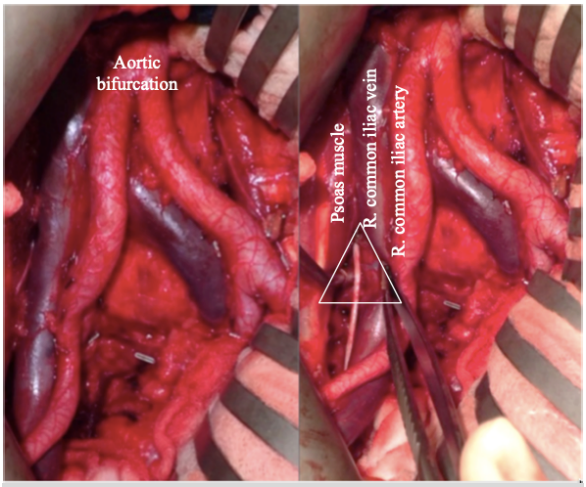

Figure 3: Extended lymphadenectomy template per SWOG S1011 criteria. Figure shows cephalad dissection to the paraaortic and bilateral common iliac nodes as well as triangle of Marcille (outlined).

Table 3: Boundaries of Lymphadenectomy for Muscle Invasive Bladder Cancer	
Distal	Node of Cloquet
Proximal	Dependent on extent of lymphadenectomy: • **Standard**: the bifurcation of the common iliac vessels • **Extended**: the bifurcation of the inferior abdominal aorta • **Superextended**: aorta at the origin of the inferior mesenteric artery (IMA)
Laterally	Genitofemoral nerve
Inferiorly	Internal iliac lymph nodes, floor of pelvis
Posteriorly	Sacrum

5.3 Perioperative Management and Enhanced Recovery Protocols

Many patients undergoing cystectomy have significant comorbidities often related to advanced age and long-term tobacco use.[66] **Pre-operative evaluation and optimization of cardiac, vascular and pulmonary function as well as other comorbidities (e.g. blood sugar management, diabetic control) is crucial to reduce the risk of post-operative complications and adverse perioperative outcomes**. In addition to CMP, CBC, Urinalysis, Urine culture, chest imaging, additional testing may be required for some patients. Patients with diabetes should have a recent HgbA1c. Patients with a heart murmur and/or cardiac symptoms (e.g., breathlessness, chest-pain, pre-syncope) or signs/symptoms of heart failure should undergo echocardiography prior to surgery. In some cases, a cardiac stress test may be indicated.

Frailty is an important risk factor for postoperative complications among patients undergoing cystectomy, especially elderly patients. Frailty indices address a patient's energy, strength, activities of daily living, mental capacities such as cognition, and speed of functional decline if present.

5.3.1 ERAS

Evidence-based multimodal care pathways (commonly referred to as **ERAS- enhanced recovery after surgery**) aim to optimize perioperative care for patients undergoing radical cystectomy. The goal of these protocols is to minimize perioperative gastrointestinal complications and reduce hospital stay while improving the peri-operative experience without an increase in postoperative readmission rates. ERAS protocols include several preoperative, intraoperative, and postoperative interventions, some of which are supported by Level 1 evidence.[67,68] Given lack of data supporting benefit, all bowel preparation prior to surgery are omitted but may be used if there is a preoperative plan for using the colon for continent cutaneous diversion. High-protein, high-carbohydrate liquid drinks (often referred to as 'carb-loading') are recommended for a few days prior to surgery, without any recommendation for withholding intake the day prior to surgery, i.e., a regular diet is maintained up to the night prior to surgery. Alvimopan, a μ-receptor antagonist has been shown in multiple randomized studies to reduce rates of ileus and length of stay, including one randomized controlled in cystectomy patients[69] and should be used peri-operatively if available.[70] Intraoperatively, blood loss and bowel manipulation is minimized. The routine postoperative use of nasogastric tubes should be avoided, and diet is advanced as early as post-operative day one. Pain control should focus on non-opioid alternatives while reserving opioids for breakthrough pain. Routine anti-emetics and venous thromboprophylaxis should be utilized[71,72] and early mobilization is encouraged.

5.3.2 VTE Prophylaxis

The combination of pelvic malignancy and pelvic surgery in a typically medically compromised patient population results in a high rate (3-12%) of venous thrombotic events for patients undergoing radical cystectomy.[73] Herein we summarize the American College of Chest Physicians 9th Edition Evidence-Based Clinical Guidelines for **Prevention of VTE in Nonsurgical Patients** and the **Prevention of VTE in Nonorthopedic Surgical Patients**.

Routine VTE prophylaxis prior to surgery is not recommended for outpatients with cancer without additional risk factors. Outpatients with cancer who do have additional risk factors (i.e., prior VTE, immobilization) are not recommended to receive prophylactic low molecular weight heparin (LMWH) or LDUH (low-dose unfractionated heparin).

After radical cystectomy, when the patient is no longer at high risk of major bleeding complications, mechanical prophylaxis with elastic stockings or intermittent pneumatic compression (IPC) combined with pharmacologic prophylaxis (LMWH or LDUH) is recommended. **Following surgery, extended-duration (4 weeks) pharmacologic prophylaxis is recommended** – with an acknowledgement that this may not be financially feasible for all patients. In patients who are at high risk of major bleeding or in those in whom consequences of bleeding are thought to be severe, mechanical prophylaxis with IPC is preferred over no prophylaxis until pharmacologic prophylaxis can be started.

5.3.3 Anticoagulation / Antiplatelet Agents

In general, radical cystectomy is considered at 'high-risk' of postoperative bleeding thus **therapeutic anticoagulation and antiplatelet agents are held prior to surgery**, then resumed as indicated after surgery when the risk of acute perioperative bleeding has normalized. Please follow link to the **2014 AUA and International Consultation on Urological Disease White Paper on Anticoagulation and Antiplatelet Therapy in Urologic Practice** for guidance.

6. Role of Perioperative Chemotherapy in Managing Bladder Cancer

6.1 Neoadjuvant Chemotherapy

Cisplatin-based neoadjuvant chemotherapy should be offered to eligible patients prior to radical cystectomy and is a consideration prior to chemoradiation therapy. Neoadjuvant chemotherapy using methotrexate, vinblastine, doxorubicin (adriamycin), and cisplatin (MVAC) given prior to cystectomy was associated with a significant improvement in survival. In a landmark Intergroup study, **Grossman and colleagues reported a median survival of 46 months in patients treated with surgery alone, compared to 77 months in patients randomized to neoadjuvant MVAC followed by cystectomy**.[74] This finding was supported by additional clinical trials and an overall effect of neoadjuvant chemotherapy for patients undergoing radical cystectomy has been shown to be an **absolute improvement in overall survival of 5-7% and in cancer-specific survival of 9%**.[75,76]

Classic MVAC was administered as four, 28-day cycles with treatment administered on day 1, 2, 15 and 22. (**Table 4**) This regimen included only one week of recovery prior to start of next cycle (day 29). This prolonged treatment cycle and lack of access to growth factors (e.g. pegfilgrastim which stimulates production of white blood cells) led to severe toxicity such as leukopenia, thrombocytopenia and mucositis related to bone marrow suppression with frequent treatment delays, need for dose modification in up to 63% of patients, and cessation of therapy.[7]

Table 4: Neoadjuvant Chemotherapy Regimens

Classic MVAC		Dose Dense MVAC		Gemcitabine/ Cisplatin	
Cycle repeated every	28 days	Cycle repeated every	14 days	Cycle repeated every	21 days
Methotrexate 30mg/m^2	Day 1, 15, and 22	Methotrexate 30mg/m^2	Day 1	Gemcitabine 1000mg/m^2	Day 1 and 8
Vinblastine 3mg/m^2	Day 2, 15 and 22	Vinblastine 3mg/m^2	Day 2	Cisplatin 70mg/m^2	Day 1
Doxorubicin 30mg/m^2	Day 2	Doxorubicin 30mg/m^2	Day 2		
Cisplatin 70mg/m^2	Day 2	Cisplatin 70 mg/m^2	Day 2		
		Pegylated G-CSF 6mg	Day 3		

MVAC is now commonly administered in a **dose-dense (ddMVAC)** fashion combined with **growth factors**. The drugs are administered on Day 1 and 2, combined with growth factors, followed by a 14-day treatment break. The next cycle then begins on Day 15. Two small phase II trials demonstrated that 95 % of patients were able to receive all four cycles with median time to surgery 6 weeks after finishing chemotherapy. **ddMVAC is better tolerated, has fewer treatment delays, shorter treatment course, and produces borderline statistically significant relative risk reduction of progression and death**.[78-79] The pathological complete response rate observed is similar to that seen following classic MVAC neoadjuvant chemotherapy.

Alternately, patients may receive a doublet combining cisplatin and gemcitabine. This is based on data from a phase III trial randomizing patients to either classic MVAC vs Gemcitabine and Cisplatin (GC) for locally advanced or metastatic bladder cancer. The trial was designed as a non-inferiority study which showed that **overall survival was similar between the two arms**. The critics of the study suggest that study results may not be applicable in the neo-adjuvant setting. However, **GC is widely accepted by the oncology community as an alternative to MVAC because of its better tolerability.**[77] In patients who are not eligible for full dose cisplatin, split dose regimens are commonly used.[80] However, if there is an absolute contraindication for cisplatin, carboplatin should not be substituted and patients should be enrolled on to a clinical trial or taken for radical cystectomy. Patients who are not candidates for radical cystectomy or who desire bladder preservation can still explore trimodality therapy.

A number of trials are underway to assess the feasibility and response of combination chemotherapy with immune check point inhibitors for both cisplatin-eligible and ineligible patients.

Historically, surgery had a very limited role for patients with metastatic disease, therefore the use of chemotherapy has been employed to improve survival for patients undergoing radical cystectomy. Consolidative cystectomy in the setting of metastatic disease and resection of oligometastatic disease has been employed in select cases, largely due to increase responses in the era of chemo- and immunotherapy for treating metastatic bladder cancer but is not the standard of care. Cisplatin-based chemotherapy should be given immediately prior to surgery (neoadjuvant). In patients who are not suitable candidates for cisplatin-based chemotherapy, radical cystectomy alone is an appropriate treatment option.

6.2 Adjuvant therapy

Adjuvant therapy for bladder cancer is defined as treatment given after radical cystectomy, but prior to disease recurrence or metastasis – with the aim of improving oncologic outcomes. In general practice, adjuvant chemotherapy **is offered to patients at high-risk for disease recurrence, such as those with extravesical disease (i.e. T3-T4) or the presence of positive lymph nodes at the time of cystectomy (N+) who did not receive chemotherapy preoperatively. Unlike neoadjuvant chemotherapy, there is no data to date which demonstrates definitive improvement in oncologic outcomes with adjuvant chemotherapy**[81-82-83] Several adjuvant chemotherapy trials have been conducted but they were limited by poor accrual and failure to reach predetermined endpoints, although meta-analyses have shown an overall survival benefit.[81-82-83] The rationale for the use of neoadjuvant rather than adjuvant chemotherapy includes a lack of level I evidence demonstrating a survival benefit in the adjuvant setting, as well as concerns about patients' ability to tolerate adjuvant therapy following radical cystectomy and associated complications.[84] The AUA and NCCN guidelines recommend that eligible patients who have not received cisplatin-based neoadjuvant chemotherapy and have non-organ confined (pT3/T4, node-positive, or positive margins) disease at cystectomy should be offered adjuvant cisplatin-based chemotherapy. DDMVAC is preferred regimen over GC. Carboplatin should not be used in replacement of cisplatin.

In August 2021, the FDA approved nivolumab, an immune checkpoint inhibitor, for adjuvant therapy in patients with urothelial cancer who are at high risk of recurrence after radical cystectomy. 'High risk' patients are broadly classified in two groups: 1) patients who have not received neoadjuvant cisplatin-based chemotherapy and are ineligible for adjuvant or decline adjuvant cisplatin-based chemotherapy with pathological stage of pT3, pT4a, or pN+. 2) patients who received neoadjuvant chemotherapy and had persistent pathological stage of ypT2 to ypT4a or ypN+. The trial that resulted in FDA approval for nivolumab was Checkmate 274 – a phase 3 double-blind study with two primary end points: disease-free survival (DFS) in patients with tumors expressing PD-L1 level of 1% or more and DFS in the intention to treat population. The trial met its primary end point of significant improvement in DFS in the intention to treat population with a hazard ratio of 0.70, while in patients who had ≥ 1% PD-L1 expression, the HR for DFS was 0.55 in patients receiving adjuvant nivolumab. Nivolumab (240 mg) or placebo was administered every 2 weeks as a 30-minute intravenous infusion for up to 1 year or until disease recurrence or discontinuation from the trial. The most common treatment-related adverse events of any grade in the nivolumab group were pruritus (23.1%), fatigue (17.4%), and diarrhea (16.8%). The most common treatment-related adverse events of grade 3 or higher in the nivolumab group were elevations in the serum levels of lipase (5.1%) and amylase (3.7%) as well as diarrhea (0.9%), colitis (0.9%), and pneumonitis (0.9%). It is important to note that immunotherapy is associated with a low but non-zero risk of treatment-related mortality (~1%). Because of lack of overall survival data immunotherapy should be offered after discussion regarding risk and benefit of the treatment. In contrast to the results of the Checkmate 274 trial, the IMvigor 010 trial did not demonstrate a difference in DFS between patients who were observed vs. those receiving adjuvant atezolizumab.[85] The AMBASSADOR trial evaluating pembrolizumab in the adjuvant setting is closed to accrual. Results in future will demonstrate if pembrolizumab has any role in adjuvant treatment of bladder cancer.

Adjuvant radiation therapy has been evaluated in patients who had locally advanced disease with positive margins and or lymph node metastases. These patients are at very high risk for local recurrence (27-41%).[86-87] Randomized trials have demonstrated particular locoregional control benefit to both adjuvant RT and combination adjuvant chemoradiation in cohorts dominated by squamous cell histology.[88-89] Prospective data is more limited in urothelial predominant disease, and studies are ongoing (i.e. GETUG AFU-30 NCT03333356). Overall at present, **adjuvant radiation therapy is associated with improvement in local control and disease-free survival but not overall survival** NCCN guidelines assign a category 2 B recommendation for adjuvant radiation with or without concurrent chemotherapy. Patients are recommended to have a discussion of the risk/benefit ratio of radiation therapy with their treating physician in these settings and to consider open clinical trials.

7. Outcomes

MIBC is one of the most aggressive solid tumors with a predilection for early systemic metastasis. **Five-year overall survival after radical cystectomy depends heavily on stage**. In patients undergoing radical cystectomy alone in the control arm of the SWOG 8710 study, **5-year OS for pT0 patients was 85%**. In a cohort of over 1,000 patients who underwent radical cystectomy at the University of Southern California (USC) who were node-negative and pT0, pTa, pTis, the 5-year OS was similarly 85%.[90-91] A multicenter study of over 2,700 radical cystectomy cases found that **5-year OS was pT2 (65%), pT3 (50%), pT4 (47%) and node positive (31%)**.[92] The cancer-specific survival for each stage is generally higher than overall survival due to competing causes of death.

The use of neoadjuvant chemotherapy is associated with improved survival, although those with significant disease following neoadjuvant cisplatin-based chemotherapy have a very poor prognosis. **Surgical factors influencing outcome include soft tissue margin and the extent of lymph node dissection**.[93] Isolated local recurrence is uncommon (<15%). **Following radical cystectomy, peri-operative mortality rates are 1-3% at large centers** but can be twice that in community hospitals with less experience.[94] Perioperative complications however are far more frequent.[95] In a prospective series from Memorial Sloan-Kettering Cancer Center, **64% of patients undergoing radical cystectomy experienced at least one perioperative complication within 90 days of surgery and 13% experienced a high-grade complication (grade 3 or higher)**.[96]

Table 5: Complications following radical cystectomy using standardized reporting methodology

Gastrointestinal*	Ileus, small bowel obstruction, emesis, peptic ulcer, anastomotic bowel leak, enterocutaneous fistula, ascites, GI bleed, diarrhea, c. difficile
Infection*	Fever of unknown origin, pelvic/retroperitoneal abscess, urinary tract infection, pyelonephritis, cellulitis other than incisional, peritonitis, diverticulitis, cholecystitis, sepsis
Wound	Dehiscence, wound seroma, wound infection, cellulitis
Cardiac	Myocardial infarction (MI), Arrhythmia, Congestive heart failure, hypotension, hypertension, Ischemia without MI, angina
Genitourinary	Acute renal failure, hydro, ureteral stricture, urinary leak (anastomosis or pouch), urinary fistula to bowel or skin, urinary retention, bladder neck contracture, urinary ascites, parastomal hernia, stomal stenosis, venous congestion/ischemia stoma
Pulmonary	Atelectasis, pneumonia, ARDS, dyspnea, pneumothorax, pleural effusion, empyema
Bleeding	Anemia requiring transfusion, significant (> or =1 liter) intraop or post op hemorrhage, flank hematoma, wound hematoma, scrotal hematoma, Disseminated intravascular coagulopathy
Thromboembolic	Deep venous thrombosis, pulmonary embolus, superficial phlebitis, subclavian vein thrombosis
Neurologic	Nerve palsy, paralysis, loss of consciousness, agitation, delirium, CVA, vertigo
Miscellaneous	Psych illness, tendonitis, dermatitis, acidosis, thrombocytopenia without bleeding, foot ulcer, lymphocele, decubitus ulcer
Surgical	Incisional hernia, vascular injury, retained drain, rectal injury, obturator nerve injury, enterotomy

* most common complication

See reference [96]

Survival also varies based on histologic subtype. For example, the overall 5-year survival outcomes in the series from Mansoura (Egypt), where the majority of cases were squamous cell carcinoma (59%) is 48%, whereas overall survival following diagnosis with plasmacytoid urothelial carcinoma is less than 2 years.[97]

8. Urinary Reconstruction

The type of urinary tract reconstruction is determined after a careful pre-operative evaluation of the patient and co-morbidities and discussion regarding the patients' priorities. **No randomized data exist regarding the superiority of one type of diversion over another.** Patient preferences, surgeon biases, and experience influence the choice of diversion to a great extent. Urinary diversions can be classified into **incontinent** (ileal or colon conduit) versus continent (**orthotopic** and **continent cutaneous**). Diversions using the anal sphincter as the continence mechanism (such as ureterosigmoidostomy, or variations such as the Mainz II pouch using the rectosigmoid as a reservoir) are rarely used as a form of urinary diversion today.[98] **Lifelong follow-up is necessary with any form of diversion**.

8.1 Ileal Conduit

The ileal conduit remains the most commonly used form of urinary diversion performed today. **Although it is technically simpler, complications are often underestimated and include upper tract deterioration over the long term, ureteral stricture, stomal stenosis, urinary tract infections, stomal or parastomal hernia, and peri-stoma skin irritation, infection or ulceration**.

8.2. Orthotopic

Absolute contraindications for an orthotopic ileal reservoir vary from center to center and depend on experience and princi-ples. These contraindications are related to the oncological status, the comorbidity and/or the functional status of the patient. **The most commonly performed urinary diversion is the Studer pouch**, which has an afferent limb draining into a low-pressure ileal reservoir. The most important intraoperative consideration is the urethral margin. **A positive invasive urethral margin on frozen-section analysis during a radical cystectomy represents an absolute contraindication in female and male patients.**[99] Other relative contraindications for orthotopic reconstruction are listed in **Table 6**.

Table 6: Relative Contraindications to Performing an Orthotopic or Continent Urinary Diversion
Positive intraoperative urethral margin
Gross positive margins
Pubic bone involvement
Neurological diseases impairing patient’s dexterity or continence
Severe urethral stricture disease in male patients
Chronic renal failure (Cr >1.8 mg/dl or GFR <40 ml/min/1.73 m2)
Hepatic insufficiency
Chronic enteric inflammatory diseases
Malignant bowel diseases
Unwillingness/inability to perform self-catheterization

8.3 Continent Cutaneous Diversion

There are a number of continent cutaneous diversions described in the literature, most of which include the **right colon as the reservoir.** Continence mechanisms include a tapered ileal segment (**Indiana pouch**) or the appendix using the **Mitrofanoff principle**. One advantage of the right colon reservoir with a cutaneous appendico-umbilicos-tomy is that the ileocecal valve can be used as the anti-reflux mechanism. The Kock ileal reservoir has for the most part been abandoned due to the high complication rate associated with the stapled intussuscepted afferent and efferent limbs.

8.4 Results

Urinary continence for patients with an orthotopic diversion depends mostly on the pelvic floor muscles including the ure-thral rhabdosphincter. In a pooled analysis of 2238 patients with different types of orthotopic diversions, **the rate of daytime incontinence ranged between 10-15%.**[100,101] Daytime continence is typically defined as the use of one pad or less per day 1 year after radical cystectomy and orthotopic diversion. **Night-time incontinence is generally higher, and most patients wear some form of protection at night All forms of diversion have potential long-term complications and long-term follow-up is mandatory**. (see **Table 7** and **Table 8**)

Table 7: Diversion-Specific Long-Term Complications

Study Center	N	Median Follow-up (years)	Reoperation Rate (%)	Complications n (%)						
				Bowel	UTI	Stoma	Anastomosis	Urolithiasis	Renal Function	Total
Conduit										
Bern[102]	131	8.1	40	32 (24.0)	30 (23.0)	32 (24.0)	18 (14.0)	12 (9.0)	35 (27.0)	87 (66.0)
Mayo[103]	1057	6.3	6	215 (20.3)	174 (16.5)	163 (15.2)	122 (11.5)	162 (15.3)	213 (20.2)	643 (61.0)
Cairo[104]	36	6.8	39	4 (11.1)	9 (25)	7 (19.4)	5 (13.8)	4 (11.1)	9 (25)	22 (61)
Neobladder										
Ulm[105]	923	6	NR	31 (3.4)	46 (5.0)	NR	102 (11.5)	3 (0.2)	NR	376 (40.8)
Bern[106]	482	2.6	10	34 (7)	28 (5.8)	NR	33 (6.8)	NR	5 (1)	265 (54.9)
Sapporo[107]	57	4.8	15.7	7 (12.3)	1 (1.8)	NR	4 (7)	7	0 (0)	31 (54)

Table 8: Urinary Continence and Retention after Orthotopic Neobladder

Study	N	Mean follow-up (months)	Continence (%)		Self-catheterization (%)
			Daytime	Nighttime	
Male					
Thomas[101]	188	N/A	92	51	10
Ahmadi[108]	179	54	83	47	9.5
Studer[106]	482	31	92	79	2.9
Tanaka[107]	57	57	95.6	88.4	8.7
Female					
Hautmann[109,110]	116	60	83	83	50
Ali-el-Dein[107]	192	51	92	72	16
Stein[111]	56	103	87	66	61
Bartsch[104]	56	63	76	67	62

8.5 Metabolic Complications of Urinary Diversion

Use of an intestinal segment for urinary diversion is associated with a number of metabolic and long-term consequences. **The typical pattern of metabolic abnormality seen is dependent on the segment of bowel used for urinary diversion and is more pronounced with continent urinary diversions. Most commonly, urinary diversion is accomplished with the use of ileum or colon and associated with hyperchloremic, hypokalemic metabolic acidosis**. Other abnormalities include renal failure, bone density loss, diarrhea, urolithiasis, Vit B_{12} deficiency, and hyperammonemia (extremely rare in the absence of liver disease). See AUA Core Curriculum **Consults and Emergencies: Metabolic Acidosis**.

Table 9: Summary of Common Metabolic Disturbances with Urinary Diversion

Metabolic Disturbance	Notes	Management
Metabolic Acidosis	Decrease in bone mineral density, fatigue, altered temperature regulation, failure to thrive. Rapid shallow breathing, confusion in severe cases.	Correction of hyperchloremic metabolic acidosis with hydration and oral sodium bicarbonate (preferred), sodium citrate, nicotinic acid, chlorpromazine
Hypokalemia	Fatigue, constipation, weakness, muscle spasms	Replace potassium
Renal failure	May be related to anatomic obstruction, severe dehydration, poor emptying, chronic reflux, recurrent infection	Ensure proper emptying of diversion, consider catheterization of neobladder or conversion to non-continent diversion if conservative measures fail.
Diarrhea	may be associated bile acid malabsorption, loss of ileocecal value, shortened intestinal transit time	High fiber diet, consider bile salt binding resin such as cholestyramine or intestinal mobility inhibitors such as loperamide, Consider check levels of fat-soluble vitamins (A, D, E, K).
Vitamin B12 deficiency	megaloblastic macrocytic anemia, neuropathy	Check annually, vitamin B12 supplementation intramuscularly or high-dose oral treatment
Calcium oxalate stones	Nephrolithiasis, Infections, urinary tract obstruction	Calcium supplementation to bind oxalate in recurrent stone formers
Hyperammonemic encephalopathy	Mental disturbances, confusion, lethargy, vomiting, coma	Treat for possible urea-splitting bacteria, place catheter to minimize reabsorption of ammonia through bowel wall

9. Bladder Preservation

While radical cystectomy with or without neoadjuvant chemotherapy remains considered the gold standard therapy for MIBC, the associated morbidity has driven study of alternatives. **AUA/ASCO/ ASTRO guidelines currently recommend discussion of bladder preservation therapies for patients who desire to retain their bladder and/or for those with significant comorbidities for whom radical cystectomy is not a viable treatment option. Options for bladder preservation therapies include partial cystectomy, chemoradiation/trimodal therapy (TMT), and 'radical' transurethral resection (TUR). Of these,** TMT is the best supported by prospective data **but all require careful selection.** Consequently, these treatment options should be considered after a **multidisciplinary evaluation** with a urologist, medical oncologist and radiation oncologist.

9.1 Partial Cystectomy

In **selected patients with a solitary tumor in the absence of CIS**, partial cystectomy can offer reasonable cancer control rates. The key to selection is tumor size and location with the most common site being at the bladder dome. **In a series with a median follow-up of 33 months, the overall 5-year survival was 69%, with 74% of these patients maintaining an intact bladder**.[112] Carcinoma in situ and multifocal lesions were a risk factor for non-muscle invasive recurrence (80%), while positive surgical margins and lymph node involvement were factors for advanced recurrence. **Another indication for a partial cystectomy may be a tumor within a bladder diverticulum** as definitive TURBT is contraindicated in this situation, although scant data exists regarding the long-term efficacy of this approach. Salvage radical cystectomy following prior partial cystectomy can provide prolonged survival for recurrent disease within the bladder. Prognosis, however, is highly dependent on pathological tumor stage and nodal status at salvage surgery with only 15% of patients with locally advanced recurrent disease surviving long-term![113]

9.2 Radical TUR

Radical transurethral resection of MIBC has been described as an alternative to cystectomy in selected patients who are generally not considered candidates for radical cystectomy. Repeat TUR is performed until there is no residual tumor left. The bladder remains at risk for local recurrence therefore careful endoscopic and imaging surveillance is mandatory and there is significant risk of pathologic and nodal understaging. Older series suggest the potential for long-term disease-free survival in select patients with 5-year survival rates reported at 30%.[114] The combination of complete TUR and chemotherapy is associated with improved results with 5-year survival being 60% in one series.[115]

9.3 Chemoradiation

For patients with MIBC who have elected **multi-modal bladder preserving therapy**, clinicians should offer **'maximal' safe debulking transurethral resection of bladder tumor, chemotherapy combined with external beam radiation therapy, termed triple modality therapy (TMT). (Strong Recommendation; Evidence Level: Grade B).**[116] **Radiation should always be administered with radiosensitizing chemotherapy.** Patients should be counseled about the need for continued cystoscopic surveillance.

Patient selection for TMT: multidisciplinary evaluation is critical in the indication of pa patient for TMT. The patient should be able to tolerate radiotherapy with appropriate chemosensitizing chemotherapy. Contraindications include prior pelvic radiation, severe LUTS or bowel dysfunction at baseline (due to risk of subsequent poor functional outcomes), concomitant upper tract disease or tumor extending into the ureter beyond the intramural tunnel (Tumor merely overlying the ureteric orifice or extending just within the ureteral tunnel can be managed with TUR alone). Inability to achieve full TURBT and hydronephrosis are relative contraindication for this approach due to surrogacy for more advanced stage. Patients with diffuse CIS in addition to MIBC may have a relative contraindication to TMT because of the risk of persistent disease post radiation. These patients may require radical cystectomy or have increased risk of future recurrence of MIBC due to persistent CIS![17]

Importantly, radiation alone is considered palliative, and only concurrent chemoradiation should be offered as curative therapy due to level 1 data for superior locoregional control and multiple regimen options.[118] **Peri-operative systemic has not demonstrated improvement in outcome in historical studies, however, these were limited by small number and excess hematologic toxicity in an era before growth factor support i.e RTOG 89-03. Adjuvant chemotherapy has been similarly limited, as in RTOG 97-06 in which <50% full compliance was observed** .[119] Nonetheless, about one in three patients received and tolerated neoadjuvant chemotherapy in the more contemporary BC2001 trial, making its use a reasonable option and the standard approach in the high-volume UK centers. [118]

In general, **radiosensitizing chemotherapy**, which is administered at lower doses with radiation has more systemic tumoricidal effect. Commonly used regimens include a **combination of 5 – fluorouracil (or capecitabine as alternative) and mitomycin-C**,[118] **single agent cisplatin as bolus or weekly dosing, and low dose gemcitabine**. These offer tolerable options for a broad array of patients based upon renal function, performance status and other medical factors. There is no data to suggest superiority of a given regimen at this time.

Radiotherapy may be given in conventional (1.8-2Gy/fraction) or hypofractionated courses (i.e. 2.75Gy/fraction). Recent data suggestion non-inferiority of toxicity and potential superiority of locoregional control for hypofractionation.[120] Multi-disciplinary 'mapping' of initial disease location is important for ensuring generous coverage to full dose of disease areas, which can be aided by cystoscopic placement of fiducial markers.[121] Extending the radiation field to cover broader margins on the bladder or elective nodes is of unclear added benefit.[122] As noted, these regimens should be given with concurrent chemotherapy. In contrast, palliative therapy such as for bleeding from bladder tumors appear to be more effective when given as hypofractioanted course. [123]

Following completion of bladder preserving therapy, clinicians should perform **regular surveillance** with CT or MRI scans, cystoscopy, and urine cytology. In patients who are **medically fit and have residual or recurrent muscle-invasive disease following bladder-preserving therapy, clinicians should offer salvage radical cystectomy with bilateral pelvic lymphadenectomy** In patients with limited non-muscle invasive recurrence after bladder preserving therapy, clinicians may offer either **local measures, such as transurethral resection of bladder tumor**[124] **with intravesical therapy, or radical cystectomy with bilateral pelvic lymphadenectomy**.

The outcomes for **salvage radical cystectomy** (radical cystectomy following pelvic radiation) are generally worse than those of primary cystectomy, although there is limited data in this area.[125] Among 91 patients treated with salvage cystectomy following definitive chemoradiation for bladder cancer at the Massachusetts General Hospital, the 90-day complication rate was 69%, with major complications in 16%, 90-day mortality in 2.2%, and readmission in 21%. Another series from MGH evaluating RC's done at their institution observed similar immediate complication rates between primary RC and salvage RC. However, the rate of late complications (more than 90 days after RC) was higher in salvage RC compared to primary RC.[126]

Recent meta-analysis of 9 studies in trimodality therapy, of which 3 studies provided data on complications after salvage RC found that overall complication rates were not significantly worse for salvage radical cystectomy compared to primary RC. However, the rate of major complication related to surgery were higher following SV-RC compared to primary RC (22% vs 12%). Individual series also demonstrated higher rate of overall urinary anastomosis related complications![127]

In select cases, surgery can offer a prolonged survival even in the presence of gross nodal disease. For example, in a series of 84 patients from Memorial Sloan Kettering, 10-year survival was 24%.[128]

There is conflicting comparative efficacy data regarding TMT vs. radical cystectomy due to a lack of level 1 evidence from clinical trials comparing the two approaches directly. The only trial to have randomized patients to bladder preservation vs radical cystectomy was closed early due to lack of accrual![29] **Retrospective studies comparing TMT vs. radical cystectomy have demonstrated similar 5-year disease-specific survival (TMT: 76.6 % vs radical cystectomy: 73.2%, P=0.49 after matching for age, comorbidities, nodal status, clinical stage and performance status) with salvage cystectomy rate of 10.7%.**[130] Mak et al. reported long-term outcomes from a pooled analysis of RTOG protocols 8802, 8903, 9506, 9706, 9906 and 0233, a 5-year survival of 57% for all study patients, of whom, 80% of the patients who were alive had an

intact bladder.[131] However, approximately 20% of the patients ultimately underwent cystectomy with virtually all patients receiving an ileal conduit. Among patient undergoing salvage cystectomy, the 5-year OS rate was 45%. The proportion of patients who initially elect bladder preservation but ultimately require cystectomy in a non-study setting is unclear. The reported bladder preservation rates may be dependent upon the degree of initial patient evaluation, selection, and later appetite or ability to undergo cystectomy. Based upon these data, **current AUA guidelines state that multi-modal bladder preserving therapy should be the preferred treatment option in patients desiring bladder preservation who understand the risks associated with this approach or those who are medically unfit for surgery**. It is the treating provider's responsibility to explain to the patient that chemoradiation can potentially treat current bladder cancer but may not prevent future recurrences and the particular need for close monitoring using cystoscopy, urine cytology and imaging at routine intervals to monitor for salvageable recurrence, which may include cystectomy with more limited urinary diversion options.

10. Treatment of Metastatic Bladder Cancer

10.1 Systemic Chemotherapy and Survival

Metastatic bladder cancer is generally responsive to chemotherapy, albeit with poor prognosis.[132] In fact, **response rates of 70% are reported in metastatic disease and pathologic complete response has been reported in up to 30% in the neoadjuvant chemotherapy setting**. As noted above, the best known and most rigorously studied chemotherapy combination for treating bladder cancer is **MVAC** (methotrexate, vinblastine, Adriamycin [doxorubicin], and cisplatin), which was first described in the early 1980s. In the 1990s several new agents and combinations were tested for treatment of metastatic disease. The combination of **gemcitabine plus cisplatin** (GC) demonstrated comparable efficacy with significantly less toxicity than MVAC, and thus is also commonly prescribed.[133]

10.1.1 Cisplatin and Cisplatin Analogues

(see reference 132)

Cisplatin is the principal component of MVAC and GC and is responsible for the high response rates to these regimens. Indeed, these agents without cisplatin is associated with substantially reduced efficacy. Cisplatin binds deoxyribonucleic acid (DNA) and produces intra-strand crosslinks and DNA adducts, thus inhibiting DNA replication. **The dose-limiting toxicity of cisplatin is nephrotoxicity, which peaks at 2 weeks following treatment and is generally reversible**. Other potential adverse effects include **neurotoxicity** (peripheral neuropathy) and **ototoxicity** (hearing loss).

Carboplatin is a cisplatin analogue. Advantages of carboplatin over cisplatin include that it can be dose-modified in the setting of reduced renal function. Carboplatin is also more convenient to administer given that it does not require prolonged hydration and extensive anti-emetic premedication. **The principal dose-limiting toxicity of carboplatin is bone marrow suppression, particularly thrombocytopenia. However, carboplatin has not been demonstrated to have equivalent efficacy to cisplatin** In fact, in other malignancies, studies have clearly shown a superiority of cisplatin over carboplatin.[134,135]

10.1.2 Taxane

(see reference 132)

Single agent **paclitaxel** has one of the highest reported response rates in bladder cancer with 27% of patients experiencing a complete response and 15% experiencing a partial response (median duration of response is however only 7 months). Paclitaxel blocks cell cycle in mitosis by binding to tubulin and interfering with assembly of microtubules. **Its principal dose-limiting toxicity is hypersensitivity**, **peripheral neuropathy**, **and myelosuppression**.

10.1.3 Gemcitabine

(see reference 132)

Gemcitabine is a cytidine analog that inhibits DNA synthesis. **The main dose-limiting toxicity of gemcitabine is myelosuppression**. It has a considerable response rate (22-28%) and is commonly used in previously treated patients and in combination with cisplatin in the neoadjuvant setting.

10.2 Checkpoint Blockade Therapy in Bladder Cancer

Programmed Death-1 (PD-1) is another member of the CD28 family that is expressed on activated T cells and on other immune cells. **PD-1 has two binding partners: PD-L1 (B7-H1) and PD-L2 (B7-DC).** PD-L1 is broadly expressed on both hematopoietic and non-hematopoietic cells, including many tumor cells. **When bound to these receptors, PD-1 produces an inhibitory signal to the T cell.** PD-1 is upregulated upon initial activation of T cells but sustained activation eventually renders the T cell poorly functional (termed "exhausted"). Thus, antibodies targeting PD-1 and PD-L1 are thought to generate anti-tumor immunity by inhibiting these negative T cell signaling in the PD-1/PD-L1 axis. PD-1/PD-L1 therapies are now a principal component in the management of metastatic bladder cancer and are expected to impact less advanced disease states as well. These are commonly called immune-checkpoint inhibitors (ICI) or immuno-oncology therapies (IO) ICIs that target the PD-1/PD-L1 axis which are currently approved for use in metastatic bladder cancer are described in **Table 10**.

Table 10: Immune check point inhibitor in second line or cis ineligible patients[7,136,137,138,139]

Drug	Indication	Clinical trial Phase	Number of patient	ORR	Median PFS(mths)	Median OS PD –L1 high(% RR)	Median OS PD-L1 low(%RR)	Median OS total
Atezo (Imvigor 210)[140]	Platinum ineligible	II	119	23%	2.7	12.3mths(28%)	19.1mths(18%)	15.9
Pembro (Keynote 045)[137]	Platinum failure	III	265	21.1%	2.0	NR(21.7%)	NR(20.1%)	10.3
Nivo (Checkmate 275)[138]	Platinum failure	II	265	19.6%	2.1	11.3(28%)	5.9(23%)	8.74
Avelumab (JAVELIN)[7]	Platinum refractory	Ib	161	17 %	1.5	8.2(24%)	6.2(13%)	6.5
Pembro (keynote -052)	**First line cis-ineligible**	II	374	24%	2	NR(38%)	NR(11%)	NR

These drugs are approved for different indications in urothelial carcinoma. Pembrolizumab and Atezolizumab are approved for the primary treatment of metastatic bladder cancer patients who are cisplatin-ineligible and have high PD-L1 expression. Pembrolizumab, avelumab and nivolumab are approved for second-line use after progression on platinum-containing chemotherapy. **Avelumab also received FDA approval as maintenance therapy** following first-line platinum-based chemotherapy. This approval is based on a phase III trial (JAVELIN Bladder 100) which randomized patients whose disease either remained stable or responded to first-line gemcitabine plus cisplatin or carboplatin to avelumab plus best standard of care vs. standard of care alone. In this trial, patients received avelumab until progression of disease, unacceptable toxicity, or withdrawal. Patients randomized to the avelumab arm had significantly longer median overall survival (21.4 months vs. 14.3 months). Thus, **avelumab maintenance following chemotherapy represents the new standard of care for patients with metastatic or unresectable locally advanced disease**.[141]

Within the medical oncology community, there is consensus that all immune checkpoint inhibitor have comparable activity in bladder cancer. **However, pembrolizumab is the only drug with data from phase III trial demonstrating overall survival benefit vs. chemotherapy in the second-line setting for metastatic bladder cancer with an overall response rate in an unselected patient population of 15-20%**. Thus, most patients will ultimately progress on this therapy. Clinical trials have evaluated various biomarkers with the goal of predicting response to these agents, finding that patients with a **high tumoral immune cell expression of PD-L1, high tumor mutational burden and luminal subtype are probably more responsive to checkpoint inhibitors**. However, these therapies received approval for use in all patients due to high response rates across patients even in the absence of such biomarkers, suggesting a role of other mechanisms. Many immune related biomarkers are being investigated further in ongoing clinical trials. On the basis of current evidence, **the FDA advised against enrolling patients with low expression of PD-L1 in their tumors on clinical trials involving single agent immune checkpoint inhibitor in first line setting and also mandated this information in the drug label**.

ICI offer the potential for patients to achieve **durable remission**. However, as mentioned, **most patients will progress on immunotherapy alone**, which led to interest in exploring combinations of immunotherapy with other agents. Some of these strategies include radiation combined with chemo-immunotherapy, immunotherapy with chemotherapy, dual checkpoint inhibitors and immunotherapy in combination with vascular endothelial receptor tyrosine kinase inhibitors. These clinical trials are ongoing, and we will have more insight into their activity in the near future.

10.3 Side effect profiles

ICI are generally tolerable for most patients. Grade 1-2 side effects are observed in more than 10%, most commonly fatigue or rash. (**Table 11**) However, **15-20% patients report grade 3-5 adverse events, which may require holding treatment and initiating immunosuppression with steroids or other agents**. Severe toxicity leading to death has been reported and patients on immunotherapy must be followed closely by the provider prescribing these drugs with familiarity with immune adverse events.

Most patients will develop toxicity within first 6 – 12 weeks of starting therapy. If a patient develops an endocrinopathy such as hypo- or hyperthyroidism, diabetes, hypoadrenalism and hypopituatrism, treatment can continue as long as the side effects can be medically managed. **Other serious side effects like pneumonitis, cardiomyopathy, neurological complications or serious liver and GI toxicity may warrant stopping the therapy altogether**

Table 11: Toxicities associated with Immune checkpoint inhibitor
Common Toxicities observed in >10% of patients
• Fatigue • Pruritis • Nausea • Diarrhea • Asthenia • Anemia
Toxicities observed in < 10% of patients
• Endocrinopathies • Pneumonits • Colitis • Myostis • Severe Skin reactions

Novel immune regulators such as IDO, LAG3 and TIM-3 inhibitors are currently under investigation in bladder cancer in early phase clinical trials.

10.4 Fibroblast growth factor receptor inhibitor

Erdafitinib is a fibroblast growth factor receptor tyrosine kinase inhibitor. It has been granted accelerated FDA-approval for patients with metastatic urothelial carcinoma with FGFR2 or FGFR3 genetic alterations that progressed on platinum-based chemotherapy. The approval was based on a small single arm study of 87 patients who met the above criteria, in which the objective response rate was 32%, with a median response duration of 5.4 months.[142] The drug is administered orally. The most common AEs include hyperphosphatemia, nausea, stomatitis, dysgeusia and dry mouth. Patients require routine monitoring for hyperphosphatemia. Ocular side effects like central serous retinopathy or retinal pigment epithelial detachment may occur in up to 25% of patients and require cessation of therapy. The accelerated approval is contingent on the results of a confirmatory trial.

10.5 Antibody drug conjugate

Antibody drug conjugates represent another class of drugs (e.g., enfortumab vedontin, Sacituzumab govitecan) which has shown promising clinical activity in early phase clinical trials and are currently in late phase clinical trials. [143-144]

Enfortumumab vedontin (EV) is a new molecule in this class which was FDA-approved in 2020 for patients with metastatic bladder cancer who had previously been treated with platinum-based chemotherapy and immunotherapy. The drug is primarily a form of chemotherapy which is carried by an antibody targeting Nectin-4 protein, which is expressed by various tissues including urothelial cells. Thus, the drug preferentially targets tumor cells, delivering a **"payload" of chemotherapy**. EV-201 was a single arm phase II multi-institutional trial which enrolled 125 patients with metastatic urothelial carcinoma. Patients received enfortumab 1.25mg/kg on day 1, 8 and 15 of a 28-day cycle until disease progression or toxicity. Investigators observed a 44% overall response rate with a complete response rate of 12%, representing a significant incremental gain for this group of patients who have exhausted chemotherapy and immunotherapy as an option.[145]

The common side effects include fatigue, alopecia, nausea, dysgeusia, and diarrhea. Skin and eye toxicity was significant and may warrant close monitoring. Diabetic ketoacidosis and death were also observed in the patients treated on this early phase trial. EV has received accelerated approval, pending data from large phase III trial.

Sacituzumab govitecan (SG) is another similar molecule with IgG1 kappa antibody-targeting antitrophoblast cell-surface antigen 2 (Trop-2) expressed on carcinoma cells. The antibody is attached to SN38, a topoisomerase 1 inhibitor, which is an active moiety of irinotecan. The linker attaching the chemotherapy to the antibody is hydrolysable in the tumor microenvironment and also lysosomal cleavage inside the cells. This allows more release of the drug and potentially more toxicity. SG also received accelerated approval in April 2021 in patients with metastatic bladder cancer progressed on platinum-based chemotherapy and immune checkpoint therapy. The approval was based on small phase II study (TROPHY) evaluating patients with prior platinum chemotherapy and ICI therapy. Overall response rate was observed to be 27.7% and over 5% patients achieving complete response. The median duration of response was 7.2 months. Most common treatment related adverse events were related to bone marrow toxicity (46%), gastrointestinal toxicity (65%), fatigue (52%) and infections (8%). Skin toxicity and neuropathy which was observed with EV was infrequent with SG. There is an ongoing phase III trial (TROPiCS-04) comparing SG vs physician choice chemotherapy after progression on platinum-based chemotherapy and immune checkpoint inhibitor which will further study the role of SG in advanced disease![146] SG is given 10mg/kg on day 1 and 8 of a 21-day cycle. Patients with known UGT1A1 homozygous *28/*28 genotype are at increased risk of toxicity, however routine screening is not advocated but close monitoring of all patients is recommended.

Videos

Robotic anterior exenteration in females– tips and tricks

Demonstration of nerve-spring technique during robotic radical cystectomy

Robotic-Assisted Extended Lymph Node Dissection for Pelvic Malignancies

Robot Assisted Intracorporeal Ileal Conduit: Simplified Step-By-Step Technique

THE STEPWISE APPROACH TO ROBOTIC-ASSISTED LAPAROSCOPIC INTRACORPOREAL URINARY DIVERSION.

Intracorporeal ileal conduit urinary diversion

Robotic repair of left uretero

Robot-Assisted Laparoscopic Intracorporeal Ileal Conduit Urinary Diversion: Step-By-Step

Modified Studer Orthotopic Ileal Neobladder

In-Situ Robotic Ileal Neobladder: Tips to Avoid Complications

USC Technique for Robot-assisted Intracorporeal Studer Neobladder

Robot-Assisted Laparoscopic Bladder Diverticulectomy: Surgical Technique and Intermediate Follow Up

ROBOTIC BLADDER DIVERTICULECTOMY: TECHNIQUES AND OUTCOMES

Robotic Pelvic Lymph Node Dissection

Extended Bilateral Pelvic Lymph Node Dissection

Robotic Intracorporeal Urinary Diversion: Ileal Conduit

Robotic Partial Cystectomy for Muscle Invasive Bladder Cancer of the Bladder Dome

Presentations

BLADDER NEOPLASMS: MUSCLE INVASIVE BLADDER CANCER Presentation 1

References

1 American Cancer Society. Cancer Facts & Figures 2022. Atlanta, Ga: American Cancer Society; 2022. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Cancer Stat Facts: Bladder Cancer, 2010-2014. National Cancer Institute, Bethesda, MD. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed on January 5, 2018.

2 Calò, B., Marchioni, M., Sanguedolce, F., Falagario, U. G., Chirico, M., Carrieri, G., & Cormio, L. (2021). Neoadjuvant Chemotherapy Before Radical Cystectomy: Why We Must Adhere?. Current Drug Targets, 22(1), 14-21.

3 Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer: American Urological Association/American Society of Clinical Oncology/American Society for Radiation Oncology/Society of Urologic Oncology Clinical Practice Guideline Summary. Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, Lotan Y, Meeks JJ, Michalski JM, Morgan TM, Quale DZ, Rosenberg JE, Zietman AL, Holzbeierlein JM. J Oncol Pract. 2017 Sep;13(9):621-625. doi: 10.1200/JOP.2017.024919. Epub 2017 Aug 10. No abstract available.

4 Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. Eur Urol. 2016 Jul;70(1):106-119. doi: 10.1016/j.eururo.2016.02.028. Epub 2016 Mar 17. PMID: 26996659.

5 Veskimäe E, Espinos EL, Bruins HM, Yuan Y, Sylvester R, Kamat AM, Shariat SF, Witjes JA, Compérat EM. What Is the Prognostic and Clinical Importance of Urothelial and Nonurothelial Histological Variants of Bladder Cancer in Predicting Oncological Outcomes in Patients with Muscle-invasive and Metastatic Bladder Cancer? A European Association of Urology Muscle Invasive and Metastatic Bladder Cancer Guidelines Panel Systematic Review. Eur Urol Oncol. 2019 Nov;2(6):625-642. doi: 10.1016/j.euo.2019.09.003. Epub 2019 Oct 8. PMID: 31601522.

6 Hansel et al. A Contemporary Update on Pathology Standards for Bladder Cancer: Transurethral Resection and Radical Cystectomy Specimens, Eur Urol 63 (2013) p 321-332.

7 ☆ Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, Pruthi R, Quale DZ, Ritch CR, Seigne JD, Skinner EC, Smith ND, McKiernan JM. J Urol. 2016 Oct;196(4):1021-9.

8 ☆ Dahm P, J.E. G. Primary Non-urothelial Neoplasms of the Bladder. AUA Update Series. 2004;23(Lesson: 6):42-43.

9 Abufaraj M, Foerster B, Schernhammer E, Moschini M, Kimura S, Hassler MR, Preston MA, Karakiewicz PI, Remzi M, Shariat SF. Micropapillary Urothelial Carcinoma of the Bladder: A Systematic Review and Meta-analysis of Disease Characteristics and Treatment Outcomes. Eur Urol. 2019 Apr;75(4):649-658. doi: 10.1016/j.eururo.2018.11.052. Epub 2018 Dec 13. PMID: 30553613.

10 Diamantopoulos LN, Holt SK, Khaki AR, Sekar RR, Gadzinski A, Nyame YA, Vakar-Lopez F, Tretiakova MS, Psutka SP, Gore JL, Lin DW, Schade GR, Hsieh AC, Lee JK, Yezefski T, Schweizer MT, Cheng HH, Yu EY, True LD, Montgomery RB, Grivas P, Wright JL. Response to Neoadjuvant Chemotherapy and Survival in Micropapillary Urothelial Carcinoma: Data From a Tertiary Referral Center and the Surveillance, Epidemiology, and End Results (SEER) Program. Clin Genitourin Cancer. 2021 Apr;19(2):144-154. doi: 10.1016/j.clgc.2020.10.002. Epub 2020 Oct 14. PMID: 33160889; PMCID: PMC8044249.

11 Lin O, Cardillo M, Dalbagni G, Linkov I, Hutchinson B, Reuter VE. Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 12 cases. Mod Pathol. 2003 Dec;16(12):1289-98. doi: 10.1097/01.MP.0000094091.04541.FC. PMID: 14681330.

12 Wasco MJ, Daignault S, Bradley D, Shah RB. Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. Hum Pathol. 2010 Feb;41(2):163-71. doi: 10.1016/j.humpath.2009.07.015. Epub 2009 Oct 1. PMID: 19800100.

13 Lee, Y. H., Lee, M. M., De Silva, D. M., Roy, A., Wright, C. E., Wong, T. K., ... & Bottaro, D. P. (2021). Autocrine signaling by receptor tyrosine kinases in urothelial carcinoma of the bladder. Plos one, 16(7), e0241766.

14 Kim DK, Kim JW, Ro JY, Lee HS, Park JY, Ahn HK, Lee JY, Cho KS. Plasmacytoid Variant Urothelial Carcinoma of the Bladder: A Systematic Review and Meta-Analysis of Clinicopathological Features and Survival Outcomes. J Urol. 2020 Aug;204(2):215-223. doi: 10.1097/JU.0000000000000794. Epub 2020 Jan 31. PMID: 32003614.

15 Diamantopoulos LN, Khaki AR, Grivas P, Gore JL, Schade GR, Hsieh AC, Lee JK, Yezefski T, Yu EY, Schweizer MT, Cheng HH, Psutka SP, Lin DW, Tretiakova MS, Vakar-Lopez F, Montgomery RB, Wright JL. Plasmacytoid urothelial carcinoma: response to chemotherapy and oncologic outcomes. Bladder Cancer. 2020;6(1):71-81. doi: 10.3233/blc-190258. Epub 2020 Mar 28. PMID: 34109262; PMCID: PMC8186525.

16 Dayyani F, Czerniak BA, Sircar K, Munsell MF, Millikan RE, Dinney CP, Siefker-Radtke AO. Plasmacytoid urothelial carcinoma, a chemosensitive cancer with poor prognosis, and peritoneal carcinomatosis. J Urol. 2013 May;189(5):1656-61. doi: 10.1016/j.juro.2012.11.084. Epub 2012 Nov 15. PMID: 23159581; PMCID: PMC4243847.

17 Droller M. Urothelial Tumors (ACS ATLAS OF CLINICAL ONCOLOGY). 1st ed: pmph usa; 2004.

18 Kassouf W, Spiess PE, Siefker-Radtke A, Swanson D, Grossman HB, Kamat AM, Munsell MF, Guo CC, Czerniak BA, Dinney CP. Outcome and patterns of recurrence of nonbilharzial pure squamous cell carcinoma of the bladder: a contemporary review of The University of Texas M D Anderson Cancer Center experience. Cancer. 2007 Aug 15;110(4):764-9. doi: 10.1002/cncr.22853. PMID: 17614317.

19 Gad el Mawla N, Mansour MA, Eissa S, Ali NM, Elattar I, Hamza MR, Khaled H, Habboubi N, Magrath I, Elsebai I. A randomized pilot study of high-dose epirubicin as neoadjuvant chemotherapy in the treatment of cancer of the bilharzial bladder. Ann Oncol. 1991 Feb;2(2):137-40. doi: 10.1093/oxfordjournals.annonc.a057877. PMID: 2054316.

20 Galsky MD, Iasonos A, Mironov S, Scattergood J, Donat SM, Bochner BH, Herr HW, Russo P, Boyle MG, Bajorin DF. Prospective trial of ifosfamide, paclitaxel, and cisplatin in patients with advanced non-transitional cell carcinoma of the urothelial tract. Urology. 2007 Feb;69(2):255-9. doi: 10.1016/j.urology.2006.10.029. PMID: 17320659.

21 Zaghloul, M. S., Christodouleas, J. P., Smith, A., Abdallah, A., William, H., Khaled, H. M., Hwang, W. T., & Baumann, B. C. (2018). Adjuvant Sandwich Chemotherapy Plus Radiotherapy vs Adjuvant Chemotherapy Alone for Locally Advanced Bladder Cancer After Radical Cystectomy: A Randomized Phase 2 Trial. JAMA surgery, 153(1), e174591. https://doi.org/10.1001/jamasurg.2017.4591

22 Lopez?Beltran, A, Henriques, V, Montironi, R, Cimadamore, A, Raspollini, M R & Cheng, L (2019) Histopathology 74, 77– 96. https://doi.org/10.1111/his.13752 Variants and new entities of bladder cancer

23 Eble JN. Abnormalities of the urachus. New York, NY: Churchill-Livingstone; 1989.

24 Vetterlein MW, Wankowicz SAM, Seisen T, Lander R, Löppenberg B, Chun FK, Menon M, Sun M, Barletta JA, Choueiri TK, Bellmunt J, Trinh QD, Preston MA. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. Cancer. 2017 Nov 15;123(22):4346-4355. doi: 10.1002/cncr.30907. Epub 2017 Jul 25. PMID: 28743155.

25 Zaghloul MS, Nouh A, Nazmy M, Ramzy S, Zaghloul AS, Sedira MA, Khalil E. Long-term results of primary adenocarcinoma of the urinary bladder: a report on 192 patients. Urol Oncol. 2006 Jan-Feb;24(1):13-20. doi: 10.1016/j.urolonc.2005.05.027. PMID: 16414487.

26 Chang, M. T., Penson, A., Desai, N. B., Socci, N. D., Shen, R., Seshan, V. E., Kundra, R., Abeshouse, A., Viale, A., Cha, E. K., Hao, X., Reuter, V. E., Rudin, C. M., Bochner, B. H., Rosenberg, J. E., Bajorin, D. F., Schultz, N., Berger, M. F., Iyer, G., Solit, D. B., … Taylor, B. S. (2018). Small-Cell Carcinomas of the Bladder and Lung Are Characterized by a Convergent but Distinct Pathogenesis. Clinical cancer research : an official journal of the American Association for Cancer Research, 24(8), 1965–1973. https://doi.org/10.1158/1078-0432.CCR-17-2655

27 Swapna Thota, Gaurav Kistangari, Hamed Daw, Timothy Spiro, A Clinical Review of Small-Cell Carcinoma of the Urinary Bladder, Clinical Genitourinary Cancer, Volume 11, Issue 2, 2013, Pages 73-77.

28 Mattes, M. D., Kan, C. C., Dalbagni, G., Zelefsky, M. J., & Kollmeier, M. A. (2015). External beam radiation therapy for small cell carcinoma of the urinary bladder. Practical radiation oncology, 5(1), e17–e22. https://doi.org/10.1016/j.prro.2014.03.013

29 Messing EM, Catalona, W. Urothelial tumors of the urinary tract. In: Wein AJ, Kavousi, LR, ed. Campbell's Walsh Urology. 9th ed. Philadelphia, PA: Saunders/Elsevier; 2007.

30 Svatek RS, Shariat SF, Novara G, et al. Discrepancy between clinical and pathological stage: external validation of the impact on prognosis in an international radical cystectomy cohort. BJU Int. Mar 2011;107(6):898-904.

31 Turker P, Bostrom PJ, Wroclawski ML, et al. Upstaging of urothelial cancer at the time of radical cystectomy: factors associated with upstaging and its effect on outcome. BJU Int. Sep 2012;110(6):804-811.

32 Ahmadi H, Mitra AP, Abdelsayed GA, et al. Principal component analysis based pre-cystectomy model to predict pathological stage in patients with clinical organ-confined bladder cancer. BJU Int. Apr 2013;111(4 Pt B):E167-172.

33 Panebianco V, Narumi Y, Altun E, Bochner BH, Efstathiou JA, Hafeez S, Huddart R, Kennish S, Lerner S, Montironi R, Muglia VF, Salomon G, Thomas S, Vargas HA, Witjes JA, Takeuchi M, Barentsz J, Catto JWF. Multiparametric Magnetic Resonance Imaging for Bladder Cancer: Development of VI-RADS (Vesical Imaging-Reporting And Data System). Eur Urol. 2018 Sep;74(3):294-306. doi: 10.1016/j.eururo.2018.04.029. Epub 2018 May 10. PMID: 29755006; PMCID: PMC6690492.

34 Del Giudice F, Barchetti G, De Berardinis E, Pecoraro M, Salvo V, Simone G, Sciarra A, Leonardo C, Gallucci M, Catalano C, Catto JWF, Panebianco V. Prospective Assessment of Vesical Imaging Reporting and Data System (VI-RADS) and Its Clinical Impact on the Management of High-risk Non-muscle-invasive Bladder Cancer Patients Candidate for Repeated Transurethral Resection. Eur Urol. 2020 Jan;77(1):101-109. doi: 10.1016/j.eururo.2019.09.029. Epub 2019 Nov 5. PMID: 31699526.

35 Daneshmand S, Ahmadi H, Huynh LN, Dobos N. Preoperative staging of invasive bladder cancer with dynamic gadolinium-enhanced magnetic resonance imaging: results from a prospective study. Urology. Dec 2012;80(6):1313-1318.

36 Braendengen M, Winderen M, Fossa SD. Clinical significance of routine pre-cystectomy bone scans in patients with muscle-invasive bladder cancer. Br J Urol. Jan 1996;77(1):36-40.

37 Lu YY, Chen JH, Liang JA, et al. Clinical value of FDG PET or PET/CT in urinary bladder cancer: a systemic review and meta-analysis. Eur J Radiol.Sep 2012;81(9):2411-2416.

38 Swinnen, G., Maes, A., Pottel, H., Vanneste, A., Billiet, I., Lesage, K., & Werbrouck, P. (2010). FDG-PET/CT for the preoperative lymph node staging of invasive bladder cancer. European urology, 57(4), 641–647. https://doi.org/10.1016/j.eururo.2009.05.014

39 ☆ Quek ML, Stein JP, Nichols PW, et al. Prognostic significance of lymphovascular invasion of bladder cancer treated with radical cystectomy. J Urol. Jul 2005;174(1):103-106.

40 May M, Herrmann E, Bolenz C, et al. Lymph node density affects cancer-specific survival in patients with lymph node-positive urothelial bladder cancer following radical cystectomy. Eur Urol. May 2011;59(5):712-718.

41 Stephenson AJ, Gilligan TD.: Neoplasms of the Testis. Campbell-Walsh Urology, 10th Edition:837-70, 2011.

42 ☆ Esrig D, Freeman JA, Elmajian DA, et al. Transitional cell carcinoma involving the prostate with a proposed staging classification for stromal invasion. J Urol. Sep 1996;156(3):1071-1076.

43 AJCC Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer; 2017

44 ☆ Daneshmand S, Stein JP, Lesser T, et al. Prognosis of seminal vesicle involvement by transitional cell carcinoma of the bladder. J Urol. Jul 2004;172(1):81-84.

45 ☆ Bruins HM, Djaladat H, Ahmadi H, et al. Incidental prostate cancer in patients with bladder urothelial carcinoma: comprehensive analysis of 1,476 radical cystoprostatectomy specimens. J Urol. Nov 2013;190(5):1704-1709.

46 ☆ Revelo MP, Cookson MS, Chang SS, Shook MF, Smith JA, Jr., Shappell SB. Incidence and location of prostate and urothelial carcinoma in prostates from cystoprostatectomies: implications for possible apical sparing surgery. J Urol. May 2008;179(5 Suppl):S27-32.

47 Kessler TM, Burkhard FC, Studer UE. Clinical indications and outcomes with nerve-sparing cystectomy in patients with bladder cancer. Urol Clin North Am. May 2005;32(2):165-175.

48 ☆ † Djaladat H, Bruins HM, Miranda G, Cai J, Skinner EC, Daneshmand S. Reproductive organ involvement in female patients undergoing radical cystectomy for urothelial bladder cancer. J Urol. Dec 2012;188(6):2134-2138.

Study assessing oncologic impact of reproductive organs in women undergoing radical cystectomy.

49 ☆ Bree KK, Hensley PJ, Westerman ME, Kokorovic A, Nogueras-Gonzalez GM, Dinney CP, Kamat AM, Navai N. Contemporary Rates of Gynecologic Organ Involvement in Females with Muscle Invasive Bladder Cancer: A Retrospective Review of Women Undergoing Radical Cystectomy following Neoadjuvant Chemotherapy. J Urol. 2021 Sep;206(3):577-585. doi: 10.1097/JU.0000000000001784. Epub 2021 Apr 19. PMID: 33872050.

50 Liedberg, F., Jancke, G., Sörenby, A., and Kannisto, P. Should we refrain from performing oophorectomy in conjunction with radical cystectomy for bladder cancer?. Eur Urol. 2017; 71: 851–853

51 Nik, N.N., Vang, R., Shih, I.M., and Kurman, R.J. Origin and pathogenesis of pelvic (ovarian, tubal, and primary peritoneal) serous carcinoma. Annu Rev Pathol. 2014; 9: 27–45

52 ☆ Labbate C, Werntz RP, Adamic B, Steinberg GD. The Impact of Omission of Intraoperative Frozen Section Prior to Orthotopic Neobladder Reconstruction. J Urol. 2019;202(4):763-769.

53 Djaladat H, Mitra AP, Miranda G, Skinner EC, Daneshmand S. Radical cystectomy and orthotopic urinary diversion in male patients with pT4a urothelial bladder carcinoma: oncological outcomes. Int J Urol. 2013;20(12):1229-1233

54 Chen J, Djaladat H, Schuckman AK, Aron M, Desai M, Gill IS, Clifford TG, Ghodoussipour S, Miranda G, Cai J, Daneshmand S.Surgical approach as a determinant factor of clinical outcome following radical cystectomy: Does Enhanced Recovery After Surgery (ERAS) level the playing field? Urol Oncol. 2019 Jul 5

55 Novara G, Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. Eur Urol. 2012 Sep;62(3):431-52. doi: 10.1016/j.eururo.2012.05.044. Epub 2012 Jun 2. PMID: 22749853.

56 Parekh, D. J., Reis, I. M., Castle, E. P., Gonzalgo, M. L., Woods, M. E., Svatek, R. S., Weizer, A. Z., Konety, B. R., Tollefson, M., Krupski, T. L., Smith, N. D., Shabsigh, A., Barocas, D. A., Quek, M. L., Dash, A., Kibel, A. S., Shemanski, L., Pruthi, R. S., Montgomery, J. S., ... Thompson, I. M. (2018). Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. The Lancet, 391(10139), 2525-2536

57 Mantica G, Smelzo S, Ambrosini F, Tappero S, Parodi S, Pacchetti A, De Marchi D, Gaboardi F, Suardi N, Terrone C. Port-site metastasis and atypical recurrences after robotic-assisted radical cystectomy (RARC): an updated comprehensive and systematic review of current evidences. J Robot Surg. 2020 Dec;14(6):805-812. doi: 10.1007/s11701-020-01062-x. Epub 2020 Mar 9. PMID: 32152900.

58 Bochner et al. Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial. EUROPEAN UROLOGY 67 (2015) 1042 – 1050

59 ☆ Venkatramani V, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, Weizer AZ, Konety BR, Tollefson M, Krupski TL, Smith ND, Shabsigh A, Barocas DA, Quek ML, Dash A, Kibel AS, Pruthi RS, Montgomery JS, Weight CJ, Sharp DS, Chang SS, Cookson MS, Gupta GN, Gorbonos A, Uchio EM, Skinner E, Soodana-Prakash N, Becerra MF, Swain S, Kendrick K, Smith JA Jr, Thompson IM, Parekh DJ. Predictors of Recurrence, and Progression-Free and Overall Survival following Open versus Robotic Radical Cystectomy: Analysis from the RAZOR Trial with a 3-Year Followup. J Urol. 2020 Mar;203(3):522-529. doi: 10.1097/JU.0000000000000565. Epub 2019 Sep 24. PMID: 31549935; PMCID: PMC7487279.

60 ☆ Becerra MF, Venkatramani V, Reis IM, Soodana-Prakash N, Punnen S, Gonzalgo ML, Raolji S, Castle EP, Woods ME, Svatek RS, Weizer AZ, Konety BR, Tollefson M, Krupski TL, Smith ND, Shabsigh A, Barocas DA, Quek ML, Dash A, Parekh DJ. Health Related Quality of Life of Patients with Bladder Cancer in the RAZOR Trial: A Multi-Institutional Randomized Trial Comparing Robot versus Open Radical Cystectomy. J Urol. 2020 Sep;204(3):450-459. doi: 10.1097/JU.0000000000001029. Epub 2020 Apr 9. PMID: 32271690.

61 Bochner BH. Role of lymphadenectomy in bladder cancer. In: Vogelzang NJ, Scardino PT, Shipley WU, Debruyne FMJ, Linehan WM ed. Comprehensive Textbook of Genitourinary Oncology. Vol 2. 3rd ed: Lippincott Williams & Wilkins; 2006:501-505.

62 † Stein JP, Skinner DG. The role of lymphadenectomy in high-grade invasive bladder cancer. Urol Clin North Am. May 2005;32(2):187-197.

Review of importance of lymph node dissection in patients with bladder cancer.

63 Current controversies on the role of lymphadenectomy for bladder cancer. Ghodoussipour S, Daneshmand S. Urol Oncol. 2018 Jun 14. pii: S1078-1439(18)30157-1. doi: 10.1016/j.urolonc.2018.05.005. [Epub ahead of print] Review. PMID: 29909945

64 Eur Urol. 2018 Oct 15. pii: S0302-2838(18)30737-1. doi: 10.1016/j.eururo.2018.09.047. [Epub ahead of print] Extended Versus Limited Lymph Node Dissection in Bladder Cancer Patients Undergoing Radical Cystectomy: Survival Results from a Prospective, Randomized Trial. Gschwend JE1, Heck MM2, Lehmann J3, Rübben H4, Albers P5, Wolff JM6, Frohneberg D7, de Geeter P8, Heidenreich A9, Kälble T10, Stöckle M11, Schnöller T12, Stenzl A13, Müller M14, Truss M15, Roth S16, Liehr UB17, Leißner J18, Bregenzer T3, Retz M2.

65 Svatek R, Zehnder P. Role and extent of lymphadenectomy during radical cystectomy for invasive bladder cancer. Curr Urol Rep. Apr 2012;13(2):115-121.

66 ☆ Garg T, Young AJ, Kost KA, Danella JF, Larson S, Nielsen ME, Kirchner HL. Burden of Multiple Chronic Conditions among Patients with Urological Cancer. J Urol. 2018 Feb;199(2):543-550. doi: 10.1016/j.juro.2017.08.005. Epub 2017 Aug 5. PMID: 28789948.

67 ☆ Daneshmand S, Ahmadi H, Schuckman AK, et al: Enhanced recovery protocol after radical cystectomy for bladder cancer. J Urol. 2014 Jul;192(1):50-5

68 Tyson MD, Chang SS. Enhanced Recovery Pathways Versus Standard Care After Cystectomy: A Meta-analysis of the Effect on Perioperative Outcomes. Eur Urol. 2016 Dec;70(6):995-1003.

69 Lee CT1, Chang SS2, Kamat AM3, Amiel G4, Beard TL5, Fergany A6, Karnes RJ7, Kurz A6, Menon V6, Sexton WJ8, Slaton JW9, Svatek RS10, Wilson SS11, Techner L12, Bihrle R13, Steinberg GD14, Koch M13. Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. Eur Urol. 2014 Aug;66(2):265-72. doi: 10.1016/j.eururo.2014.02.036. Epub 2014 Feb 26.

70 Lee CT, Chang SS, Kamat AM, et al. Alvimopan accelerates gastroin- testinal recovery after radical cystectomy: a multicenter random-ized placebo-controlled trial. Eur Urol 2014;66:265–72.

71 ☆ John T. Stoffel, MD (Chair), Jeffery S. Montgomery, MD, Anne M. Suskind, MD, MS, FACS, Christopher Tucci, MS, RN, BC, CURN, Alex J. Vanni, MD (Co-Chair) NEW - Optimizing Outcomes in Urological Surgery: Pre-Operative Care for the Patient Undergoing Urologic Surgery or Procedure. Published 2018

72 ☆ Angela Smith, MD, MS, FACS, (Chair), Megan Anders, MD, Gregory Auffenberg, MD, Siamak Daneshmand, MD, Chad Elllimootil, MD, Jane Fellows, MSN, CWOCN, Scott Gilbert, MD, John L. Gore, MD, Suzanne Merrill, MD, Kenneth Nepple, MD, Leanne Richbourg, MSN, APRN-BC, CWON-AP, CCCN, GCNS-BC, Charlene Vollmer, BSN, RN-BC. NEW - Optimizing Outcomes in Urologic Surgery: Postoperative. Published 2018

73 ☆ Klaassen Z, Arora K, Goldberg H, Chandrasekar T, Wallis CJD, Sayyid RK, Fleshner NE, Finelli A, Kutikov A, Violette PD, Kulkarni GS. Extended Venous Thromboembolism Prophylaxis after Radical Cystectomy: A Call for Adherence to Current Guidelines. J Urol. 2018 Apr;199(4):906-914. doi: 10.1016/j.juro.2017.08.130. Epub 2017 Nov 4. PMID: 29113840.

74 Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med.Aug 28 2003;349(9):859-866.

75 Black P, So A. Perioperative chemotherapy for muscle-invasive bladder cancer. Can Urol Assoc J.Dec 2009;3(6 Suppl 4):S223-227.

76 Black PC, Brown GA, Grossman HB, Dinney CP. Neoadjuvant chemotherapy for bladder cancer. World J Urol. Nov 2006;24(5):531-542.

77 J Clin Oncol. 2000 Sep;18(17):3068-77. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. von der Maase H1, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM, Conte PF. PMID: 11001674 DOI: 10.1200/JCO.2000.18.17.3068

78 BJU Int. 2006 Sep;98(3):487-9. What has been learned from meta-analyses of neoadjuvant and adjuvant chemotherapy in bladder cancer? Sternberg CN1, Collette L.

79 Neoadjuvant induction dose-dense MVAC for muscle invasive bladder cancer: efficacy and safety compared with classic MVAC and gemcitabine/cisplatin.van de Putte EE, Mertens LS, Meijer RP, van der Heijden MS, Bex A, van der Poel HG, Kerst JM, Bergman AM, Horenblas S, van Rhijn BW. World J Urol. 2016 Feb;34(2):157-62. doi: 10.1007/s00345-015-1636-y. Epub 2015 Jul 17. PMID: 26184106

80 Hussain SA, Palmer DH, Lloyd B, et al. A study of split-dose cisplatin-based neo-adjuvant chemotherapy in muscle-invasive bladder cancer. Oncol Lett. 2012;3(4):855-859. doi:10.3892/ol.2012.563

81 Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol. Aug 2005;48(2):189-199; discussion 199-201.

82 Bria E, Ruggeri EM, Pollera CF, Terzoli E, Cognetti F, Giannarelli D. Adjuvant chemotherapy for bladder cancer: the chance for meta-analyses comparison. Eur Urol. Feb 2007;51(2):576-577.

83 Ruggeri EM, Giannarelli D, Bria E, et al. Adjuvant chemotherapy in muscle-invasive bladder carcinoma: a pooled analysis from phase III studies. Cancer. Feb 15 2006;106(4):783-788.

84 Donat SM, Shabsigh A, Savage C, Cronin AM, Bochner BH, Dalbagni G, Herr HW, Milowsky MI. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. Eur Urol. 2009 Jan;55(1):177-85. doi: 10.1016/j.eururo.2008.07.018. Epub 2008 Jul 14. PMID: 18640770.

85 Bellmunt J, Hussain M, Gschwend JE, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(4):525-537. doi:10.1016/S1470-2045(21)00004-8

86 Christodouleas, J. P., Baumann, B. C., He, J., Hwang, W. T., Tucker, K. N., Bekelman, J. E., Tangen, C. M., Lerner, S. P., Guzzo, T. J., Malkowicz, S. B., & Herr, H. (2014). Optimizing bladder cancer locoregional failure risk stratification after radical cystectomy using SWOG 8710. Cancer, 120(8), 1272–1280. https://doi.org/10.1002/cncr.28544

87 Hassan, J. M., Cookson, M. S., Smith, J. A., Jr, & Chang, S. S. (2006). Patterns of initial transitional cell recurrence in patients after cystectomy. The Journal of urology, 175(6), 2054–2057. https://doi.org/10.1016/S0022-5347(06)00323-5

88 Zaghloul MS, Christodouleas JP, Hwang WT, et al. Randomized phase III trial of adjuvant sequential chemotherapy plus radiotherapy versus adjuvant radiotherapy alone for locally advanced bladder cancer after radical cystectomy: Urothelial carcinoma subgroup analysis. J Clin Oncol . 2019;37(7_suppl):351.

89 Zaghloul MS, Christodouleas JP, Zaghloul T, et al. Randomized trial of adjuvant chemotherapy versus adjuvant radiation therapy for locally advanced bladder cancer after radical cystectomy. J Clin Oncol . 2019;37(15_suppl):4507-4507.

90 Stein, J. P., Lieskovsky, G., Cote, R. et al.: Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol, 19: 666, 2001

91 Grossman, H. B., Natale, R. B., Tangen, C. M. et al.: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med, 349: 859, 2003

92 Sonpavde, G., Khan, M. M., Lerner, S. P. et al.: Disease-free survival at 2 or 3 years correlates with 5-year overall survival of patients undergoing radical cystectomy for muscle invasive bladder cancer. J Urol, 185: 456, 2011

93 Herr HW, Faulkner JR, Grossman HB, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol. Jul 15 2004;22(14):2781-2789.

94 ☆ Quek ML, Stein JP, Daneshmand S, et al. A critical analysis of perioperative mortality from radical cystectomy. J Urol. Mar 2006;175(3 Pt 1):886-889; discussion 889-890.

95 Woldu SL, Sanli O, Clinton TN, Lotan Y. Validating the predictors of outcomes after radical cystectomy for bladder cancer. Cancer. 2019 Jan 15;125(2):223-231. doi: 10.1002/cncr.31799. Epub 2018 Oct 6. PMID: 30291813.

† Shabsigh A, Korets R, Vora KC, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol. Jan 2009;55(1):164-174.

96

Study evaluating early complications from radical cystectomy.

Patient (pt) characteristics, treatment patterns, outcomes and prognostic factors in plasmacytoid urothelial carcinoma (PUC). Leonidas Nikolaos Diamantopoulos, Ali Raza Khaki, Funda Vakar-Lopez, Maria S. Tretiakova, John L. Gore, George R Schade, Sarah P. Psutka, Andrew Caleb Hsieh, John Kyung Lee, Todd Yezefski, Michael Thomas Schweizer, Heather H. Cheng, Evan Y. Yu, Petros Grivas, Robert B. Montgomery, and Jonathan L. Wright Journal of Clinical Oncology 2019 37:15_suppl, e16007-e16007

97

Daneshmand S, Bartsch G. Improving selection of appropriate urinary diversion following radical cystectomy for bladder cancer. Expert Rev Anticancer Ther. Jun 2011;11(6):941-948.

98

☆ Stein JP, Clark P, Miranda G, Cai J, Groshen S, Skinner DG. Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. J Urol. Apr 2005;173(4):1163-1168.

99

† Hautmann RE, Volkmer BG, Schumacher MC, Gschwend JE, Studer UE. Long-term results of standard procedures in urology: the ileal neobladder.World J Urol. Aug 2006;24(3):305-314.

100

Study evaluating long term outcomes associated with ileal neobladders.

☆ Clifford TG, Shah SH, Bazargani ST, Miranda G, Cai J, Wayne K, Djaladat H, Schuckman AK, Daneshmand S. Prospective Evaluation of Continence Following Radical Cystectomy and Orthotopic Urinary Diversion Using a Validated Questionnaire. J Urol. 2016;196(6):1685-91. doi: 10.1016/j.juro.2016.05.093. PubMed PMID: 27256205.

101

☆ † Madersbacher S, Schmidt J, Eberle JM, et al. Long-term outcome of ileal conduit diversion. J Urol. Mar 2003;169(3):985-990.

102

Study reviewing long term outcomes in patients undergoing ileal conduit diversions.

☆ Shimko MS, Tollefson MK, Umbreit EC, Farmer SA, Blute ML, Frank I. Long-term complications of conduit urinary diversion. J Urol. Feb 2011;185(2):562-567.

103

† Bartsch G, Daneshmand S, Skinner EC, Syan S, Skinner DG, Penson DF. Urinary functional outcomes in female neobladder patients. World J Urol. Feb 2014;32(1):221-228.

104

Study reviewing quality of life outcomes in patients undergoing continent urinary diversion in women.

☆ Hautmann RE, de Petriconi RC, Volkmer BG. Lessons learned from 1,000 neobladders: the 90-day complication rate. J Urol. Sep 2010;184(3):990-994; quiz 1235.

105

☆ Studer UE, Burkhard FC, Schumacher M, Kessler TM, Thoeny H, Fleischmann A, Thalmann GN. Twenty years experience with an ileal orthotopic low pressure bladder substitute--lessons to be learned. J Urol. 2006;176(1):161-6. Epub 2006/06/07. doi: 10.1016/s0022-5347(06)00573-8. PubMed PMID: 16753394.

106

☆ Ali-el-Dein B, Shaaban AA, Abu-Eideh RH, el-Azab M, Ashamallah A, Ghoneim MA. Surgical complications following radical cystectomy and orthotopic neobladders in women. J Urol. Jul 2008;180(1):206-210; discussion 210.

107

☆ † Ahmadi H, Skinner EC, Simma-Chiang V, et al. Urinary Functional Outcome Following Radical Cystoprostatectomy and Ileal Neobladder Reconstruction in Male Patients. The Journal of Urology. 2013;189(5):1782-1788.

108

Study reviewing quality of life outcomes in patients undergoing continent urinary diversion in men.

☆ Hautmann RE, Paiss T, de Petriconi R. The ileal neobladder in women: 9 years of experience with 18 patients. J Urol. Jan 1996;155(1):76-81.

109

Hautmann RE, de Petriconi R, Kleinschmidt K, Gottfried HW, Gschwend JE. Orthotopic ileal neobladder in females: impact of the urethral resection line on functional results. Int Urogynecol J Pelvic Floor Dysfunct. 2000;11(4):224-229; discussion 230.

110

Stein JP, Ginsberg DA, Skinner DG. Indications and technique of the orthotopic neobladder in women. Urol Clin North Am. Aug 2002;29(3):725-734, xi.

111

Holzbeierlein JM, Lopez-Corona E, Bochner BH, et al. Partial cystectomy: a contemporary review of the Memorial Sloan-Kettering Cancer Center experience and recommendations for patient selection. J Urol. Sep 2004;172(3):878-881.

112

Bruins HM, Wopat R, Mitra AP, et al. Long-term outcomes of salvage radical cystectomy for recurrent urothelial carcinoma of the bladder following partial cystectomy. BJU Int. Mar 2013;111(3 Pt B):E37-42.

113

☆ Henry K, Miller J, Mori M, Loening S, Fallon B. Comparison of transurethral resection to radical therapies for stage B bladder tumors. J Urol. Nov 1988;140(5):964-967.

114

Thomas DJ, Roberts JT, Hall RR, Reading J. Radical transurethral resection and chemotherapy in the treatment of muscle-invasive bladder cancer: a long-term follow-up. BJU Int. Mar 1999;83(4):432-437.

115

☆ Chang SS, Bochner BH, Chou R et al: Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. J Urol 2017; 198: 552.

116

Feldman AS, Kulkarni GS, Bivalacqua TJ, et al. Surgical challenges and considerations in Tri-modal therapy for muscle invasive bladder cancer [published online ahead of print, 2021 Feb 25]. Urol Oncol. 2021;S1078-1439(21)00012-0. doi:10.1016/j.urolonc.2021.01.013

117

James, N. D., Hussain, S. A., Hall, E., Jenkins, P., Tremlett, J., Rawlings, C., Crundwell, M., Sizer, B., Sreenivasan, T., Hendron, C., Lewis, R., Waters, R., Huddart, R. A., & BC2001 Investigators (2012). Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. The New England journal of medicine, 366(16), 1477–1488. https://doi.org/10.1056/NEJMoa1106106

118

119 Hagan MP1, Winter KA, Kaufman DS, Wajsman Z, Zietman AL, Heney NM, Toonkel LM, Jones CU, Roberts JD, Shipley WU. RTOG 97-06: initial report of a phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. Int J Radiat Oncol Biol Phys. 2003 Nov 1;57(3):665-72.

120 Choudhury, A., Porta, N., Hall, E., Song, Y. P., Owen, R., MacKay, R., West, C., Lewis, R., Hussain, S. A., James, N. D., Huddart, R., Hoskin, P., & BC2001 and BCON investigators (2021). Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. The Lancet. Oncology, 22(2), 246–255. https://doi.org/10.1016/S1470-2045(20)30607-0

121 Biancia, C. D., Yorke, E., & Kollmeier, M. A. (2014). Image guided radiation therapy for bladder cancer: assessment of bladder motion using implanted fiducial markers. Practical radiation oncology, 4(2), 108–115. https://doi.org/10.1016/j.prro.2013.07.008

122 Huddart, R. A., Hall, E., Hussain, S. A., Jenkins, P., Rawlings, C., Tremlett, J., Crundwell, M., Adab, F. A., Sheehan, D., Syndikus, I., Hendron, C., Lewis, R., Waters, R., & James, N. D. (2013). Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 trial (CRUK/01/004). International journal of radiation oncology, biology, physics, 87(2), 261–269. https://doi.org/10.1016/j.ijrobp.2013.06.2044

123 Huddart, R., Hafeez, S., Lewis, R., McNair, H., Syndikus, I., Henry, A., Staffurth, J., Dewan, M., Vassallo-Bonner, C., Moinuddin, S. A., Birtle, A., Horan, G., Rimmer, Y., Venkitaraman, R., Khoo, V., Mitra, A., Hughes, S., Gibbs, S., Kapur, G., Baker, A., … HYBRID Investigators (2021). Clinical Outcomes of a Randomized Trial of Adaptive Plan-of-the-Day Treatment in Patients Receiving Ultra-hypofractionated Weekly Radiation Therapy for Bladder Cancer. International journal of radiation oncology, biology, physics, 110(2), 412–424. https://doi.org/10.1016/j.ijrobp.2020.11.068

124 Mitin, T., George, A., Zietman, A. L., Heney, N. M., Kaufman, D. S., Uzzo, R. G., Dreicer, R., Wallace, H. J., 3rd, Souhami, L., Dobelbower, M. C., Sandler, H. M., & Shipley, W. U. (2016). Long-Term Outcomes Among Patients Who Achieve Complete or Near-Complete Responses After the Induction Phase of Bladder-Preserving Combined-Modality Therapy for Muscle-Invasive Bladder Cancer: A Pooled Analysis of NRG Oncology/RTOG 9906 and 0233. International journal of radiation oncology, biology, physics, 94(1), 67–74. https://doi.org/10.1016/j.ijrobp.2015.09.030

125 Eswara JR1, Efstathiou JA, Heney NM, Paly J, Kaufman DS, McDougal WS, McGovern F, Shipley WU. Complications and long-term results of salvage cystectomy after failed bladder sparing therapy for muscle invasive bladder cancer. J Urol. 2012 Feb;187(2):463-8. doi: 10.1016/j.juro.2011.09.159. Epub 2011 Dec 15.

126 Eswara, J. R., Efstathiou, J. A., Heney, N. M., Paly, J., Kaufman, D. S., McDougal, W. S., McGovern, F., & Shipley, W. U. (2012). Complications and long-term results of salvage cystectomy after failed bladder sparing therapy for muscle invasive bladder cancer. The Journal of urology, 187(2), 463–468. https://doi.org/10.1016/j.juro.2011.09.159

127 Iwai A, Koga F, Fujii Y, Masuda H, Saito K, Numao N, Sakura M, Kawakami S, Kihara K. Perioperative complications of radical cystectomy after induction chemoradiotherapy in bladder-sparing protocol against muscle-invasive bladder cancer: a single institutional retrospective comparative study with primary radical cystectomy. Jpn J Clin Oncol. 2011 Dec;41(12):1373-9. doi: 10.1093/jjco/hyr150. Epub 2011 Oct 11. PMID: 21994208.

128 ☆ Herr HW, Donat SM. Outcome of patients with grossly node positive bladder cancer after pelvic lymph node dissection and radical cystectomy.J Urol. Jan 2001;165(1):62-64; discussion 64.

129 Huddart RA1, Hall E, Lewis R, Birtle A; SPARE Trial Management Group. Life and death of spare (selective bladder preservation against radical excision): reflections on why the spare trial closed. BJU Int. 2010 Sep;106(6):753-5. doi: 10.1111/j.1464-410X.2010.09537.x. Epub 2010 Jul 26.

130 Kulkarni GS1, Hermanns T1, Wei Y1, Bhindi B1, Satkunasivam R1, Athanasopoulos P1, Bostrom PJ1, Kuk C1, Li K1, Templeton AJ1, Sridhar SS1, van der Kwast TH1, Chung P1, Bristow RG1, Milosevic M1, Warde P1, Fleshner NE1, Jewett MAS1, Bashir S1, Zlotta AR1. Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic. J Clin Oncol. 2017 Jul 10;35(20):2299-2305. doi: 10.1200/JCO.2016.69.2327. Epub 2017 Apr 14.

131 Mak DK1, Macharia E1, Wragg R1, Parashar K1. Congenital bladder diverticulum with benign bladder wall lesion resembling rhabdomyosarcoma. J Surg Case Rep. 2010 Jun 1;2010(4):7. doi: 10.1093/jscr/2010.4.7.

132 Chatta G, Trump D. Systemic Chemotherapy for Metastatic Urothelial Cancer. Hamilton, Ontario: BC Decker Inc; 2004.

133 von der Maase H, Hansen SW, Roberts JT, et al. . Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study J Clin Oncol. Sep 2000;18(17):3068-3077.

134 Bajorin DF, Sarosdy MF, Pfister DG, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. J Clin Oncol. Apr 1993;11(4):598-606.

135 Horwich A, Sleijfer DT, Fossa SD, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. J Clin Oncol. May 1997;15(5):1844-1852.

136 Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, Srinivas S, Retz MM, Grivas P, Joseph RW, Galsky MD, Fleming MT, Petrylak DP, Perez-Gracia JL, Burris HA, Castellano D, Canil C, Bellmunt J, Bajorin D, Nickles D, Bourgon R, Frampton GM, Cui N, Mariathasan S, Abidoye O, Fine GD, Dreicer R. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387(10031):1909-20. doi: 10.1016/S0140-6736(16)00561-4. PubMed PMID: 26952546.

137 Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, Necchi A, Gerritsen W, Gurney H, Quinn DI, Culine S, Sternberg CN, Mai Y, Poehlein CH, Perini RF, Bajorin DF, Investigators K-. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017;376(11):1015-26. doi: 10.1056/NEJMoa1613683. PubMed PMID: 28212060; PMCID: PMC5635424.

138 Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, Plimack ER, Vaena D, Grimm MO, Bracarda S, Arranz JA, Pal S, Ohyama C, Saci A, Qu X, Lambert A, Krishnan S, Azrilevich A, Galsky MD. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017. doi: 10.1016/S1470-2045(17)30065-7. PubMed PMID: 28131785.

139 Massard V1, Salleron J2, Krakowski I1,3, Conroy T1, Weber B1. J Palliat Med. 2015 Aug;18(8):658-9. doi: 10.1089/jpm.2015.0134. Epub 2015 Jun 18. Chemotherapy at the End of Life: Factors of Prescription.

140 Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial [published correction appears in Lancet. 2017 Aug 26;390(10097):848]. Lancet. 2017;389(10064):67-76. doi:10.1016/S0140-6736(16)32455-2

141 ASCO2020 - Thomas Powles, Se Hoon Park, Eric Voog, et al: Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC): JAVELIN Bladder 100 phase III interim analysis. DOI: 10.1200/JCO.2020.38.18_suppl.LBA1 Journal of Clinical Oncology 38, no. 18_suppl

142 Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019.CA Cancer J Clin. 2019 Jan;69(1):7-34.

143 Scott T. Tagawa, Allyson J. Ocean, Elaine Tat Lam, Philip James Saylor, Aditya Bardia, Julio Hajdenberg, Alicia Katherine Morgans, Kevin Kalinsky, Matthew Galsky, Bishoy Faltas, Ana M. Molina, Emerson A. Lim, Pius Maliakal, Robert M. Sharkey, Boyd Mudenda, William A. Wegener, and David M Goldenberg. Therapy for chemopretreated metastatic urothelial cancer (mUC) with the antibody-drug conjugate (ADC) sacituzumab govitecan (IMMU-132). Journal of Clinical Oncology 2017 35:6_suppl, 327-327

144 J Clin Oncol 36, 2018 (suppl; abstr 4504)

145 Thomas Powles, M.D., Jonathan E. Rosenberg, M.D., Guru P. Sonpavde, M.D., Yohann Loriot, M.D., Ph.D., Ignacio Durán, M.D., Ph.D., Jae-Lyun Lee, M.D., Ph.D., Nobuaki Matsubara, M.D., Christof Vulsteke, M.D., Ph.D., Daniel Castellano, M.D., Chunzhang Wu, Ph.D., Mary Campbell, M.D., Maria Matsangou, M.B., Ch.B., M.D., and Daniel P. Petrylak, M.D. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med 2021; 384:1125-1135 DOI: 10.1056/NEJMoa2035807

146 Study of Sacituzumab Govitecan-hziy (IMMU-132) Versus Treatment of Physician's Choice in Participants With Metastatic or Locally Advanced Unresectable Urothelial Cancer (TROPiCS-04). https://www.clinicaltrials.gov/ct2/show/NCT04527991