Position Paper

Current Management of Localized Muscle-Invasive Bladder Cancer: A Consensus Guideline from the Genitourinary Medical Oncologists of Canada

Di Maria Jia, Scott A. Northb, Christina Canilc, Michael Kolinskyb, Lori A. Woodd, Samantha Graye, Bernhard J. Eigfl, Naveen S. Basappab, Normand Blaisg, Eric Winquisth, Som D. Mukherjeei, Christopher M. Boothj, Nimira S. Alimohamedk, Piotr Czaykowskil, Girish S. Kulkarnim, Peter C. Blackh, Peter W. Chungo, Wassim Kassoufp, Theodorus van der Kwastg and Srikala S. Sridhara

aDepartment of Medicine, Division of Medical Oncology and Hematology, University Health Network, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada
bDepartment of Oncology, Division of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada
cDepartment of Internal Medicine, Division of Medical Oncology, The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada
dDepartment of Medicine, Division of Medical Oncology, Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, NS, Canada
eDepartment of Oncology, Saint John Regional Hospital, Department of Medicine, Dalhousie University, Saint John, NB, Canada
fDepartment of Medicine, Division of Medical Oncology, BC Cancer - Vancouver, University of British Columbia, Vancouver, BC, Canada
gDepartment of Medicine, Division of Medical Oncology and Hematology, Centre Hospitalier de l’Université de Montréal; Université de Montréal, Montreal, QC, Canada
hDepartment of Oncology, London Health Sciences Centre, University of Western Ontario, London, ON, Canada
iDepartment of Oncology, Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada
jDepartment of Oncology, Queen’s University, Kingston, ON, Canada
kDepartment of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada
lDepartment of Medical Oncology and Hematology, Cancer Care Manitoba, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada
mDepartments of Surgery and Surgical Oncology, Division of Urology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

*Correspondence to: Srikala S. Sridhar, MD MSc FRCPC, Medical Oncologist, Princess Margaret Cancer Centre, Associate Professor, University of Toronto; Chair, GU Medical Oncologists of Canada (GUMOC), 7-625 OPG, 610 University Avenue, Toronto, Ontario M5G 6M9, Canada. Tel.: +1 416 946 4501 /Ex: 2662; Fax: +1 416 946 6546; E-mail: srikala.sridhar@uhn.ca.
Abstract

BACKGROUND: Despite recent advances in the management of muscle-invasive bladder cancer (MIBC), treatment outcomes remain suboptimal, and variability exists across current practice patterns.

OBJECTIVE: To promote standardization of care for MIBC in Canada by developing a consensus guidelines using a multidisciplinary, evidence-based, patient-centered approach who specialize in bladder cancer.

METHODS: A comprehensive literature search of PubMed, Medline, and Embase was performed; and most recent guidelines from national and international organizations were reviewed. Recommendations were made based on best available evidence, and strength of recommendations were graded based on quality of the evidence.

RESULTS: Overall, 17 recommendations were made covering a broad range of topics including pathology review, staging investigations, systemic therapy, local definitive therapy and surveillance. Of these, 10 (59%) were level 1 or 2, 7 (41%) were level 3 or 4 recommendations. There were 2 recommendations which did not reach full consensus, and were based on majority opinion. This guideline also provides guidance for the management of cisplatin-ineligible patients, variant histologies, and bladder-sparing trimodality therapy. Potential biomarkers, ongoing clinical trials, and future directions are highlighted.

CONCLUSIONS: This guideline embodies the collaborative expertise from all disciplines involved, and provides guidance to further optimize and standardize the management of MIBC.

Keywords: Urinary bladder neoplasms, consensus, diagnosis, follow-up, treatment, neoadjuvant therapy, adjuvant therapy

INTRODUCTION

Urothelial carcinoma of the bladder (UCB) is the most common malignancy of the urinary tract [1], and the 5th most common cancer in Canada, accounting for an estimated 11,800 new cases and 2,500 deaths in 2019 [2]. Most patients present with non-muscle invasive bladder cancer (NMIBC), but 15–25% will have muscle-invasive (≥pT2) bladder cancer (MIBC) [3, 4]. Outcomes of MIBC remain poor [5]. However, increased utilization of perioperative chemotherapy [6] and a growing emphasis on a multidisciplinary and patient-centred approach will likely translate into improved overall outcomes.

Genitourinary Medical Oncologists of Canada (GUMOC) is a non-governmental organization comprised of Canadian medical oncologists specializing in genitourinary cancers. The main objective of this consensus guideline is to summarize the current evidence and develop evidence-based recommendations to promote standardization of care for patients with MIBC in Canada. The target audience of this guideline is any clinician treating MIBC. It may also be referenced by patients, caregivers and regulatory agencies. The recommendations are intended to provide general guidance with a focus on the use of systemic therapy, but are not meant to supersede the clinical discretion of a qualified clinician for individual patients. The guideline is current at the time of publication.

METHODOLOGY

The guideline review committee co-chairs outlined and approved the key topics to be included in this guideline. The target population were patients with MIBC planned for curative intent therapy. The main focus of this guideline was on the use of of systemic therapy given in the perioperative or concurrent settings. The primary outcome of interest was the impact of various approaches on overall survival (OS). Particular topics such as the management of patients who are cisplatin-ineligible and
those with variant histologies, which are more controversial topics, were also addressed. Discussions on baseline evaluations optimal local definitive therapy, and surveillance strategies were also included based on multidisciplinary input.

To ensure multidisciplinary representation, Canadian experts in medical oncology, radiation oncology, uro-oncology, and pathology were included on the guideline panel. All authors agreed to disclose any perceived and actual competing interests during the guideline development process. There were no direct financial competing interests specific to any recommendations in this guideline.

Guideline development was based on a comprehensive literature search of PubMed, Medline, and Embase for best available evidence published in the English language since January 1, 1980. The search strategy involved the keywords: “bladder cancer”, “urothelial carcinoma”, “transitional cell carcinoma”, “invasive” and “muscle invasive”. Bibliographies of review articles were searched for relevant articles not captured by our search strategy. Phase III clinical trials published in the form of proceedings from major international oncology conferences (European Society for Medical Oncology [ESMO] and American Society of Clinical Oncology [ASCO]) were also included. Most recent recommendations from ASCO [7, 8], European Association of Urology (EAU) [9, 10], National Comprehensive Network Cancer (NCCN) [11], International Bladder Cancer Network [12, 13], International Consultation on Urological Diseases [ICUD] [14–16], Canadian Urological Association (CUA) [17] and Canadian provincial organizations (British Columbia, Alberta Health Services, Cancer Care Ontario [CCO] [18–20]) were sought for each topic.

Recommendations were drafted by DMJ based on the best available evidence, and sent to all coauthors for written feedback. Each recommendation along with its evidence grading were developed through an iterative consensus process. All coauthors submitted written input. If consensus was reached, no additional modifications were made. For topics where disagreements were raised, a voting system was used to collect written feedback from all coauthors. Expert opinions of the majority (>50% of coauthors) were presented as consensus, with level of consensus (marked by *) and opposing arguments included in full text to ensure a balanced discussion was presented.

To enhance the critical appraisal process, both the ICUD [21] (based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence) and GRADE [22, 23] (the Grading of Recommendations Assessment, Development and Evaluation) classifications were used to rate the quality of the evidence. Strength of the recommendations were graded according to definitions proposed by ICUD [21].

**Epidemiology and Risk Factors**

According to the 2019 Canadian Cancer Society report, 5-year OS rates for NMIBC, MIBC, regional (node positive), and distant disease were 95%, 69%, 35%, and 5% respectively [2]. The 5-year OS rates of patients with MIBC treated between 1994 and 2008 in Ontario ranges from 30 to 40% [24]. More contemporary data from the US show 5-year OS rates ranging between 50 and 60% [25]. Adverse prognostic factors include lymphovascular invasion [26], hydronephrosis [27, 28], multifocal disease [29], and variant histology [30]. If left untreated, patients with MIBC have a median survival of less than 10 months [31, 32].

### Table 1

<table>
<thead>
<tr>
<th>Levels of Evidence and Grades of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levels of Evidence</strong></td>
</tr>
<tr>
<td><strong>ICUD classification</strong></td>
</tr>
<tr>
<td>Level 1 Meta-analysis of RCTs or a good quality RCT</td>
</tr>
<tr>
<td>Level 2 Low-quality RCT or meta-analysis of good-quality prospective cohort studies</td>
</tr>
<tr>
<td>Level 3 Good-quality retrospective case-control studies or case series</td>
</tr>
<tr>
<td>Level 4 Expert opinion based on “first principles” or bench research, not on evidence</td>
</tr>
<tr>
<td><strong>GRADE classification</strong></td>
</tr>
<tr>
<td>High quality Further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Moderate quality Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Low quality Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate</td>
</tr>
<tr>
<td>Very low quality Any estimate of effect is very uncertain</td>
</tr>
<tr>
<td><strong>Grades of Recommendation (ICUD classification)</strong></td>
</tr>
<tr>
<td>Grade A Usually consistent level 1 evidence</td>
</tr>
<tr>
<td>Grade B Consistent level 2 or 3 evidence or “majority evidence” from RCTs</td>
</tr>
<tr>
<td>Grade C Level 4 evidence, “majority evidence” from level 2 or 3 studies, expert opinion</td>
</tr>
<tr>
<td>Grade D No recommendation possible because of inadequate or conflicting evidence</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial.
Table 2
Established risk factors associated with bladder cancer

<table>
<thead>
<tr>
<th>Established risk factors</th>
<th>Risk estimate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoking</td>
<td>HR 2.2 – 4.1</td>
<td>[33]</td>
</tr>
<tr>
<td>Male gender</td>
<td>Age-adjusted IRR</td>
<td>3.8 [293]</td>
</tr>
<tr>
<td>Exposure to arsenic in drinking water</td>
<td>RR 3.6 [294]</td>
<td></td>
</tr>
<tr>
<td>Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons; for example in paint, dye, metal, and petroleum products</td>
<td>OR 1.0 – 3.4</td>
<td>[33, 295]</td>
</tr>
<tr>
<td>Chronic hair dye exposure in women with N-acetyltransferase 2 (NAT2) slow acetylation phenotype</td>
<td>OR 7.3 [296]</td>
<td></td>
</tr>
<tr>
<td>Lower urinary tract symptoms, chronic urinary retention</td>
<td>RR 1.6 [297]</td>
<td></td>
</tr>
<tr>
<td>Prior cyclophosphamide chemotherapy</td>
<td>HR 1.4 [298]</td>
<td></td>
</tr>
<tr>
<td>Prior pelvic radiotherapy*</td>
<td>Age-adjusted IRR</td>
<td>1.6 [299]</td>
</tr>
<tr>
<td>Chronic inflammation and urinary schistosomiasis in endemic areas*</td>
<td>OR 1.7 [300]</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk. *specifically associated with squamous cell carcinoma in addition to urothelial carcinoma of the bladder.

Bladder cancer incidence increases with age. It is three times more common in men, and occurs more commonly in developed countries [33]. The median age at diagnosis is 69 years in men and 71 in women [34, 35]. Established risk factors are summarized in Table 2. Smoking is by far the most common and important risk factor accounting for approximately half of all cases [33]. Female gender is often associated with aggressive disease biology [35], advanced stage at presentation [36], and delayed referrals [37]. There is conflicting data however on whether women have inferior survival compared to men after adjusting for age and stage [24, 36, 38–41].

PATHOLOGY

Diagnostic confirmation of muscle invasion (T2) is obtained by transurethral resection of bladder tumor (TURBT) and cystoscopic examination under anesthesia. Inter-observer variation of staging based on TURBT specimens may be considerable [42–44]. Therefore, review by an experienced GU pathologist is advised whenever possible, in line with prior Canadian recommendations [45]. Tumor grade should be reported according to the latest WHO 2016 criteria [46].

Approximately, 10–25% of bladder cancers have a component of variant histology [47–50]. The World Health Organization and International Consultation on Bladder Cancer recognizes more than 10 unique histologic variants in bladder cancer [46, 51], summarized in Table 3. Variant histology includes any malignancy other than pure urothelial histology, such as urothelial with divergent differentiation, urothelial with mixed nonurothelial histology, or pure nonurothelial variant histology. Pure variant histology in particular may confer a distinct clinical behavior and tends to have a high propensity for relapse [52–54]. Variant histology is often challenging to identify on TURBT specimens [48, 55]. As a result, pathology review by an experienced GU pathologist can be informative, and lead to major changes in management [43, 44].

Box 1. Recommendations for Pathology Review
Pathology review of TURBT specimens used to diagnose MIBC by dedicated GU pathologists is recommended (Level 3, moderate quality, Grade C).

STAGING CLASSIFICATION

MIBC is clinically staged according to the Tumor, Node, Metastasis (TNM) system (Table 4). The most recent American Joint Committee on Cancer (AJCC) 8th edition reclassified nodal (cN) staging based on the number and location of involved regional lymph nodes [56]. Regional lymph nodes including perivesical, obturator, internal and external iliac, or sacral
lymph nodes are designated as cN1 or cN2 disease (Table 4). Common iliac nodes are designated as regional (cN3) disease. Although previously classified as stage IV metastatic disease [57], regional lymph node involvement is now designated as stage III disease which has important treatment implications.

Table 4
American Joint Committee on Cancer for Staging of UBC, 8th Edition

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tn</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Ta</td>
<td>Papillary noninvasive carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria</td>
</tr>
<tr>
<td>pT2a</td>
<td>Tumor invades superficial muscularis propria</td>
</tr>
<tr>
<td>pT2b</td>
<td>Tumor invades deep muscularis propria (inner half)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades the muscularis propria</td>
</tr>
<tr>
<td>pT3a</td>
<td>Tumor invades perivesical soft tissue microscopically</td>
</tr>
<tr>
<td>pT3b</td>
<td>Tumor invades perivesical soft tissue macroscopically (extravesical mass)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades perivesical soft tissue</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades adjacent organs</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades directly into prostatic stroma, seminal vesicles, uterus, vagina</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades pelvic wall, abdominal wall</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Node (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)</td>
</tr>
<tr>
<td>N2</td>
<td>Multiple regional lymph node metastasis in the true pelvis</td>
</tr>
<tr>
<td>N3</td>
<td>Lymph node metastasis to the common iliac lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Distant metastases cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant metastasis limited to lymph nodes beyond the common iliacs</td>
</tr>
<tr>
<td>M1b</td>
<td>Non-lymph-node distant metastases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ta or Tis N0M0</td>
</tr>
<tr>
<td>0a</td>
<td>TaN0M0</td>
</tr>
<tr>
<td>0is</td>
<td>Tis N0M0</td>
</tr>
<tr>
<td>I</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>II</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3 or T4a N0M0, T1–T4a N1M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1–T4a N2–3M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4b N0M0 or Any T any N M1a</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T any N M1b</td>
</tr>
</tbody>
</table>

**DIAGNOSTIC INVESTIGATIONS**

**Patient evaluation**

A full history, physical exam and routine laboratory evaluation (including a complete blood count, kidney function tests, liver function tests, and alkaline phosphatase) should be performed prior to curative therapy. Baseline evaluation should include bladder function, performance and nutritional status, medical comorbidities including hearing impairments, prior operations and procedural complications, current medications, family history and presence of any risk factors.

According to ASCO recommendations, comprehensive geriatric assessment may be considered in patients over 65 years of age to identify vulnerabilities or geriatric impairments not routinely captured by oncology assessments [16, 58]. Smoking cessation should also be discussed, as cigarette smoking can reduce response to chemotherapy, increase surgical complication rates [59], and increase risk of developing a second urothelial primary.

**Clinical staging**

The goal of staging is to assess the extent of local disease, rule out distant metastases, and accurately select patients for curative-intent therapy. There is considerable variation in staging investigations used to assess MIBC [60]. Inadequate staging is common, and may adversely impact outcomes [61].

Contrast-enhanced computed tomography (CT) is limited in local tumor staging due to an inability to adequately evaluate the depth of bladder wall invasion [62]. Up to half of patients with MIBC are understaged by CT compared to pathologic staging at the time of cystectomy [61]. Magnetic resonance imaging (MRI) has superior soft tissue contrast resolution [63, 64], however is not routinely performed due to its cost and limited availability. More recently, multiparametric MRI and the Vesical Imaging-Reporting and Data System (VI-RADS) have shown promise in improving detection of muscle invasion [65, 66], however further prospective and multicentre studies are needed. Notably, 2 – 4% of patients with UCB will also develop upper tract disease, thus evaluation of the entire urothelial tract with intravenous contrast and delayed images is also important [67].

For nodal staging, contrast-enhanced CT of the abdomen and pelvis is the current standard [68]. For distant staging, data comparing chest CT versus chest...
of micro-metastatic disease at presentation [78–80]. This provides the rationale for using chemotherapy to maximize chance of cure. The goal of neoadjuvant chemotherapy (NAC) is to eradicate micro-metastases and achieve pathologic complete response (pCR), which is associated with improved overall survival.

Neoadjuvant chemotherapy has several advantages over adjuvant chemotherapy including the ability to assess disease response as well as better tolerability due to absence of postoperative complications and/or reduced performance status. Cisplatin-based NAC has a pCR rate of 30–40% [81, 82]. The 5-year cancer-specific survival rate for NAC-responders (cyPT2) reaches 90%, compared to 30–40% for non-responders [83–85]. Importantly NAC does not increase surgical morbidity [84, 87, 88].

Select landmark publications of NAC in MIBC are summarized in Table 5. The Advanced Bladder Cancer (ABC) Meta-analysis Collaboration in 2005 reported a significant 5% absolute survival benefit at 5 years [89]. Cisplatin-based combination NAC such as MVAC (methotrexate, vinblastine, doxorubicin and cisplatin), dose-dense (dd)MVAC, and GC (gemcitabine and cisplatin) are strongly recommended, similar to other international guideline recommendations [8, 9, 11]. Single agent platinum has not shown benefit [90]. ddGC is not recommended due to potentially increased rates of cardiovascular toxicity and lack of prospective data [91].

The optimal NAC regimen remains controversial. Most commonly used regimens are ddMVAC, MVAC, and GC which are based on level II evidence. Neoadjuvant ddMVAC or accelerated MVAC with G-CSF prophylaxis is associated with a shorter time to surgery than classic MVAC, and a more favorable toxicity profile in two phase II trials [92, 93]. Rates of pCR were 38% and 26% respectively. Although comparative trials are lacking, these results support ddMVAC as the preferred regimen over classic MVAC. GC has only been tested in comparative trials in metastatic UCB, showing similar efficacy and a more favorable safety profile compared to MVAC [94]. Extrapolated to the neoadjuvant setting, GC has become a commonly accepted NAC regimen [81, 95–99]. SWOG S1314 was a phase II trial which randomized MIBC patients to neoadjuvant GC versus ddMVAC [100]. This trial was not designed to compare efficacy of the two regimens but rather to determine the utility of a gene expression model-based biomarker approach in predicting pCR. In this trial, GC and ddMVAC yielded comparable rates of

### Box 2. Recommendations for Diagnostic Investigations

| Complete staging investigations should include CT chest, abdomen and pelvis with intravenous contrast if no contraindications, or MRI of abdomen and pelvis plus non-contrast CT chest if contrast administration is prohibited (Level 3, moderate quality, Grade C). |

### SYSTEMIC THERAPY

**Neoadjuvant chemotherapy (NAC)**

MIBC is a chemo-sensitive disease with high propensity for distant relapse, likely due to presence
Table 5

<table>
<thead>
<tr>
<th>Publication, Year</th>
<th>Phase</th>
<th>n</th>
<th>MIBC stage</th>
<th>Experimental Arm</th>
<th>Control Arm</th>
<th>Definitive Local Therapy</th>
<th>Median FU</th>
<th>PCR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA06 30894, 1999 [121, 301]</td>
<td>III</td>
<td>976</td>
<td>Clinical T2 grade 3, T3, or T4a and N0 (65%) /Nx, M0</td>
<td>Neoadjuvant CMV* q21d × 3 cycles</td>
<td>Observation</td>
<td>RC or radiation or both</td>
<td>8.0 years</td>
<td>32.5% vs 12.3%</td>
<td>36% vs 30%, HR 0.84 at 10 years, ( p = 0.037 )</td>
</tr>
<tr>
<td>SWOG 8710, 2003 [84]</td>
<td>III</td>
<td>317</td>
<td>Clinical T2–T4 N0M0</td>
<td>Neoadjuvant MVAC* q28d × 3 cycles</td>
<td>Observation</td>
<td>RC</td>
<td>8.7 years</td>
<td>38% vs 15%, ( p &lt; 0.001 )</td>
<td>57% vs 43% at 5 years, ( p = 0.06 )</td>
</tr>
<tr>
<td>ABC Meta-analysis, 2003, 2005 [302]</td>
<td>3005</td>
<td>Clinical T2–T4a</td>
<td>Neoadjuvant chemotherapy</td>
<td>Observation</td>
<td>RC or radiation or both</td>
<td>6.2 years</td>
<td>–</td>
<td>50% vs 45%, HR 0.86 at 5 years, ( p = 0.003 )</td>
<td></td>
</tr>
<tr>
<td>Winquist Meta-analysis, 2004 [303]</td>
<td>3315</td>
<td>Clinical T2–T4a</td>
<td>Neoadjuvant chemotherapy</td>
<td>Observation</td>
<td>RC or radiation or both</td>
<td>–</td>
<td>–</td>
<td>55% vs 50%, HR 0.90, ( p = 0.02 )</td>
<td></td>
</tr>
<tr>
<td>Yin Meta-analysis, 2016 [170]</td>
<td>3285</td>
<td>Clinical T2–T4a</td>
<td>Platinum-based neoadjuvant chemotherapy</td>
<td>Observation</td>
<td>RC or radiation or both</td>
<td>–</td>
<td>–</td>
<td>HR 0.87, ( p = 0.004 )</td>
<td></td>
</tr>
</tbody>
</table>

pCR, pathologic complete response; RC, radical cystectomy. *Methotrexate 30 mg/m² and vinblastine 4 mg/m² day 1/8, cisplatin 100 mg/m² day 2, and folinic acid 15 mg day 2/9. *methotrexate 30 mg/m² day 1/15/22, vinblastine 3 mg/m² day 2/15/22, adriamycin 30 mg/m² and cisplatin 70 mg/m² day 2.

pCR (35% and 32% respectively) and downstaging to \( \leq \text{pT1} \) (50% and 56% respectively). Mature OS data is still pending at this time. Other studies have shown neoadjuvant GC have similar pCR rates (20–25%) as MVAC [81, 98, 101] and slightly lower pCR rates than ddMVAC (30–40%) [92, 93, 99, 102, 103]. Survival outcomes of neoadjuvant GC and MVAC/ddMVAC are likely similar [98, 99, 103].

Restaging imaging should be performed at the end of NAC prior to local definitive therapy. Restaging cystoscopy can be considered for two indications: 1) to further assess disease status if clinically indicated [86], and 2) to add fiducial markers such as injected lipiodol to facilitate image-guided radiotherapy for patients who are planned to receive bladder-sparing trimodality therapy (TMT) [104, 105]. If using GC or standard dose MVAC, mid-treatment imaging may be used to rule out disease progression during NAC, however it is not standard practice [17]. Locally progressive disease or unacceptable toxicity at any point should trigger a discussion regarding immediate RC. Following NAC, local definitive therapy should occur within 4–6 weeks if possible. Up to 10 weeks between NAC and RC should represent the maximal target time interval limit, as longer intervals may compromise survival outcomes [106–109].

Despite level I evidence, less than 25% of patients receive cisplatin-based NAC [110–115], likely due to age/baseline frailty/comorbidities [97, 116], inability to predict response to NAC at the outset, risk of delay in local definitive therapy in non-responders and a perceived marginal therapeutic benefit. Significant systematic variation in NAC utilization rates also exist [117]. In settings where a multidisciplinary approach is used, rates of NAC use are higher, up to 50% [118, 119]. This highlights the importance of ongoing multidisciplinary collaboration, patient and provider education. Over the years, NAC utilization rates have steadily increased [6, 120], which is anticipated to translate into improved outcomes.

It is important to note that in patients who are cisplatin-eligible, NAC should also be considered prior to TMT with concurrent chemoradiotherapy (see section 8). The goals of NAC prior to TMT remain similar - to eliminate micro-metastatic disease and achieve pCR. In the BA06 30894 trial, neoadjuvant CMV reduced the risk of death by 20% in patients who received radiation alone and 26% in patients who received RC [121]. In another Danish trial, the addition of NAC to radiotherapy alone in 153 patients improved median OS from...
16.3 to 19.2 months, although statistical significance was not reached [122]. One would speculate that patients treated with TMT may also derive similar benefit from NAC. In the large BC2001 phase III trial evaluating concurrent chemoradiotherapy, use of NAC did not impact the benefit of concurrent 5-fluorouracil plus mitomycin, and no significant increase in late toxicity was observed [123]. Radiation Therapy Oncology Group (RTOG) 89-03 was a phase III trial published in 1998 which randomized patients to neoadjuvant CMV (without growth factor support and modern antiemetics at the time) followed by TMT versus TMT alone [124]. The trial was powered to detect a 15% difference in absolute survival, which greatly exceeded the observed survival benefit in RC trials [84]. It closed prematurely after 123 patients were randomized (target accrual was 174 patients) due to increased rates of sepsis and neutropenia. NAC completion rate was only 67%, which significantly limited statistical power [124]. Only two cycles of NAC were used, which likely limited the impact on OS [84, 121]. RTOG 89-03, perhaps not surprisingly, did not detect improved locoregional control, distant control, or OS with the addition of NAC, and dampened earlier enthusiasm for using NAC prior to TMT. Meta-analyses suggest NAC improves survival outcomes regardless of whether patients received TMT or surgery, although differences were not statistically significant [90, 125]. Investigators at the Princess Margaret Cancer Centre and other centres recently reported encouraging outcomes and tolerability of NAC prior to TMT [126, 127]. It is important to note that historically TMT was reserved for patients who were ineligible for RC (and often ineligible for cisplatin-based NAC). By comparison, younger and fitter patients opting for bladder preservation in the contemporary setting are more likely to tolerate and benefit from NAC. While currently there is no proven benefit for NAC prior to TMT, trials are ongoing now evaluating the use of NAC in this setting (NCT03620435, NCT03768570). Further data are warranted to evaluate the use of this approach.

Prior landmark NAC trials excluded patients with lymph node positive disease as stage IV metastatic disease under the previous AJCC staging system [57]. The AJCC 8th Edition now designates N1–3 disease as stage III [56], highlighting their superior outcomes compared to other patients with metastatic disease. Two phase II trials evaluating neoadjuvant ddMVAC included patients with N1 disease [92, 93]. Large retrospective series suggest potential benefit even in N2–N3 disease, yielding pCR rates of 15–27% [128, 129] and an absolute 20% improvement in OS at 3 years [98, 128, 129]. Based on current data, lymph node positive MIBC should be managed with induction systemic therapy, and subsequent local definitive therapy in responders. Cisplatin-based chemotherapy should be given for 4 cycles. However, 6 cycles were administered in previous trials evaluating patients with node only metastatic disease [130]. Based on expert opinion, in select patients with node positive disease, 6 cycles of induction chemotherapy could be considered if a patient is tolerating treatment well and there is ongoing disease response [128, 131]. Whether 6 cycles instead of 4 cycles improves outcomes in node positive MIBC unknown, and requires further study.

**Box 3. Recommendations for Neoadjuvant Systemic Therapy**

Neoadjuvant cisplatin-based combination chemotherapy is recommended for cisplatin-eligible patients with cT2-T4aN0+ bladder cancer planned for radical cystectomy (Level 1, high quality, Grade A).

Neoadjuvant cisplatin-based combination chemotherapy can be considered prior to trimodality therapy in cisplatin-eligible patients (Level 2, moderate quality, Grade B).# 

Node positive (N1-3) disease can also be considered for induction chemotherapy and subsequent definitive local therapy. #Level of consensus: Level 2, moderate quality, Grade B – 65%; Level 3/4, low quality, Grade C – 25%; Level 1, high/moderate quality, Grade A – 5%; no response – 5%.

**Complete clinical response following NAC**

pCR at the time of RC is achieved in 30–40% of patients treated with cisplatin-based NAC [84, 98]. The standard of care for patients who achieve complete clinical response (CR, defined as absence of disease on urinary cytology, TURBT and imaging) following NAC is to proceed with planned local definitive therapy. Retrospective data have reported 5-year disease-free survival reaching 50–80% in these patients opting for surveillance [132–135], however supporting evidence is limited and discrepancy between CR defined by clinical staging and pCR limits the reliability of CR [86, 136]. Ongoing work is exploring a risk adapted approach of selecting certain patients for active surveillance (NCT0272710 734, NCT03609216). However, such strategies should only be performed in the setting of a clinical trial.
Adjuvant Chemotherapy (AC)

To date, no prospective trial has demonstrated any significant difference in OS comparing NAC to AC in MIBC [137]. AC utilization rates remain low at approximately 20% [6, 120]. About a third of patients may be precluded from AC due to complications from RC and/or reduced performance status [138]. AC trials have historically been difficult to accrue, and were often underpowered, making the overall data in AC less robust than NAC. At least 11 AC trials have been conducted, with only 3 of which demonstrating a similar survival benefit to NAC [139–142] (Appendix 1). While the ABC meta-analyses in 2005 reported insufficient evidence to guide treatment decisions [89], several recent meta-analyses have suggested an OS benefit with AC [143, 144].

Recently, a large retrospective study from the National Cancer Data Base showed potential OS benefit (HR 0.70) in high risk patients (pT3/T4 or node positive disease) [145]. The hazard ratio mirrors data from the Ontario Cancer Registry (HR 0.71) and other reports (HR 0.74–0.77) [146, 147]. Therefore, for patients with high risk disease who did not receive NAC, AC should be considered. Patients should start AC as soon as they are medically fit to do so, ideally within 12 weeks of surgery [113]. However, delay of more than 12 weeks from surgery should not be the sole reason to exclude AC. The benefit of AC in variant histology is unclear, and should be discussed at experienced centres [148].

The use of AC after cisplatin-based NAC is not recommended, given conflicting results from observational series and lack of prospective data [30, 149–154]. Biologically, it is presumed tumor cells resistant to cisplatin-based NAC will also be refractory to AC.

Overall, given the lack of robust data in the adjuvant setting, clinical trial participation is encouraged for patients with high risk MIBC. Trials evaluating adjuvant immune checkpoint inhibitors are underway (Table 7). Adjuvant radiotherapy is an area also requiring further study.

### Box 4. Recommendations for Adjuvant Systemic Therapy

In cisplatin-eligible patients who did not receive cisplatin-based neoadjuvant chemotherapy and have muscle-invasive disease on surgical pathology, adjuvant cisplatin-based chemotherapy should be considered (Level 2, moderate quality, Grade B). Patients with pT3/pT4 or pN+ disease has the highest level of evidence for adjuvant chemotherapy.

### Table 6

<table>
<thead>
<tr>
<th>Cisplatin-ineligibility criteria in metastatic bladder cancer proposed by Galsky et al. 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any one of the following:</td>
</tr>
<tr>
<td>WHO or ECOG PS $\geq 2$, or Karnofsky PS $\leq 60–70%$</td>
</tr>
<tr>
<td>Creatinine clearance (calculated or measured) $&lt;60$ mL/min</td>
</tr>
<tr>
<td>CTCAE v4 grade $\geq 2$ peripheral neuropathy</td>
</tr>
<tr>
<td>CTCAE v4 grade $\geq 2$ audiometric hearing loss</td>
</tr>
<tr>
<td>NYHA Class III/IV heart failure</td>
</tr>
</tbody>
</table>


### Cisplatin-ineligible patients

Standard ineligibility criteria for cisplatin-based chemotherapy were proposed by Galsky et al. in 2011 and are shown in Table 6 [155]. Unfortunately, nearly half of all patients fit for RC are deemed cisplatin-ineligible [116], likely due to baseline frailty and comorbidities inherent to the MIBC patient population, as well as obstructive uropathy from direct disease invasion. Malignant urinary obstruction should be decompressed which may allow more patients to receive cisplatin-based NAC. Percutaneous nephrostomy tube insertion is preferred over stenting, given the latter’s lower success rates [156] and risk of upper tract recurrence associated with stenting [157].

Renal function is often a limiting factor for cisplatin-based therapy, and can be estimated by the Cockcroft Gault, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations. The latter two may be more accurate in patients with cancer [158–161]. Timed urine collections, although preferable, are infrequently utilized due to inconvenience and cost. In patients with impaired renal function (renal clearance $\geq 50$ mL/min), split dose GC (cisplatin 35 mg/m² on day 1 and day 8) [81, 91, 162–165] and dose reduction (25–50%) of standard GC (cisplatin 70 mg/m² every 3 weeks) are options, although data supporting these approaches remains limited [166–168]. For patients with baseline renal function $<50$ mL/min, generally the use of cisplatin-based NAC is not supported by adequate safety data. However multidisciplinary discussion including onco-nephrology at experienced centers and informed discussion with patients are recommended. The risk of permanent renal injury and limited accuracies of existing tools for estimating renal function are important to highlight. Admin-
istering cisplatin in patients with renal function of <40 ml/min is not recommended given lack of safety data. Some reports suggest cisplatin-based NAC can be administered to patients undergoing hemodialysis with appropriate dose reduction [169], and these patients should be treated at experienced centers.

Carboplatin-based perioperative chemotherapy should not be offered, given the lack of evidence for a survival benefit [170], unnecessary toxicity and risk of delaying local definitive therapy. Multiple studies have shown inferior outcomes with carboplatin-compared to cisplatin-based chemotherapy in UCB [171–174, 99]. The SWOG S0219 study evaluated neoadjuvant carboplatin, gemcitabine and paclitaxel showed that 60% of patients with clinical T0 disease had residual cancer at cystectomy, and survival rates were only 60% at 2 years [136].

Box 5. Recommendations for Systemic Therapy in cisplatin-ineligible patients

Patients with calculated renal function of 50–60 ml/min, or measured creatinine clearance of 50–60 ml/min using a 24 hour urine collection, who are otherwise cisplatin-eligible may be considered for neoadjuvant or adjuvant cisplatin-based chemotherapy (Level 2, low quality, Grade C).

In cisplatin-ineligible MIBC patients, definitive local therapy alone (cystectomy or trimodality therapy) or enrollment in a clinical trial is recommended (Level 2, moderate quality, Grade B).

Variant histology

Given the rarity of variant histology, data guiding the management of these tumors are limited to observational studies only. Variant histologies generally have worse prognosis and more upstaging at the time of surgery compared to conventional UCB [175–177]. Pure variant histology may have inferior OS compared to mixed variant histologies treated with RC [54].

The benefit of cisplatin-based NAC in variant histology is not clearly established. Neuroendocrine (or small cell carcinoma) variants have a high tendency for systemic relapse. Tumors with pure, mixed neuroendocrine histology, and neuroendocrine differentiation should be treated with neoadjuvant cisplatin etoposide similar to small cell lung cancer, which leads to pathologic downstaging in 60–80% of patients [178, 179]. Management of neuroendocrine variants is outlined in a separate consensus guideline from GUMOC [180]. Pure non-bilharzial squamous cell carcinomas responds poorly to NAC and radiation, thus should be treated with upfront RC [181–185]. Research is ongoing to identify distinct clinical phenotypes and novel therapeutic targets [186]. On the other hand, urothelial tumors with squamous and glandular differentiation often respond to NAC [187–192]. The SWOG S8710 trial evaluating neoadjuvant MVAC included 59 patients with mixed nonurothelial histologies (such as squamous or glandular differentiation) and showed a significant benefit in OS in this cohort [187]. Many experts on this panel considered these data as moderate or high level evidence supporting the use of NAC in this setting.

Box 6. Recommendations for Systemic Therapy for Variant Histology

Patients with resectable pure squamous cell carcinoma and adenocarcinoma of the bladder should be considered for upfront surgery (Level 3, low quality, Grade C).

Cisplatin-based neoadjuvant chemotherapy is recommended for resectable pure neuroendocrine, neuroendocrine histology mixed with urothelial carcinoma, and tumors with neuroendocrine differentiation (Level 2, moderate quality, Grade C).

Cisplatin-based neoadjuvant chemotherapy should be considered for urothelial tumors with squamous and glandular differentiation (Level 3, low quality, Grade C).# Level of consensus: Level 3, low quality, Grade C – 60%; Level 2, moderate/high quality, Grade B – 20%; Level 1, high quality, Grade A – 15%; no response – 5%.

DEFINITIVE LOCAL THERAPY

Radical cystectomy and bilateral pelvic lymph node dissection

Following NAC, RC with bilateral pelvic lymph node dissection (PLND) remains the historical stan-
Currently active and completed trials evaluating checkpoint inhibitors and targeted therapies in muscle invasive bladder cancer (based on search on clinicaltrials.gov on May 6, 2020 for “muscle invasive bladder cancer” and “muscle-invasive bladder cancer” start date “01/01/2010 to 05/06/2020”). Trials with recruiting centres in Canada are marked with **

<table>
<thead>
<tr>
<th>Neoadjuvant</th>
<th>Cisplatin eligible</th>
<th>Cisplatin ineligible or declined</th>
<th>Trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03924895(KEYNOTE 905)**</td>
<td></td>
<td></td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab 200mg iv every 3 weeks for 3 cycles + adjuvant for 14 cycles</td>
<td>No</td>
<td>Yes</td>
<td>Neoadjuvant pembrolizumab 200mg iv every 3 weeks for 4 doses</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab 200 mg iv every 3 weeks for 3 doses</td>
<td>Yes</td>
<td>Yes</td>
<td>Recruiting; reported</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab 200 mg</td>
<td>No</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab 200 mg iv every 3 weeks for 4 cycles + GC</td>
<td>Yes</td>
<td>Yes</td>
<td>Active, not recruiting; reported</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab 200 mg IV every 3 weeks for 4 cycles + GC or gemcitabine</td>
<td>Yes</td>
<td>Yes</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab 200 mg IV every 3 weeks for 3 cycles + epacadostat 300 mg BID po every 28 days for 3 cycles</td>
<td>Yes</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab 200 mg IV every 3 weeks for 2 doses + entinostat 5 mg po weekly for 3 weeks</td>
<td>No</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy +/- nivolumab, BMS-986205; adjuvant nivolumab, BMS-986205</td>
<td>Yes</td>
<td>No</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant nivolumab + NKTR-214</td>
<td>No</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant nivolumab 360 mg iv every 3 weeks + GC for 4 cycles</td>
<td>Yes</td>
<td>No</td>
<td>Active, not recruiting; reported</td>
</tr>
<tr>
<td>Neoadjuvant nivolumab 360 mg iv every 3 weeks + GC for 4 cycles. Maintenance nivolumab 240 mg every 2 weeks for up to 8 cycles</td>
<td>Yes</td>
<td>No</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab 200 mg/kg every 2 weeks for 5 cycles, or nivolumab 1mg/kg + ipilimumab 3 mg/kg every 6 weeks for 2 cycles, or nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 3 cycles</td>
<td>No</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab 240 mg iv + urelumab 8 mg every 2 weeks for 2 cycles</td>
<td>No</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant nivolumab 480 mg iv+/- lirilumab 240 mg IV every 4 weeks for 2 doses</td>
<td>No</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant nivolumab every week for 4 cycles + GemRIS/TAR 200</td>
<td>No</td>
<td>Yes</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Neoadjuvant pembrolizumab every 3 weeks for 2 cycles</td>
<td>No</td>
<td>Yes</td>
<td>Active, not recruiting; reported</td>
</tr>
<tr>
<td>Neoadjuvant atezolizumab 1200 mg every 3 weeks for 2 or 3 doses</td>
<td>No</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Neoadjuvant atezolizumab1200 mg IV every 3 weeks for 3 cycles + cabozantinib 40 mg orally daily for 3 cycles</td>
<td>No</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

(Continued)
Table 7
(Continued)

<table>
<thead>
<tr>
<th>Neoadjuvant</th>
<th>Cisplatin</th>
<th>Cisplatin</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eligible</td>
<td>ineligible or declined</td>
<td>status</td>
</tr>
<tr>
<td>NCT02989584 (MSKCC 16-1428)</td>
<td>Phase I/II</td>
<td>Neoadjuvant atezolizumab + GC or 4 cycles</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT03732677 (NIAGARA)**</td>
<td>Phase III</td>
<td>Neoadjuvant GC +/- durvalumab, adjuvant durvalumab</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT03234153 (NITIMIB)</td>
<td>Phase II</td>
<td>Neoadjuvant durvalumab 1500 mg iv + tremelimumab 75 mg iv every 4 weeks for 4 cycles</td>
<td>No</td>
</tr>
<tr>
<td>NCT03472274 (DUTRENEO)</td>
<td>Phase II</td>
<td>Neoadjuvant durvalumab 1500 mg + tremelimumab 75 mg every 4 weeks × 3 cycles or cisplatin-based chemotheraphy</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT02812420 (NCI-2016-01147)</td>
<td>Phase I</td>
<td>Neoadjuvant durvalumab 1500 mg + tremelimumab 75 mg on weeks 1 and 5</td>
<td>No</td>
</tr>
<tr>
<td>NCT03534492 (NEODURVARIB)</td>
<td>Phase II</td>
<td>Neoadjuvant durvalumab 1500 mg iv every 4 weeks + olaparib 300 mg BID for up to 2 months</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT03773666 (BLASST-2)</td>
<td>Phase I</td>
<td>Neoadjuvant durvalumab every 2 weeks +/- Opleclumab</td>
<td>No</td>
</tr>
<tr>
<td>NCT03674424 (AURA)</td>
<td>Phase II</td>
<td>Neoadjuvant avelumab 10 mg/kg every 2 weeks +/- ddMVAC/GC/GP</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT03473730 (MDACC 2017-0688)</td>
<td>Phase I</td>
<td>Neoadjuvant daratumumab IV weekly for 4 weeks</td>
<td>No</td>
</tr>
<tr>
<td>NCT04099589 (NCC2121)</td>
<td>Phase II</td>
<td>Neoadjuvant toripalimab 240 mg injection every 3 weeks for 2–4 cycles + GC</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT03288545(EV-103)</td>
<td>Phase I</td>
<td>Neoadjuvant enfortumab vedotin (cohort H) Neoadjuvant enfortumab vedotin + pembrolizumab (cohort J)</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Cisplatin</th>
<th>Cisplatin</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eligible</td>
<td>ineligible or declined</td>
<td>status</td>
</tr>
<tr>
<td>NCT03244384 (AMBASSADOR)</td>
<td>Phase III</td>
<td>Adjuvant pembrolizumab every 3 weeks for up to 18 cycles, or observation</td>
<td>No</td>
</tr>
<tr>
<td>NCT02632409 (Checkmate 274)</td>
<td>Phase III</td>
<td>Adjuvant nivolumab</td>
<td>No</td>
</tr>
<tr>
<td>NCT02450331 (IMvigor010)</td>
<td>Phase III</td>
<td>Adjuvant atezolizumab 1200 mg every 3 weeks up to 1 year</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trimodality Therapy</th>
<th>Cisplatin</th>
<th>Cisplatin</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eligible</td>
<td>ineligible or declined</td>
<td>status</td>
</tr>
<tr>
<td>NCT04241185 (KEYNOTE-992)</td>
<td>Phase III</td>
<td>Concurrent pembrolizumab 400 mg every 6 weeks + cisplatin, 5FU MMC, or gemcitabine</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT02662062(PCR-MIB)</td>
<td>Phase II</td>
<td>Concurrent pembrolizumab 200 mg every 3 weeks + cisplatin, pembrolizumab continued until 12 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT02621151 (NYU 15-00220)</td>
<td>Phase II</td>
<td>Concurrent pembrolizumab 200 mg every 3 weeks for 3 doses + gemcitabine</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT02560636(PLUMMB)</td>
<td>Phase I</td>
<td>Concurrent pembrolizumab 100–200 mg every 3 weeks starting 2 weeks prior to radiotherapy, continued for a maximum of 12 months</td>
<td>Yes</td>
</tr>
<tr>
<td>NCT03993249 (HGCG 000020479)</td>
<td>Phase II</td>
<td>Concurrent nivolumab and standard of care chemoradiotherapy</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(Continued)
Table 7 (Continued)

<table>
<thead>
<tr>
<th>Trimodality Therapy</th>
<th>Cisplatin eligible</th>
<th>Cisplatin ineligible or declined</th>
<th>Trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03844256(CRIMI)</td>
<td>Yes</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03775265(SWOG S1806)</td>
<td>Yes</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT03620435 (ML-39576)**</td>
<td>Yes</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT04186013 (ATEZOBLAGGER-RESERVE)</td>
<td>Yes</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT03702179 (IMMUNOREPRESERVE)</td>
<td>Yes</td>
<td>Yes+</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT0347419 (DFCI 18-464)</td>
<td>Yes</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT03617913 (MC1752)</td>
<td>Yes</td>
<td>Yes</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>NCT04073160 (TRIO Bladder)</td>
<td>Yes</td>
<td>Yes+</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT03171025(NEXT)</td>
<td>Yes</td>
<td>Yes</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT03768570(CCTG BL13)**</td>
<td>Yes</td>
<td>Yes+</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

ddMVAC, dose dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine cisplatin; GP, gemcitabine paclitaxel; 5FU, 5-fluorouracil; MMC, mitomycin. *except poor ECOG and neuropathy ≥Grade 2.

Trimodality therapy (TMT)

Multiple bladder preservation options exist including radical TURBT, radiotherapy alone, and “tetramodal” therapy consisting of TURBT, chemoradiation and partial cystectomy [225]. However TMT is the most favored approach as it offers the highest curative potential with the highest level of supporting data.

TMT consists of maximal TURBT followed by definitive chemoradiotherapy [123, 226, 227], with salvage cystectomy reserved for localized bladder relapse. Radiotherapy is typically given with total standard local definitive therapy approach in patients with MIBC [7, 214–216]. PLND should include removal of pelvic nodes up to the common iliac bifurcation (internal, external, and obturator nodes), although the optimal extent of lymphadenectomy is not established [217–221]. Some authors have proposed thresholds of 10 to 16 removed lymph nodes (as a surrogate for surgical quality) for adequate pathological staging and optimal survival outcomes [45, 218, 222–224]. In patients with pelvic or retroperitoneal node positive disease, the role of postchemotherapy lymph node resection may be limited [131].
Box 7. Recommendations for Definitive Local Therapy
Radical cystectomy with bilateral pelvic lymphadenectomy should be offered to patients with resectable MIBC (Level 1, high quality, Grade A).

Although direct comparisons are lacking, trimodality therapy should be offered as an accepted and reasonable alternative to radical cystectomy in select patients ideally meeting the following criteria: small (<5 cm) and unifocal tumor, absence of extensive CIS, no hydronephrosis, good bladder function, no prior pelvic radiotherapy, and compliance for regular cystoscopy surveillance (Level 2, high quality, Grade B). Patients who are not candidates for or who decline radical cystectomy should be offered trimodality therapy if feasible (Level 2, high quality, Grade B).

Options for radiosensitizing agents in trimodality therapy include cisplatin (either 100 mg/m² every 3 weeks [Level 1, high quality, Grade A], or 35–40 mg/m² weekly [Level 2, moderate quality, Grade B]), 5-FU with mitomycin (Level 1, high quality, Grade A), or single agent weekly gemcitabine 100 mg/m² (Level 2, moderate quality, Grade B).

doses of 60 Gy (2 Gy/day) or above delivered to the bladder and/or pelvic lymph nodes, or 55 Gy (2.75 Gy/day) delivered to the bladder alone. Concurrent systemic therapy improves local control [123, 228], and possibly OS [229–231], although no standard regimen exists. Concurrent cisplatin was used in the RTOG, National Cancer Institute of Canada (NCIC) and Trans Tasman Radiation Oncology Group (TROG) trials, and is the most commonly used radiosensitizer [124, 227, 228, 230, 232–235]. Concurrent cisplatin can be administered as 35–40 mg/m² weekly or 100 mg/m² every 3 weeks. The use of concurrent 5-fluorouracil plus mitomycin C (5-fluorouracil administered as a continuous infusion at 500 mg/m² daily on days 1 to 5 and 16–20 of radiotherapy, mitomycin administered as an intravenous bolus dose of 12 mg/m² on day 1) is supported by a large randomized phase III trial [123]. Low dose gemcitabine [236–239] is another alternative especially in more frail patients. Comparative trials are needed to elucidate the optimal radiosensitizer in TMT.

Adequate level 1 evidence directly comparing RC with TMT is lacking after the SPARE trial failed to accrue [240], RC remains the most commonly used treatment approach and the historical standard [241, 242]. For patients who are ineligible for RC, or desire bladder preservation, TMT is the preferred bladder-sparing approach. Radiotherapy alone in the treatment of localized MIBC is only acceptable in extremely frail patients who are ineligible for both RC and TMT.

Ideal candidates for TMT are patients with 1) cT2 with tumors <5 cm [243], 2) solitary tumors without extensive carcinoma in situ (CIS) [244–246], 3) minimal to no hydronephrosis [124, 247], 4) good bladder function [243], 5) completion of maximal TURBT without visible residual tumor [229, 246, 248, 249], and 6) agreeable to long-term surveillance with regular cystoscopy and imaging [243]. TMT is likely equivalent to RC in these patients, as shown by data with long-term follow up [229, 243, 250–255], and up to 89% of patients successfully retain their native bladders [243]. Short-term treatment mortality likely favors TMT, especially in elderly patients [256]. Patients should be carefully selected for TMT (and NAC) through a multidisciplinary approach in experienced centres [257]. A multidisciplinary bladder clinic has been shown to significantly impact treatment selection and has potential to improve patient outcomes [119].

POST-TREATMENT SURVEILLANCE

Surveillance enables early detection of recurrences and curative-intent salvage therapy. It also serves to monitor the development of a second primary and metachronous upper tract malignancy after local definitive therapy which occurs in 5% of patients [258]. Currently, the optimal frequency, modality and duration of surveillance is subject to debate given lack of robust evidence [8, 9, 12, 16, 79, 259–261]. Suggested surveillance protocols are included to emphasize the overall importance of surveillance, provide some general guidance and promote care standardization, however these recommendations are based on very limited data. Risk of disease recurrence and patient preference should also be considered. Ultimately prospective clinical trials are needed to elucidate the optimal surveillance approach in MIBC.

CT of the abdomen and pelvis with or without intravenous contrast together with excretory imaging can be employed to evaluate both upper tract and abdominopelvic recurrences, and is the preferred imaging modality for surveillance. The optimal surveillance chest imaging (chest X ray or CT chest) is unknown.

Following RC, up to 20% of patients develop local recurrence, and 50% develop distant recurrences (most commonly to bone, distant lymph nodes, and lung) [78, 262]. Most recurrences occur within the first 2–3 years. Late recurrences (or development of a new primary) can rarely occur [79, 260, 263], although there is scant data to guide surveillance...
beyond 5 years. A risk-adapted strategy based on pathological stage can be employed, although further prospective studies are needed for validation [12, 79, 259–261, 264]. Multivariate nomograms including additional prognostic factors may be more accurate in predicting an individual’s survival following RC, compared to pathologic stage alone [265].

Local recurrence after TMT can be either NMIBC or MIBC. Recurrent NMIBC should be managed according to usual guidelines, including TURBT and adjuvant intravesical therapy as indicated. Recurrent MIBC and some higher risk NMIBC can be successfully salvaged with RC. Therefore, all patients require close cystoscopic surveillance post TMT. Based on published TMT surveillance protocols [123, 243, 248, 252] and extrapolating from the NMIBC setting, cystoscopy and urine cytology are generally recommended every 3–6 months for the first three years followed by every 6 months for two additional years, and annually thereafter. Delayed local recurrence (or development of a new primary) at 10 years have been reported in up to 10% of patients following TMT, therefore long term cystoscopic surveillance may be warranted [250, 252].

**Box 8. Recommendations for Surveillance**

Surveillance following radical cystectomy should include history, physical exam, blood work, and surveillance CT abdomen pelvis and chest imaging (Level 4, very low quality, Grade C).

Based on expert consensus, a suggested surveillance protocol following radical cystectomy includes CT abdomen pelvis and chest imaging every 3–6 months for the first 3 years, every 6 months for 2 additional years, then annually thereafter (Level 4, very low quality, Grade C). A risk based surveillance approach can be considered.

Based on expert consensus, a suggested surveillance protocol following trimodality therapy includes urine cytology, cystoscopy, CT abdomen pelvis and chest imaging every 3–6 months for the first 3 years, every 6 months for 2 additional years, then annually thereafter (Level 4, very low quality, Grade C).

**FUTURE DIRECTIONS**

**Immune checkpoint inhibitors (CPIs) and targeted therapies**

The landscape of UCB has changed rapidly in recent years with the use of CPIs, with multiple agents approved since 2016. Pembrolizumab was shown to have a 3-month OS advantage over chemotherapy in the second line metastatic setting by the Keynote 045 phase III trial [266]. In the neoadjuvant setting, pembrolizumab (PURE-01 trial) and atezolizumab (ABACUS trial) have phase II data demonstrating pCR rates of 42% and 29% respectively, with acceptable toxicity profile [267, 268]. In the PURE-01 trial, all treated patients underwent RC. In the ABACUS trial, 2 out of 74 patients treated died prior to RC, 1 was treatment related. Another 3 had clinical deterioration, 1 experienced disease progression prior to RC. Combination CPI with nivolumab and ipilimumab was evaluated in the phase Ib trial NABUCCO. Among 24 patients with clinical stage T3/4 or N+ MIBC 46% achieved pCR (60% in PD-L1+, and 22% in PD-L1– group), and all underwent RC [269]. Ipilimumab, a CTLA-4 inhibitor, has also been tested as monotherapy [270]. Although 66.7% patients were downstaged at cystectomy, preoperative ipilimumab produced grade 3 toxicity in 4 out of 12 patients, and 2 experienced surgical delays due to toxicity. Durvalumab and tremelimumab was also evaluated as a neoadjuvant regimen in a single arm trial [271]. Among 35 patients, 9 (43%) achieved pCR, 14 (67%) had downstaging, 2 (7%) resulted in surgery delay for >30 days. In a phase Ib/II trial, combination pembrolizumab with chemotherapy was administered in 40 patients prior to RC [272]. There were 5 patients who did not proceed with RC (4 refused, 1 due to adverse event). Downstaging to <T2 disease occurred in 22 patients (61%), and pCR occurred in 16 patients (40%). BLASST-1 is a phase II trial evaluating combination nivolumab, which reported pCR rates of 49% [273]. These results seem to suggest that the addition of immunotherapy to standard of care NAC does not result in synergy with respect to pCR rates, however long term OS data is still awaited and phase III trials are underway. Emerging data suggest neoadjuvant CPI do not adversely affect surgical safety of RC [274].

Combination strategies with targeted therapies are also being investigated. Phase II results have been reported from durvalumab plus olaparib (NEO-DURVARIB trial) and nintedanib, a tyrosine kinase inhibitor, plus GC (NEO-BLADE trial), with pCR rates 50% and 37% respectively [275, 276]. The NEO-BLADE trial also reported improved OS over GC alone with HR 0.38, \( p = 0.018 \). Further randomized trials are required to further establish the role of these combination strategies in the neoadjuvant setting.

Table 7 lists currently active phase III RCTs investigating the safety and efficacy of CPI and targeted therapies in MIBC [277].
Biomarkers

There is an urgent need to develop predictive biomarkers in MIBC to improve treatment selection [278–281]. In general, molecular subtyping of MIBC reveals basal, luminal (similar to breast cancer), and neuroendocrine-like subtypes [282]. Several molecular classifications exist, and an international consensus was recently published [283]. Basal subtype seems to derive the most benefit from NAC [279, 284]. Luminal subtype has lower risk of upstaging at surgery compared with non-luminal tumors [285]. Genomic alterations in DNA-repair pathways including ERCC2, ERBB2, ATM, RB1 and FANCC also seem to enrich response to NAC [281, 286, 287]. A predictive gene expression model (COXEN) that compares a tumor’s gene expression to established signatures which correlate with response failed to predict response to NAC in a prospective trial [100].

With respect to local definitive therapy, low expression of MRE11 (a protein involved in double-stranded DNA damage repair and cell cycle checkpoint) and high expression of TIP60 (tat-interactive protein 60 kDa) have been associated with improved outcomes with RC [288, 289]. Molecular determinants of response to radiotherapy may include miR-23a and miR-27a [290], genomically unstable and squamous cell cancer-like tumor subtypes [291], and tumors with higher immune infiltration [292].

Currently, no predictive biomarker have been rigorously validated for routine clinical use at this time. However, individual molecular testing and biomarker-driven precision oncology hold promise and may become standard of care for MIBC in the future.

SUMMARY

MIBC has seen many treatment advances in the last several years. Improving utilization of cisplatin-based perioperative therapy to address the risk of systemic relapse through a multidisciplinary effort is critical in optimizing outcomes of this lethal disease. The management of cisplatin-ineligible patients remains an area of high unmet need. Many questions still remain unanswered with regards to patient selection, predictive biomarkers, and the role of immunotherapy in MIBC. Enrollment of patients in clinical trials is encouraged whenever possible.

ACKNOWLEDGMENTS

The authors have no acknowledgements.

FUNDING

The authors report no funding.

AUTHOR CONTRIBUTIONS

Conception: DMJ, SSS
Performance of work: DMJ, SSS
Interpretation or analysis of data: all authors
Writing the article: all authors

ETHICAL CONSIDERATIONS

This paper does not present any primary results of the studies it described herein. As such, it is exempt from any requirement for Institutional Review Board approval

CONFLICT OF INTEREST

There are no direct conflict of interests from any authors. Indirect conflicts of interests are as follows.

DMJ: honoraria and/or consulting fees from Bayer.
CC: advisory role for Janssen, Astellas, Pfizer, Ipsen, BMS, Roche, Merck, Bayer, Eisai; Educational travel grants from Pfizer and Sanofi Genzyme.
MK: honoraria and/or consulting fees from Janssen, Ipsen, Astellas, BMS, Merck, AstraZeneca, Bayer; travel support from Novartis.
LAW: advisory boards from Pfizer, BMS, Ipsen, Merck – no personal financial compensation; research funding from Pfizer, BMS, Merck, Roche, Ipsen, AZ – financial compensation to my institution.
GSK: advisory boards for Ferring, Janssen, Bayer, Astellas, Merck, Roche, Thearalase; Investigator for trials from Merck, AstraZeneca, BMS, Abbvie, Theralase, Sesen Bio.
NSM: consultant/advisory role for Merck, Astellas, Pfizer, Astra Zeneca, Janssen, Sanofi.
PCB: member of an advisory board or equivalent with AbbVie, Asieris, AstraZeneca, Astellas, Bayer, Biosyent, BMS, H3-Biomedicine, Janssen, Merck, Roche, Sanofi, Urogen; member of a Speakers bureau for AbbVie, Biosyent, Janssen, Ferring, TerSera, Pfizer; grant(s) or honorarium received from DeCipher Biosciences, iProgen, Sanofi, Bayer; currently participating in or have participated in a clinical trial within the past two years with Genentech, Janssen,
REFERENCES


[26] BMS, Astellas, Sitka, MDx Health, AstraZeneca; patent shared with Decipher.

SSS: advisory board member for Astellas, AstraZeneca, Bayer, Janssen, Merck, and Roche; has participated in several pharma-supported clinical trials.


[295] International collaboration of trialists. Neoadjuvant Chemotherapy in Muscle-invasive Bladder Cancer: Update of a Systematic Review and


## APPENDIX 1

Select publications of adjuvant chemotherapy in MIBC

<table>
<thead>
<tr>
<th>Publication, Year</th>
<th>Phase</th>
<th>n</th>
<th>Inclusion Criteria</th>
<th>Experimental Arm</th>
<th>Control Arm</th>
<th>Median FU</th>
<th>OS</th>
<th>DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skinner 1991 [139]</td>
<td>III</td>
<td>91</td>
<td>pT3/T4 or pN+</td>
<td>Cisplatin, doxorubicin, cyclophosphamide q28d × 4 cycles</td>
<td>Observation</td>
<td>14.5 years</td>
<td>4.3 vs 2.4 years, HR 0.75, p = 0.0062</td>
<td>HR 0.73, p = NS</td>
</tr>
<tr>
<td>Studer 1994 [304]</td>
<td>III</td>
<td>77</td>
<td>M0</td>
<td>Cisplatin q28d × 3 cycles</td>
<td>Observation</td>
<td>5.75 years</td>
<td>5y OS 57% vs 54%, p = NS</td>
<td>HR 1.02, p = NS</td>
</tr>
<tr>
<td>Stockle 1995 [140, 305]</td>
<td>III</td>
<td>49</td>
<td>pT3b/T4a or pN+</td>
<td>Methotrexate, vinblastine, cisplatin plus doxorubicin or epirubicin</td>
<td>Observation</td>
<td>14.8 years</td>
<td>10y OS 26.9% vs 17.4%, HR 2.52, p = 0.007</td>
<td>10y DFS 43.7% vs 13.0%, HR 2.84, p = 0.002</td>
</tr>
<tr>
<td>Freiha 1996 [215]</td>
<td>III</td>
<td>55</td>
<td>pT3b/T4a or pN+</td>
<td>Cisplatin, methotrexate, vinblastine q21d × 4 cycles</td>
<td>Observation</td>
<td>5.08 years</td>
<td>63 vs 36 months, HR 0.78, p = 0.32</td>
<td>37 vs 12 months, HR 46, p = 0.01</td>
</tr>
<tr>
<td>Bono 1997 [306]</td>
<td>III</td>
<td>93</td>
<td>pT2-T4a, pN0</td>
<td>Cisplatin methotrexate × 4 cycles</td>
<td>Observation</td>
<td>3.45 years</td>
<td>HR 0.75, p = NS</td>
<td>HR 0.65, p = NS</td>
</tr>
<tr>
<td>SOGUG 99/01 2010 [141]</td>
<td>III</td>
<td>142</td>
<td>pT3/T4 (77%) or pN+(70%)</td>
<td>Paclitaxel, gemcitabine, cisplatin q21d × 4 cycles</td>
<td>Observation</td>
<td>30 months</td>
<td>5y OS 60% vs 31%, p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Cognetti 2011 [307]</td>
<td>III</td>
<td>194</td>
<td>pT2G3, pT3/T4, or N+</td>
<td>GC q28d × 4 cycles</td>
<td>Observation</td>
<td>35 months</td>
<td>5y OS 43.4% vs 53.7%, HR 1.29, p = 0.24, p = 0.89</td>
<td>42.3% vs 37.2%, HR 1.08, p = 0.70, p = 0.62</td>
</tr>
<tr>
<td>Stadler 2011 [308]</td>
<td>III</td>
<td>114</td>
<td>pT1/T2 N0M0</td>
<td>MVAC × 3 cycles</td>
<td>Observation</td>
<td>64.8 months</td>
<td>7.0 years</td>
<td>5y OS 53.6% vs 47.7%, HR 0.78, p = 0.13</td>
</tr>
<tr>
<td>Sternberg 2015 [142]</td>
<td>III</td>
<td>284</td>
<td>pT3/T4 or N+</td>
<td>GC or ddMVAC with GCSF × 4 cycles</td>
<td>Same chemo × 6 cycles at relapse</td>
<td>Observation</td>
<td>9 months</td>
<td>Absolute improvement 9% at 3 years, HR 0.75, p = 0.019</td>
</tr>
<tr>
<td>ABC Meta-analysis 2005 [89]</td>
<td></td>
<td>491</td>
<td>Clinical T2–T4a</td>
<td>Adjuvant chemotherapy</td>
<td>Observation</td>
<td>5.2 years</td>
<td>Absolute improvement 9% at 3 years, HR 0.75, p = 0.019</td>
<td>Absolute improvement 12% at 3 years, HR 0.68, p = 0.004</td>
</tr>
<tr>
<td>Leow Meta-analysis 2014 [143]</td>
<td></td>
<td>945</td>
<td>Clinical T2–T4a</td>
<td>Adjuvant cisplatin-based chemotherapy</td>
<td>Observation</td>
<td>Range 30–69 months</td>
<td>HR 0.77, p = 0.049</td>
<td>HR 0.66, p = 0.014</td>
</tr>
<tr>
<td>Kim Meta-analysis 2017 [144]</td>
<td></td>
<td>1546</td>
<td>MIBC and RC</td>
<td>Adjuvant cisplatin-based chemotherapy</td>
<td>Observation</td>
<td>Range 30–168 months</td>
<td>HR 0.79, p = 0.004</td>
<td>HR 0.64, p = 0.002</td>
</tr>
</tbody>
</table>

NS, nonsignificant; GC, gemcitabine cisplatin; ddMVAC, dose dense MVAC; GCSF, granulocyte stimulating factors.