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Review

Current Management of Loco regional Muscle-Invasive Bladder Cancer: A Consensus Statement from the Genitourinary Medical Oncologists of Canada

Di Maria Jiang[a], Scott A. North[b], Christina Canil[c], Michael Kolinsky[b], Lori A. Wood[d], Samantha Gray[e], Bernhard J. Eigl[f], Naveen S. Basappa[b], Normand Blais[g], Eric Winquist[h], Som D. Mukherjee[i], Christopher M. Booth[j], Nimira S Alimohammed[k], Piotr Czaykowski[l], Girish S. Kulkarni[m], Peter C. Black[n], Peter W. Chung[o], Wassim Kassouf[p], Theodorus van der Kwast[q] and Srikala S. Sridhar[a,*]

[a]*Department of Medicine, Division of Medical Oncology and Hematology, University Health Network, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada*
[b]*Department of Oncology, Division of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada*
[c]*Department of Internal Medicine, Division of Medical Oncology, The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada*
[d]*Department of Medicine, Division of Medical Oncology, Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, NS, Canada*
[e]*Department of Oncology, Saint John Regional Hospital, Department of Medicine, Dalhousie University, Saint John, NB, Canada*
[f]*Department of Medicine, Division of Medical Oncology, BC Cancer - Vancouver, University of British Columbia, Vancouver, BC, Canada*
[g]*Department of Medicine, Division of Medical Oncology and Hematology, Centre Hospitalier de l'Université de Montréal; Université de Montréal, Montreal, QC, Canada*
[h]*Department of Oncology, London Health Sciences Centre, University of Western Ontario, London, ON, Canada*
[i]*Department of Oncology, Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada*
[j]*Department of Oncology, Queen's University, Kingston, ON, Canada*
[k]*Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*
[l]*Department of Medical Oncology and Hematology, Cancer Care Manitoba, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada*
[m]*Departments 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, OntarioM5G 6M9, Canada. Tel.: +1 416 946 4501 /Ex: 2662; Fax: +1 416 946 6546; E-mail: srikala.sridhar@uhn.ca.

[n]Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada
[o]Department of Radiation Oncology, Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada
[p]Department of Urology, McGill University Health Centre, Montreal, QC, Canada
[q]Laboratory Medicine Program, University Hospital Network, Toronto, ON, Canada

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Abstract.
BACKGROUND: Despite recent advances in the management of muscle-invasive bladder cancer (MIBC), treatment outcomes remain suboptimal, and variability exists with respect to current practice patterns.
OBJECTIVE: to promote standardization of care for MIBC in Canada, by developing consensus using an evidence-based, multidisciplinary, and patient-centered approach from experts specializing in MIBC.
METHODS: Guideline development was based on a comprehensive literature search of PubMed, Medline, and Embase. Most recent guidelines from national and international organizations were reviewed. Recommendations were made based on best available evidence, and quality of the evidence and strength of the recommendations were graded.
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 opinions of the majority. This guideline also provide further guidance in the topics of management of variant histologies, cisplatin-ineligible patients, and patient selection for 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 ($\geq$pT2) bladder cancer (MIBC) [3, 4]. Outcomes of MIBC remain poor [5]. However, increased utilization of peri operative chemotherapy [6] and a growing emphasis on a multidisciplinary and patient-centred approach will likely translate into improved outcomes.

Genitourinary Medical Oncologists of Canada (GUMOC) is a non-governmental organization comprised of Canadian Medical Oncologists specializing in the treatment of 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 for 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 statement is current as at the time of publication.

METHODOLOGY

Topics approved by the guideline review committee co-chairs were the use of systemic therapy in MIBC in the following domains: neo adjuvant, adjuvant, concurrent chemo radiation. Clinical questions were focused on selecting the most optimal treatment strategy in these treatment settings. The target population is patients with loco regional MIBC. Intervention is the use of any anti-cancer systemic therapy. Primary outcome of interest was overall survival benefit. In addition, special clinical topics in areas that

were known to be controversial or uncertain were included. These were variant histology and cisplatin-ineligible patients. Statements on baseline evaluation including pathology review, local therapy, surveillance were also included based on multidisciplinary input which the committee felt would enhance and complete the guideline.

Canadian experts in medical oncology, radiation oncology, uro-oncology, and pathology were included on the guideline panel for multidisciplinary representation. 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 trials published in the forms 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 a series of iterative consensus process. All coauthors submitted written input. If broad agreement exists, then no additional modifications were made. For topics where disagreements were raised, a voting system was used to collect written feedback from all coauthors, and expert opinions of the majority (>50% of coauthors) were presented as consensus, withlevel of consensus (marked by #) and opposing arguments included in full text discussion to ensure a balanced discussion is 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 relative survival rates for NMIBC, MIBC, regional (node positive), and distant disease were 95%, 69%, 35%, and 5% respectively [2]. For MIBC, 5-year overall survival (OS) rates of patients treated between 1994 and 2008 in Ontario ranges from 30 – 40% [24]. More contemporary data from the US show 5-year OS rates ranging between 50 – 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].

Bladder cancer increases with age, is three times more common in men, and occurs more commonly in developed countries [33]. The median age at diagnosis in men is 69 years and 71 in women [34, 35]. Established risk factors are summarized in Table 2. Smoking is the most common and important risk factor for UCB, accounting for approximately half of all cases [33]. Female gender is associated with aggressive disease biology [35], advanced stage at presentation [36], and delayed referrals [37]. There is conflicting data 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 Cana-

Table 1
Levels of Evidence and Grades of Recommendation

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

RCT, randomized controlled trial.

dian recommendations [45]. Tumor grade should be reported according to the latest WHO 2016 criteria [46].

In addition,10–25% of bladder cancers contain variant histology other than conventional pure UCB [47–50]. The World Health Organization and International Consultation on Bladder Cancer recognize more than 10 unique histologic variants in bladder cancer [46, 51], summarized in Table 3. Variant histology can present as pure non-urothelial histology, mixed histologies, or urothelial carcinoma with divergent differentiation. Pure variant histology may confer a clinical behavior that is distinct from the latter two groups and tend to have a high propensity for relapse [52–54]. Variant histology are often challenging to identify on TURBT specimens [48, 55]. As a result, pathology review by an experienced GU pathologist can be informative, and can lead to major treatment alterations [43, 44].

Table 2
Established risk factors associated withbladder cancer

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

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.

Table 3
World Health Organization'sclassification of invasive tumors of the urothelial tract

Pathology
Infiltratingurothelial carcinoma
Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid/signet ring cell/diffuse
Sarcomatoid
Giant cell
Poorly differentiated
Lipid-rich
Clear cell
Squamous cell neoplasms
Glandular neoplasms, including adenocarcinoma
Urachal carcinoma
Tumours of Mullerian type, including clear cell carcinoma
Neuroendocrine tumors
Melanocytic tumors
Mesenchymal tumors
Urothelial tract hematopoietic and lymphoid tumors
Miscellaneous tumors

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

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).

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.

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.

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, according to ASCO recommendations [16, 58]. Smoking cessation should also be discussed, as cigarette smoking can reduce response to chemotherapy and increase surgical complication rates [59].

Clinical staging

The goal of staging is to assess the extent of local disease and rule out distant metastases and accurately select patients for curative-intent therapy. There is considerable variation in staging investigations used in 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 the patients with MIBC are under-staged by CT compared to pathologic

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

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma *in situ*
T1	Tumor invades lamina propria
T2	Tumor invades the muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical soft tissue
pT3a	Tumor invades perivesical soft tissue microscopically
pT3b	Tumor invades perivesical soft tissue macroscopically (extravesical mass)
T4	Tumor invades adjacent organs
T4a	Tumor invades directly into prostatic stroma, seminal vesicles, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall
Regional Lymph Node (N)	
Nx	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis
N3	Lymph node metastasis to the common iliac lymph nodes
Distant Metastasis (M)	
Mx	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non-lymph-node distant metastases
Stage	
0	Ta or Tis N0M0
0a	TaN0M0
0is	Tis N0M0
I	T1N0M0
II	T2N0M0
IIIA	T3 or T4a N0M0, T1–T4a N1M0
IIIB	T1–T4a N2-3M0
IVA	T4b N0M0 or Any T any N M1a
IVB	Any T any N M1b

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, multi parametric 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 of care [68]. For distant staging, data comparing chest CT versus chest xray is lacking, however chest CT offers significantly higher sensitivity in detecting pulmonary malignancy (metastatic or primary) [69–71]. MIBC has a high propensity for distant metastases, and a strong association with smoking history which also predisposes patients to developing primary bronchogenic carcinoma. Chest CT is now endorsed as a routine staging modality for MIBC by EAU [9], ICUD [72], ASCO [8] and CCO [20] (especially in smokers), as well as CUA [17].

Conventional positron emission tomography (PET) scan is of limited value for assessing local stage due to the pooled activity of excreted 18fluorodeoxyglucose (FDG) in the bladder, which interferes with visualization of the primary tumor. The role of FDG-PET in distant staging remains undefined, as existing landmark trials evaluating curative-intent therapy of MIBC predate its use as a staging modality. Clinical trials testing the utility of FDG-PET are ongoing (clinicaltrials.gov NCT02462239). Staging with FDG-PET in addition to conventional CT imaging can lead to change in treatment intent from curative to palliative in10–20%of patients, however it is unknown whether these changes translate into significant improvement in outcomes [73–75]. Patients with distant disease found on FDG-PET that is occult on conventional imaging should be carefully discussed in a multidisciplinary setting.

Bone scans should be limited to patients with suspicious bony lesions on staging imaging, symptomatic bone pain and/or elevated serum alkaline phosphatase, as routine scintigraphy has been shown to affect therapeutic decision-making in only 1% of MIBC patients [8, 76, 77]. Brain metastases are rare, however baseline brain imaging should be considered in the presence of neurologic symptoms orneuroendocrine variant histology.

Box 2. Recommendations for Diagnostic Investigations

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

SYSTEMIC THERAPY

Neo adjuvant chemotherapy (NAC)

MIBC is a chemo-sensitive disease with high propensity for distant relapse likely due to micrometastatic disease [78–80]. This provides the rationale for use of chemotherapy to maximize chance of cure. The goal of NAC is to eradicate micro-metastases and achieve pathologic complete response (pCR), which is associated with improved overall survival.

Neo adjuvant chemotherapy has several advantages over adjuvant chemotherapy including ability to assess disease response and prognosis, 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% which importantly is correlated with improved OS [81, 82]. The 5-year cancer-specific survival rate for NAC responders (<ypT2) reaches 90%, compared to 30–40% for non responders [83–85]. The limited accuracy of clinical staging compared to pathologic staging represents a challenge in the neo adjuvant setting [86]. NAC does not seem to 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,

Table 5
Efficacy data in select landmark publications of neoadjuvant chemotherapy in MIBC

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

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

MVAC, and GC which are based on level II evidence. Neo adjuvant ddMVAC or accelerated MVAC with G-CSF prophylaxis associated with shorter time to surgery than classic MVAC, and 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 standard MVAC. GC has only been tested in comparative trials in metastatic UCB, showing similar efficacy and a more favorable safety profile versus MVAC [94]. Extrapolated to the neo adjuvant setting, GC has become a commonly accepted NAC regimen [81, 95–99]. SWOG S1314 was a phase II trial which randomized MIBC patients to neo adjuvant GC versus ddMVAC [100]. This trial was not designed to compare 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 pCR (35% and 32% respectively) and down staging to ≤pT1 (50% and 56% respectively). Mature overall survival data is still pending at this time. Other studies have shown neo adjuvant 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 neo adjuvant 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 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 respon-

ders, 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 chemo radiotherapy(*see section 8*). The goals of NAC prior to TMT remain similar - to eliminate micro metastatic disease and achieve down staging and complete response, with the latter associated with improved OS. In the BA06 30894 trial, neo adjuvant CMV reduced risk of death by 20% in patients who received radiation alone and 26% for patients who received RC [121]. In another Danish trial, the addition of NAC to radiotherapy alone in 153 patients improved median survival 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 chemo radiotherapy, the 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 neo adjuvant 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. 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 loco regional, distant control, or OS with the addition of NAC, and dampened earlier enthusiasm of 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 are ineligible for RC (and often ineligible for cisplatin-based NAC as well), 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 of NAC prior to TMT, ongoing trials are including 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, patients with overtly lymph node positive MIBC should receive induction systemic therapy, and subsequent local definitive therapy in responders. Cisplatin-based chemotherapy should be given for 4 cycles. However, some experts recognize that 6 cycles were administered in previous trials evaluating metastatic disease [130]. Based on expert opinion, in select patients with node positive disease, 6 cycles of induction chemotherapy could be considered if patient is tolerating treatment well and there is ongoing disease response [128, 131]. Whether 6 cycles instead of 4 cycles would allow more patients to benefit from consolidation surgery and improved outcomes is 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)[#].

[#]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 20–40% of patients treated with cisplatin-based NAC [84, 98]. The standard of care for patients who develop 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 (NCT02710734, NCT03609216). However, such strategies should only be performed in the setting of a clinical trial.

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/m^2 every 3 weeks [Level 1, high quality, Grade A], or 35–40 mg/m^2 weekly [Level 2, moderate quality, Grade B]), 5-FU with mitomycin (Level 1, high quality, Grade A), or single agent weekly gemcitabine 100 mg/m^2 (Level 2, moderate quality, Grade B).

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, only 3 of which demonstrate a similar survival benefit to NAC [139–142] (Appendix 1). While the ABC meta-analyses in 2005 reported insufficient evidence [89], several recent meta-analyses have suggested overall survival 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 survival 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 likely has benefit. 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.

Cisplatin-ineligible patients

Standard ineligibility criteria for cisplatin-based chemo therapy were proposed by Galsky et al. in 2011and are shown in Table 6 [155]. Unfortunately, nearly half of 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 lower success rates [156] and

Table 6
Cisplatin-ineligibility criteria in metastatic bladder cancer proposed by Galsky et al. 2011

Any one of the following:
WHO or ECOG PS ≥2, or Karnofsky PS ≤ 60–70%
Creatinine clearance (calculated or measured) <60 mL/min
CTCAE v4 grade ≥2 peripheral neuropathy
CTCAE v4 grade ≥2 audiometric hearing loss
NYHA Class III/IV heart failure

ECOG, Eastern Cooperative Oncology Group; PS, performance status; CTCAE, Common Terminology Criteria for Adverse Events; NYHA, New York Heart Association.

risk of upper tract recurrence associated with stenting [157].

Renal function is often a limiting factor for cisplatin-based therapy, and can be estimated bythe 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 ≥50 mL/min), split dose GC (cisplatin 35 mg/m^2 on day 1 and day 8) [81, 91, 162–165] and dose reduction (25–50%) of standard GC (cisplatin 70 mg/m^2 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 with respect to risk of permanent renal injury in the setting of inadequate data and limited accuracies of existing tools for estimating renal function. Administering 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].

Carboplatin-based perioperative chemotherapy should not be offered, given the lack of evidence for survival benefit [170], unnecessary toxicity and risk in delaying local definitive therapy. Multiple studies have shown inferior outcomes of carboplatin-compared to cisplatin-based chemotherapy in UCB [171–174, 99]. The SWOG S0219 study evaluated neo adjuvant carboplatin, gemcitabine and paclitaxel which yielded poor survival rates of only 59% at 2 years, and 60% of patients with clinical T0 disease had residual cancer at cystectomy [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 adjuvantcisplatin-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 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 neo adjuvant cisplatin etoposide similar to small cell lung cancer, which leads to pathologic down staging 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 have poor response 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 neo adjuvant MVAC included 59 patients with mixed nonurothelial histologies (such assquamous or glandular differentiation) and showed 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 patients with squamous and glandular differentiation. Bladder adenocarcinoma is rare, and surgery is the main treatment modality for both urachal and non-urachal adenocarcinomas [193–196]. Urachal

Table 7
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 **

Neoadjuvant			Cisplatin eligible	Cisplatin ineligible or declined	Trial status
NCT03924895(KEYNOTE 905)**	Phase III	Neoadjuvant pembrolizumab 200mg iv every 3 weeks for 3 cycles + adjuvant for 14 cycles	No	Yes	Recruiting
NCT03924856(KEYNOTE 866)**	Phase III	Neoadjuvant GC+/– pembrolizumab 200 mg iv every 3 weeks for 4 doses	Yes	No	Recruiting
NCT02736266(PURE-01)	Phase II	Neoadjuvant pembrolizumab 200 mg iv every 3 weeks for 3 doses	Yes	Yes	Recruiting; reported
NCT03212651 (PANDORE)	Phase II	Neoadjuvant pembrolizumab 200 mg	No	Yes	Active, not recruiting
NCT02690558 (LCCC 1520)	Phase II	Neoadjuvant pembrolizumab 200 mg IV every 3 weeks for 4 cycles + GC	Yes	No	Recruiting
NCT02365766 (HCRN GU14-188)	Phase I/II	Neoadjuvant pembrolizumab 200 mg IV every 3 weeks for 4 cycles + GC or gemcitabine	Yes	Yes	Active, not recruiting; reported
NCT03832673 (PECULIAR)	Phase II	Neoadjuvant pembrolizumab 200 mg IV every 3 weeks for 3 cycles + epacadostat 300 mg BID po every 28 days for 3 cycles	Yes	Yes	Not yet recruiting
NCT03978624 (LCCC1827)	Phase II	Neoadjuvant pembrolizumab 200 mg IV every 3 weeks for 2 doses + entinostat 5 mg po weekly for 3 weeks	No	Yes	Recruiting
NCT03661320 (ENERGIZE)**	Phase III	Neoadjuvant chemotherapy +/– nivolumab, BMS-986205; adjuvant nivolumab, BMS-986205	Yes	No	Recruiting
NCT04209114 (CA045-009)**	Phase III	Neoadjuvant nivolumab + NKTR-214	No	Yes	Recruiting
NCT03294304 (BLASST-1)	Phase II	Neoadjuvant nivolumab 360 mg iv every 3 weeks + GC for 4 cycles	Yes	No	Active, not recruiting; reported
NCT03558087 (HCRN GU16-257)	Phase II	Neoadjuvant nivolumab 360 mg iv every 3 weeks + GC for 4 cycles. Maintenance nivolumab 240 mg every 2 weeks for up to 8 cycles	Yes	No	Recruiting
NCT03520491 (MSKCC 18-042)	Phase II	Neoadjuvant nivolumab 3 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 3mg/kg every 3 weeks for 3 cycles	No	Yes	Recruiting
NCT03387761 (NABUCCO)	Phase I	Neoadjuvant nivolumab, ipilimumab at 1 mg/kg or 3 mg/kg	No	Yes	Recruiting; reported
NCT02845323 (J1682)	Phase II	Neoadjuvant nivolumab 240 mg iv + Urelumab 8mgevery 2 weeks for 2 cycles	No	Yes	Recruiting
NCT03532451 (PrE0807)	Phase I	Neoadjuvant nivolumab 480 mg iv+/– lirilumab 240 mg IV every 4 weeks for 2 doses	No	Yes	Recruiting
NCT03518320 (TAR-200-104)	Phase I	Neoadjuvant nivolumab every week for 4 cycles + GemRIS/TAR 200	No	Yes	Active, not recruiting
NCT02662309 (ABACUS)	Phase II	Neoadjuvant atezolizumab every 3 weeks for 2 cycles	No	Yes	Active, not recruiting; reported
NCT02451423 (UCSF 14524)	Phase II	Neoadjuvant atezolizumab 1200 mg every 3 weeks for 2 or 3 doses	No	Yes	Recruiting
NCT04289779 (ABATE)	Phase II	Neoadjuvant atezolizumab1200 mg IV every 3 weeks for 3 cycles + cabozantinib 40 mg orally daily for 3 cycles	No	Yes	Recruiting

(*Continued*)

Table 7
(*Continued*)

Neoadjuvant			Cisplatin eligible	Cisplatin ineligible or declined	Trial status
NCT02989584 (MSKCC 16-1428)	Phase I/II	Neoadjuvant atezolizumab + GC or 4 cycles	Yes	No	Recruiting
NCT03732677 (NIAGARA)**	Phase III	Neoadjuvant GC+/– durvalumab, adjuvant durvalumab	Yes	No	Recruiting
NCT03234153 (NITIMIB)	Phase II	Neoadjuvant durvalumab 1500 mg iv + tremelimumab 75 mg iv every 4 weeks for 4 cycles	No	Yes	Active, not recruiting
NCT03472274 (DUTRENEO)	Phase II	Neoadjuvant durvalumab 1500 mg + tremelimumab 75mg every 4 weeks × 3 cycles or cisplatin-based chemo	Yes	No	Recruiting
NCT02812420 (NCI-2016-01147)	Phase I	Neoadjuvant durvalumab 1500 mg + tremelimumab 75 mg on weeks 1 and 5	No	Yes	Active, not recruiting; reported
NCT03534492 (NEODURVARIB)	Phase II	Neoadjuvant durvalumab 1500 mg iv every 4 weeks + olaparib 300 mg BID for up to 2 months	Yes	No	Completed; reported
NCT03773666 (BLASST-2)	Phase I	Neoadjuvant durvalumab every 2 weeks+/– Oleclumab	No	Yes	Recruiting
NCT03674424 (AURA)	Phase II	Neoadjuvant avelumab 10 mg/kg every 2 weeks+/– ddMVAC/GC/GP	Yes	Yes	Recruiting
NCT03473730 (MDACC 2017-0688)	Phase I	Neoadjuvant daratumumab IV weekly for 4 weeks	No	Yes	Recruiting
NCT04099589 (NCC2121)	Phase II	Neoadjuvant toripalimab 240 mg injection ever 3 weeks for 2–4 cycles + GC	Yes	No	Recruiting
NCT03288545(EV-103)	Phase I	Neoadjuvant enfortumab vedotin (cohort H) Neoadjuvant enfortumab vedotin + pembrolizumab (cohort J)	No	Yes	Recruiting
Adjuvant			**Cisplatin eligible**	**Cisplatin ineligible or declined**	**Trial status**
NCT03244384 (AMBASSADOR)	Phase III	Adjuvant pembrolizumab every 3 weeks for up to 18 cycles, or observation	No	Yes	Recruiting
NCT02632409 (Checkmate 274)	Phase III	Adjuvant nivolumab	No	Yes	Active, not recruiting
NCT02450331 (IMvigor010)	Phase III	Adjuvant atezolizumab 1200 mg every 3 weeks up to 1 year	Yes	Yes	Active, not recruiting
Trimodality Therapy			**Cisplatin eligible**	**Cisplatin ineligible or declined**	**Trial status**
NCT04241185 (KEYNOTE-992)	Phase III	Concurrent pembrolizumab 400 mg every 6 weeks + cisplatin, 5FU MMC, or gemcitabine	Yes	Yes	Recruiting
NCT02662062(PCR-MIB)	Phase II	Concurrent pembrolizumab 200 mg every 3 weeks + cisplatin, pembrolizumab continued until 12 weeks	Yes	Yes	Recruiting
NCT02621151 (NYU 15-00220)	Phase II	Concurrent pembrolizumab 200 mg every 3 weeks for 3 doses + gemcitabine	Yes	Yes	Recruiting
NCT02560636(PLUMMB)	Phase I	Concurrent pembrolizumab 100–200 mg every 3 weeks starting 2 weeks prior to radiotherapy, continued for a maximum of 12 months	Yes	Yes	Active, not recruiting
NCT03993249 (HGCG 0000020479)	Phase II	Concurrent nivolumab and standard of care chemoradiotherapy	Yes	Yes	Recruiting

(*Continued*)

Table 7
(*Continued*)

Trimodality Therapy			Cisplatin eligible	Cisplatin ineligible or declined	Trial status
NCT03844256(CRIMI)	Phase I/II	Concurrent nivolumab 480 mg every 4 weeks, or nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, or nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks, combined with MMCand capecitabine. Optional nivolumab every 4 weeks for a maximum of 52 weeks	Yes	Yes	Recruiting
NCT03775265(SWOG S1806)	Phase III	Concurrent atezolizumab ever 3 weeks + chemotherapy (GC or 5FU MMC). Atezolizumab continued for a maximum of 6 months	Yes	Yes	Recruiting
NCT03620435 (ML-39576)**	Phase II	Concurrent atezolizumab 1200 mg iv every 3 weeks, continued for a maximum of 1 year	Yes	Yes	Recruiting
NCT04186013 (ATEZOBLADDERP-RESERVE)	Phase II	Concurrent atezolizumab 1200 mg iv every 3 weeks for 6 doses	No	Yes	Recruiting
NCT03702179 (IMMUNOPRE-SERVE)	Phase II	Concurrent durvalumab 75 mg plus tremelimumab 75 mg every 4 weeks for 3 doses	Yes	Yes^{+}	Recruiting
NCT03747419 (DFCI 18-464)	Phase II	Concurrent avelumab every 2 weeks for 6 doses	No	Yes	Recruiting
NCT03617913 (MC1752)	Phase II	Concurrent avelumab every 2 weeks for 10 courses + 5FU MMC or cisplatin	Yes	Yes	Active, not recruiting
NCT04073160 (TRIO Bladder)	Phase I	Neoadjuvant durvalumab 1500 mg plus tremelimumab 75 mg every 4 weeks followed by concurrent durvalumab 1500 mg every 4 weeks, based on molecular subtypes. Durvalumab may be continued for a maximum of 1 year	Yes	Yes	Not yet recruiting
NCT03171025(NEXT)	Phase II	Adjuvant nivolumab iv 480 mg every 4 weeks for a maximum of 12 months.	Yes	Yes	Recruiting
NCT03697850(BladderSpar)	Phase II	Adjuvant atezolizumab 1200 mg ever 3 weeks for a maximum of 12 months			
NCT03768570(CCTG BL13)**	Phase II	Adjuvant durvalumab 1500 mg every 4 weeks for a maximum of 12 months	Yes	Yes^{+}	Recruiting

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.

adenocarcinoma is covered in a separate review by the CUA and GUMOC [197]. Supporting evidence for OS benefit is limited or has conflicting results for NAC in micropapillary [198–202], plasmacytoid [203–208], nested [209, 210], and sarcomatoid variants [177, 211–213] thus recommendations cannot be made in these settings at this time, and local definitive therapy may be the most important component of curative therapy. Data is limited with respect to the benefit of TMT for tumors of variant histology, and therefore the panel did not make recommendations for this setting. RC should be considered for these cases. If feasible, multidisciplinary discussion at experienced academic centres and enrollment in clinical trials should be sought for these patients.

DEFINITIVE LOCAL THERAPY

Radical cystectomy and bilateral pelvic lymph node dissection

Following NAC, RC with bilateral pelvic lymph node dissection (PLND) remains the historical standard local definitive therapy approach in patients with MIBC [7, 214–216]. PLND should include removing pelvic nodes up to the common iliac bifurcation (internal, external, and obturator nodes), although the optimal extent of lymphadenectomy is unestablished [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].

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 neo adjuvant 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%.

In patients with node positive disease, the role of postchemotherapy surgical resection may be limited [131].

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 chemo radiotherapy (CRT) [123, 226, 227], with salvage cystectomy reserved for localized bladder relapse. Radiotherapy is typically given at total 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/m^2 weekly or 100 mg/m^2 every 3 weeks. The use of concurrent 5-fluorouacil plus mitomycin C (5-fluorouracil administered as a continuous infusion at 500 mg/m^2 daily on days 1 to 5 and 16–20 of radiotherapy, mitomycin administered as an intravenous bolus dose of 12 mg/m^2 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 I 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 RC-eligible but 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) motivation for surveillance investigations including 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 potential 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 primaryand 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 recurrence (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 first3 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 include surine 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 overall survival advantage over chemotherapy in the second line metastatic setting by the Keynote 045 phase III trial [266]. In the neo adjuvant setting, pembrolizumab (PURE-01 trial) and atezolizumab (ABACUS trial) have phase II data demonstrating pCR rates of 29% and 42% respectively, with acceptable toxicity profile [267, 268]. In the PURE-01 trial, all treated patients underwent RC. In the ABACUS trial, 2out 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 iplimumab was evaluated in the phase Ib trial NABUCCO. Among 24 patients treated (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 down-staged 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). Down staging 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 as a novel neoadjuvant regimen.

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

Biomarkers

There is an urgent need to develop predictive biomarkers in MIBC to improve treatment selection, and there have been promising developments [278–281]. In general, molecular subtyping of MIBC reveals basal, luminal (similar to breast cancer), andneuroendocrine-like subtypes [282]. Several molecular classifications exist, and an international consensus was recently published [283]. Basal subtypeseems to derive the most benefitfrom NAC [279, 284]. Luminal subtype also 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 are rigorously validated for routine clinical use at this time. However, individual molecular testing and biomarker-driven precision oncologyhold 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.

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APPENDIX 1
Select publications of adjuvant chemotherapy in MIBC

Publication, Year	Phase	n	Inclusion Criteria	Experimental Arm	Control Arm	Median FU	OS	DFS
Skinner 1991 [139]	III	91	pT3/T4 or pN+	Cisplatin, doxorubicin, cyclophosphamide q28d × 4 cycles	Observation	14.5 years	4.3 vs 2.4 years, HR 0.75, $p = 0.0062$	HR 0.73, $p =$ NS
Studer 1994 [304]	III	77	M0	Cisplatin q28d × 3 cycles	Observation	5.75 years	5y OS 57% vs 54%, $p =$ NS	HR 1.02, $p =$ NS
Stockle 1995 [140, 305]	III	49	pT3b/T4a or pN+	Methotrexate, vinblastine, cisplatin plus doxorubicin or epirubicin	Observation	14.8 years	10y OS 26.9% vs 17.4%, HR 2.52, $p = 0.007$	10y DFS 43.7% vs 13.0%, HR 2.84, $p = 0.002$
Freiha 1996 [215]	III	55	pT3b/T4a or pN+	Cisplatin, methotrexate, vinblastine q21d × 4 cycles	Observation	5.08 years	63 vs 36 months, HR 0.78, $p = 0.32$	37 vs 12 months, HR 46, $p = 0.01$
Bono 1997 [306]	III	93	pT2-T4a, pN0	Cisplatin methotrexate × 4 cycles	Observation	3.45 years	HR 0.75, $p =$ NS	HR 0.65, $p =$ NS
SOGUG 99/01 2010 [141]	III	142	pT3/T4 (77%) or pN+(70%)	Paclitaxel, gemcitabine, cisplatin q21d × 4 cycles	Observation	30 months	5y OS 60% vs 31%, $p < 0.0009$	$p < 0.0001$
Cognetti 2011 [307]	III	194	pT2G3, pT3/T4, or *N*+	GC q28d × 4 cycles	Observation	35 months	5y OS 43.4% vs 53.7%, HR 1.29, $p = 0.24$	42.3% vs 37.2%, HR 1.08, $p = 0.70$
Stadler 2011 [308]	III	114	pT1/T2 N0M0	MVAC × 3 cycles	Observation	64.8 months	$p = 0.89$	$p = 0.62$
Sternberg 2015 [142]	III	284	pT3/T4 or *N*+	GC or ddMVAC with GCSF × 4 cycles	Same chemo × 6 cycles at relapse	7.0 years	5y OS 53.6% vs 47.7%, HR 0.78, $p = 0.13$	5y DFS 47.6% vs 31.8%, HR 0.54, $p < 0.0001$
ABC Meta-analysis 2005 [89]		491	Clinical T2–T4a	Adjuvant chemotherapy	Observation	5.2 years	Absolute improvement 9% at 3 years, HR 0.75, $p = 0.019$	Absolute improvement 12% at 3 years, HR 0.68, $p = 0.004$
Leow Meta-analysis 2014 [143]		945	Clinical T2–T4a	Adjuvant cisplatin-based chemotherapy	Observation	Range 30–69 months	HR 0.77, $p = 0.049$	HR 0.66, $p = 0.014$
Kim Meta-analysis 2017 [144]		1546	MIBC and RC	Adjuvant cisplatin-based chemotherapy	Observation	Range 30–168 months	HR 0.79, $p = 0.004$	HR 0.64, $p = 0.002$

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