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GUIDELINE

2025 Canadian Urological Association Guideline: Muscle-invasive bladder cancer

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INTRODUCTION

An estimated 13 300 incident cases of bladder cancer are diagnosed annually in Canada.[1] Of these, approximately 25% will be muscle-invasive at presentation. Muscle-invasive bladder cancer (MIBC) possesses an aggressive biology with the potential to metastasize. Overall, the five-year mortality of patients diagnosed with localized MIBC is approximately 30–50%.[2-4] Long-term survival of patients with metastatic bladder cancer is rare. To help streamline treatment and optimize care, we present a national guideline on MIBC.

METHODS

All relevant articles on MIBC and locally advanced bladder cancer were sought using a combination of Medline and EMBASE searches. The search strategy involved the following keywords: "bladder cancer," "urothelial carcinoma," "invasive," "muscle-invasive," and "metastatic." Filters included English language, human studies, and an index date of 2000–2024, inclusive. Bibliographies of review articles were searched for any missing articles not captured by our search strategy. Recently published guidelines from the European Association of Urology (EAU),[5] American Society of Clinical Oncology (ASCO),[6] American Urological Association (AUA),[7] and the National Comprehensive Cancer Network (NCCN)[8] were also considered for additional content. Further, statements were generated to maintain alignment with the Genitourinary Medical Oncologists of Canada (GUMOC).[9]

An expert panel of academic clinicians with experience managing patients with MIBC and locally advanced bladder cancer was then gathered to facilitate guideline creation. Best practice statements were generated for broad categories of diagnosis, transurethral resection of bladder tumor (TURBT) pathology, staging, treatment, supportive and palliative care, followup, and quality of life (QoL). Final statements were determined by iterative feedback and consensus by the expert panel. A brief discussion for each category highlighting salient issues has been included as well.

Whenever possible, guideline statements have been assigned a level of evidence (LE) based on the Oxford Center for Evidence-Based Medicine (Table 1). A subjective consensus recommendation (strong, moderate, weak) based on the quantity, quality, and consistency of the evidence available has also been applied to each statement.[10,11] "Strong" recommendations have been given if high-quality, consistent evidence supports the statement or for situations where wide consensus among experts is present and additional research is unlikely to modify confidence in the statement. On the contrary, a "weak" recommendation represents

Moving forward, the CUA will be employing GRADE methodology for all of its major guidelines. Until we shift exclusively to this model, guidelines will be updated using the methodology in which they were originally created. In this particular document, statements have been assigned a level of evidence based on the Oxford Center for Evidence-Based Medicine[11] or deemed expert opinion.

a scenario where the level of evidence available is poor or where significant uncertainty in the statement exists. Where recommendations for treatment were supported primarily by biologically plausible mechanisms without explicit data, a label of "Expert opinion" was applied.

EVIDENCE SYNTHESIS: GUIDELINE STATEMENTS AND DISCUSSION

Multidisciplinary initial assessment

■ STATEMENT 1

MIBC patients should be assessed in a multidisciplinary manner whenever possible *(Expert opinion).*

All patients with suspected MIBC require a thorough history and physical examination to determine bladder function, presence of comorbid disease, and overall performance status. Cystoscopy should be included as part of the initial assessment, as it provides an indication of tumor location and disease extent and is invaluable in the initial assessment of all bladder cancers. While traditional therapy in the localized MIBC setting has been radical cystectomy (RC), contemporary care should involve a multidisciplinary approach, including a discussion around bladder preservation with trimodal therapy (TMT).[12-14] Since many patients with MIBC suffer from significant comorbid disease that may influence subsequent multidisciplinary management decisions, most patients with MIBC would benefit from input at a multidisciplinary case conference, where eligibility for perioperative chemotherapy, radical surgery, bladder preservation, and perioperative systemic therapy may be determined. All patients should also be considered for appropriate clinical trials.

Diagnosis

■ STATEMENT 2

MIBC should be diagnosed with a good-quality TURBT that includes muscularis propria in the sample confirming muscle invasion *(LE 3, Strong recommendation).*

The diagnosis of localized bladder cancer usually begins with a high-quality TURBT.[15] Where possible, clearance of all macroscopic disease is recommended to ensure optimal pathologic analysis and to render the patient clinically disease-free such that all treatment options, including bladder preservation with TMT, are available to the patient.[16] Despite this goal, it is recognized that complete transurethral resection for large tumors may be unsafe and thus impossible.

Inadequate sampling of the muscularis propria of the bladder generally precludes a MIBC diagnosis. In these cases, repeat resection should be strongly considered; however, in those infrequent instances where clear radiographical or clinical (e.g., bimanual examination) evidence supports a clear-cut clinical diagnosis of MIBC and where 1) tumor size precludes safely performing a complete TURBT and/or 2) complete TURBT is simply not feasible, tumor tissue should still be obtained to establish a bladder cancer diagnosis and determine final histology.

Table 1. Levels of evidence

Question	Level 1	Level 2	Level 3	Level 4	Level 5
Diagnosis	SR of cross-sectional studies with consistently applied reference standard and blinding	Individual cross-sectional study with consistently applied reference standard and blinding	Non-consecutive studies or studies without consistently applied reference standards	Case-control study, or poor or non-independent reference standard	Mechanism-based reasoning
Prognosis	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of RCT	Case series, case-control study, or poor-quality prognostic cohort study	Expert opinion
Treatment	SR of RCTs, SR of nested case-control studies, high-quality RCT	RCT (poor quality) or observational study with dramatic effect	Non-randomized controlled cohort/ followup study	Case series, case-control study, or historically controlled studies	Mechanism-based reasoning
Screening	SR of RCTs, high-quality RCT	RCT (poor quality)	Non-randomized controlled cohort/ followup study	Case series, case-control study, or historically controlled studies	Mechanism-based reasoning

Adapted from the Oxford Centre for Evidence-Based Medicine.[11] RCT: randomized controlled trial; SR: systematic review.

TURBT pathology

STATEMENT 3

The histologic type (i.e., urothelial, squamous cell, small cell carcinoma, etc.) of the tumor should be reported. For tumors displaying mixed histology, each histologic type present in the sample should be noted *(LE 3, Strong recommendation).*

STATEMENT 4

Additional pathologic data, including depth of invasion, grade, the presence of concomitant carcinoma in situ (CIS), and lymphovascular invasion (LVI), should be noted *(LE 3, Strong recommendation).*

STATEMENT 5

Divergent differentiation of urothelial carcinoma (e.g., urothelial carcinoma with squamous or glandular differentiation) and histologic subtypes (e.g. sarcomatoid, micropapillary, plasmacytoid, nested subtype, etc.), should be recorded, as well as an estimate of the proportion of each subtype and divergent differentiation *(LE 3, Strong recommendation).*

STATEMENT 6

Pathology review by a second pathologist, preferably a dedicated genito-urinary pathologist, is recommended for all cases with suspected histologic subtypes *(LE 3, Moderate recommendation).*

While urothelial carcinoma comprises 90% of MIBC, non-urothelial histologies, such as adenocarcinoma, squamous cell carcinoma, and rarer primary histologies, warrant special consideration, as these tumor types generally present at a more advanced stage, carry a higher risk of recurrence, worse overall prognosis, and may respond differently to standard therapies.[17-19] Other established negative prognostic factors that may influence subsequent treatment and surveillance decisions include the presence of LVI and CIS. Specifically, concomitant CIS has been linked to higher rates of recurrence after RC and worse cancer-specific survival (CSS) in patients with pT2 or lower disease at the time of RC.[20] It has also been associated with radioresistance.[21] Patients with LVI also have more aggressive disease, and its documentation may reinforce the need for neoadjuvant chemotherapy (NAC).[22,23]

Urothelial carcinoma may show either 1) divergent differentiation (such as squamous, glandular, trophoblastic) or 2) histologic subtypes (previously referred to as variant histology), including sarcomatoid, micropapillary, plasmacytoid, nested, microcystic, lymphoepithelioma-like, giant cell, lipid-rich, clear cell (glycogen-rich), and poorly differentiated neuroendocrine carcinoma.[24] The World Health Organization recognizes micropapillary, plasmacytoid, sarcomatoid, neuroendocrine, and poorly differentiated morphologies as associated with more aggressive behavior. Due to some reports that correlate the percentage of micropapillary and plasmacytoid subtypes with poorer prognosis, international guidelines recommend that the amount of each subtype be quantified.[25] Given reported evidence of significant interobserver variability in pathologists' identification of urothelial carcinoma subtypes, all tumors displaying such histology should undergo pathologic re-review, preferably by an expert genito-urinary pathologist.[26]

Staging

STATEMENT 7

Examination under anesthesia should be performed immediately after TURBT to accurately determine clinical stage and resectability *(LE 3, Moderate recommendation).*

STATEMENT 8

Computed tomography (CT) of the chest, abdomen, and pelvis is the ideal imaging modality to stage localized MIBC and metastatic bladder cancer *(LE 3, Moderate recommendation).*

STATEMENT 9

Magnetic resonance imaging (MRI) is an option to determine the local extent of disease *(LE 3, Moderate recommendation).*

STATEMENT 10

Bone scans are not considered mandatory but should be obtained in the setting of an elevated alkaline phosphatase (ALP), hypercalcemia, or bony pain *(LE 3, Moderate recommendation).*

STATEMENT 11

Currently, the role of positron emission tomography (PET) CT in the staging of bladder cancer remains undefined *(LE 4, Weak recommendation).*

Prior to embarking on therapy, an accurate assessment of the clinical stage is necessary. In addition to a thorough examination under anesthesia, axial imaging (CT or MRI) of the abdomen and pelvis to rule out nodal or metastatic disease is mandatory. These tests also aid

in determining the local extent of the disease, which is necessary for surgical or radiation planning. Contrast-enhanced studies should be performed, where renal function allows, with delayed images (i.e., CT or MR urography) to assess for concomitant upper tract disease and to rule out hydronephrosis. Optionally, multiparametric pelvic MRI can be performed for diagnosis prior to resection (TURBT) using the Vesical Imaging Reporting and Data System (VI-RADS) score.[27-30] Chest imaging (CXR) (CT preferable to CXR) should also be performed to rule out metastatic disease or concomitant lung cancer, given the preponderance of smoking in urothelial carcinoma patients, with CT of the chest providing the highest sensitivity to detect metastases.[31,32] Currently, there is insufficient evidence to recommend the routine use of PET-CT imaging in bladder cancer patients.

Treatment

Perioperative systemic therapy

■ STATEMENT 12

All eligible patients with cT2-T4a N0 M0 urothelial carcinoma of the bladder should be assessed by medical oncology for receipt of cisplatin-based combination chemotherapy (gemcitabine plus cisplatin [GC]; or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin [dd-MVAC]) as NAC prior to radical cystectomy *(LE 1, Strong recommendation).*

■ STATEMENT 13

In eligible patients, NAC should also be considered prior to TMT for bladder preservation *(LE 3, Strong recommendation).*

■ STATEMENT 14

Patients with contraindications to cisplatin-based NAC should proceed directly to radical local therapy *(LE 2, Strong recommendation).* Absolute contraindications to cisplatin-based NAC include: Eastern Cooperative Group (ECOG) status of 2 or higher, grade 2 hearing loss or neuropathy, untreated infection, heart failure (NYHA class III and IV), and an estimated glomerular filtration rate (eGFR) ≤50 ml/min/1.73 m^2. Relative contraindications for NAC include an eGFR of 50–60 ml/min/1.73m^2, a history of recurrent infection, and concomitant immunosuppression.

■ STATEMENT 15

To optimize renal function in patients considering and/or eligible for NAC, malignant ureteric obstruction should be relieved via percutaneous drainage nephrostomy tubes *(Expert opinion).*

■ STATEMENT 16

After 2/4 cycles of GC NAC, restaging should be considered to ensure treatment response or stable disease during chemotherapy. In the event of non-metastatic progressive disease or significant toxicity with chemotherapy that precludes its delivery, NAC should be discontinued, and cystectomy performed within 4–6 weeks of the last dose of chemotherapy. Patients receiving dd-MVAC, given every two weeks, do not need restaging during chemotherapy, as the short course of treatment precludes the need for imaging. A restaging CT scan at the end of NAC should also be considered *(Expert opinion).*

■ STATEMENT 17

Patients receiving NAC should undergo cystectomy 4–6 weeks after completion of NAC and, at most, within 10 weeks of the last dose of chemotherapy to avoid compromising survival *(LE 3, Moderate recommendation).*

■ STATEMENT 18

There is no role for NAC in pure non-urothelial carcinoma (squamous cell carcinoma, adenocarcinoma, etc.) with the exception of small cell carcinoma, which should be treated with neoadjuvant platinum/etoposide in eligible patients *(LE 3, Strong recommendation).*

■ STATEMENT 19

In patients who do not receive NAC prior to cystectomy, adjuvant cisplatin-based combination chemotherapy (GC or dd-MVAC) should be offered to eligible patients with pT3/T4 and/or pN1-3 disease *(LE 1, Strong recommendation).*

■ STATEMENT 20

Adjuvant immunotherapy with nivolumab should be offered to patients who have undergone radical resection and are at a high risk of recurrence (pT3/4 or pN1-3 disease OR ypT2-4 or ypN1-3 disease) *(LE 1, Strong recommendation).*

NAC has the dual advantage of targeting micrometastatic disease early in the disease trajectory and potentially causing local tumor regression. Two large, phase 3

clinical trials have demonstrated a survival benefit with the use of NAC prior to local radical treatment.[33,34] Meta-analyses combining individual patient data from these trials, with numerous phase 2 trials, have suggested an absolute survival benefit of 5% at five years (number-needed-to-treat of 20) and a 13% relative risk reduction in mortality for patients receiving NAC prior to surgery or exclusive radiotherapy.[35] It is important to note that evidence supportive of NAC is primarily derived in the urothelial carcinoma setting, with a lack of robust data supporting NAC in pure non-urothelial histologies. An exception to this rule is small cell carcinoma of the bladder, where NAC serves as part of the mainstay of treatment with a regimen such as cisplatin/carboplatin-etoposide. Any small cell component in the TURBT specimen warrants upfront systemic therapy prior to local consolidation.[8]

VESPER, a randomized trial comparing six cycles of dd-MVAC vs. four cycles of GC in the perioperative setting, was overall negative, where its primary endpoint of progression-free survival at three years was not met; however, important messages regarding NAC were nonetheless gleaned.

In this study, the first randomized trial of NAC involving GC, chemotherapy could be given either neoadjuvantly or adjuvantly, yet most patients (88%) received neoadjuvant therapy. Although not statistically significant, the five-year overall survival (OS) rate in the dd-MVAC group was numerically greater than in the GC group (64% vs. 56%, hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.58–1.03, p=0.078). In a preplanned subgroup analysis, disease-specific survival (DSS) (five-year rate: 72% vs. 59%, HR 0.63, 95% CI 0.46–0.86, p=0.004) and OS in the neoadjuvant subgroup (five-year rate: 66% vs. 57%, HR 0.71, 95% CI 0.52–0.97, p=0.032) were statistically significant in favor of dd-MVAC.

While these data may support dd-MVAC in the neoadjuvant setting, the survival benefit of dd-MVAC needs to be carefully balanced with its additional toxicity compared to GC.[36] Specifically, dd-MVAC may be difficult to tolerate for most patients and may be best suited for younger and fitter patients. Furthermore, the optimal number of cycles of dd-MVAC is undefined, as the VESPER study evaluated six cycles of dd-MVAC compared to four of GC, while the standard number of dd-MVAC cycles in clinical practice is four.

In a recently published study comparing neoadjuvant GC to neoadjuvant GC plus durvalumab with continued adjuvant durvalumab (the NIAGARA trial), GC plus perioperative durvalumab resulted in improved event-free survival (one of two primary endpoints) and OS compared to standard-of-care GC.[37] The 24 month OS was 82.2% vs. 75.2% (HR 0.75, 95% CI 0.59–0.93, p=0.01) favoring the durvalumab group. This regimen is not yet approved or funded in Canada, but should these criteria be met, the triplet combination of GC plus durvalumab has the potential to become a new standard of care neoadjuvant regimen for MIBC.

Despite level 1 evidence supporting NAC, until recently, uptake has been poor, with some studies suggesting a compliance rate of only 34%.[38] Reasons posited for the slow adoption include concerns regarding delayed definitive care, the risk of venous thromboembolism during NAC, NAC-related mortality, and the non-selective nature of NAC (i.e., lack of identification of those patients who may best respond to NAC). Countering these concerns is the randomized nature of the trials supporting NAC, which, by definition, already account for chemotherapy-induced venous thromboembolism (which has a higher rate of occurrence in the NAC population, risk ratio [RR] 3.39, 95% CI 1.39–8.24),[39] death directly attributable to chemotherapy, and NAC-related delays in radical therapy.[40]

Even with these potential shortcomings, a meta-analysis evaluating NAC demonstrated a survival benefit. Several reports also suggest that NAC does not increase perioperative morbidity or complication rates, lending further support to its use.[41,42] Ample time (at least 2–3 weeks) for recovery of complete blood count parameters and optimization of patient fitness after completion of NAC is required prior to delivery of definitive radical therapy. The ideal time for radical therapy after NAC is within 4–6 weeks, although a maximal window of 10 weeks has not been shown to compromise outcomes.[43,44]

To date, there are no randomized trials comparing NAC to adjuvant chemotherapy (AC). While data do support the use of AC, with an approximate 23% survival benefit (HR 0.77, 95% CI 0.59–0.99) based on a meta-analysis,[45] no single phase 3 trial has demonstrated an OS benefit with AC compared to observation. Even the phase 3 European Organization for Research and Treatment of Cancer (EORTC) trial in this setting, while demonstrating a significant progression-free survival benefit (HR 0.54, 95% CI 0.40–0.73), was ultimately underpowered to demonstrate an OS benefit (HR 0.78, 95% CI 0.56–1.08).[46]

The overall quality of evidence also favors NAC as the perioperative chemotherapy option of choice, as many AC trials suffered from poor accrual, early termination, and lack of power. Furthermore, many

patients after RC experience renal function deterioration, resulting in an estimated 24–52% rate of ineligibility to receive AC postoperatively, depending on the criteria used.[47] Postoperative complications may also limit AC use, excluding approximately 30% of patients who may have been eligible for receiving necessary treatment.[48] Given that metastatic disease is the most likely cause of death in patients with MIBC, an approach that maximizes the ability to administer multimodal therapy should be adopted, thus favoring a NAC approach.

For patients with high-risk disease at the time of cystectomy, adjuvant immunotherapy should be considered. Checkmate 274, a randomized controlled trial of adjuvant nivolumab vs. placebo in patients with pT3/4 or N1-3 disease (or ypT2-4 or ypN1-3 disease) demonstrated improved disease-free survival (DFS) in all patients.[49] Median DFS, the primary endpoint, was 20.8 months (95% CI 16.5–27.6) in the nivolumab group and 10.8 months (95% CI 8.3–13.9) in the placebo group in the intention-to-treat (ITT) population. The percentage of patients who were alive and disease-free at six months was 74.9% with nivolumab and 60.3% with placebo in the ITT population (HR for disease recurrence or death 0.70, 98.22% CI 0.55–0.90, p<0.001).

Interim OS data favor nivolumab vs. placebo in the ITT population (HR 0.76, 95% CI 0.61–0.96) and tumor PD-L1 >1% populations (HR 0.56, 95% CI 0.36–0.86), with a median OS of 69.5 months with nivolumab vs. 50.1 months with placebo in the ITT population.[50] Subgroup analyses suggested improved DFS in patients who had previously received NAC.

Likewise, adjuvant pembrolizumab has also been found to improve DFS in high-risk cystectomy patients. The AMBASSADOR trial compared adjuvant pembrolizumab to observation in a patient population similar to Checkmate 274, with the exception being the inclusion of microscopic positive margin patients in AMBASSADOR.[51] The median DFS was 29.6 months (95% CI 20.0–40.7) with pembrolizumab and 14.2 months (95% CI 11.0–20.2) with observation (HR 0.73, 95% CI 0.59–0.90, p=0.003). The co-primary endpoints of this trial were DFS and OS. There were no differences in OS between the treatment groups (HR for death 0.98, 95% CI 0.76–1.26) but the trial is considered positive given that the DFS endpoint was met. At the time of writing this guideline, nivolumab is the only adjuvant therapy approved and funded for high-risk MIBC in Canada.

For high-risk patients who did not receive NAC (i.e., pT3/4 or pN1-3), consultation with medical oncology is encouraged to determine eligibility for AC or adjuvant immunotherapy, with AC generally favored in this scenario. The ultimate decision to pursue AC vs. adjuvant immunotherapy, however, comes down to shared decision-making between the medical oncologist and patient, as there are no head-to-head trials comparing chemotherapy vs. immunotherapy in the adjuvant setting.

Surgical management

■ STATEMENT 21

For patients with localized MIBC, RC should be considered the standard therapy *(LE 2, Strong recommendation).*

■ STATEMENT 22

For patients with MIBC who do not receive NAC, RC should ideally be performed within six weeks of TURBT *(LE 3, Moderate recommendation).*

■ STATEMENT 23

Patients scheduled for RC are recommended to receive perioperative optimization according to established enhanced recovery after abdominal surgery (ERAS) protocols *(LE 2, Moderate recommendation).*

■ STATEMENT 24

In male patients, RC should entail removal of the bladder and prostate en bloc. A nerve-sparing procedure can be safely offered to select patients interested in preserving erectile activity *(LE 3, Moderate recommendation).*

■ STATEMENT 25

In female patients, RC should entail the removal of the bladder, reproductive organs (uterus and ovaries), and the anterior vagina. In situations where the tumor location allows (i.e., anterior tumors), a female organ-sparing (i.e., uterus, ovaries, and/or vagina) operation can be offered to women interested in preserving sexual and/or reproductive/hormonal function. In alignment with the gynecologic literature, the ovaries should be spared routinely in women less than 50 years of age due to the significant sequelae of surgical menopause; however, removal of the fallopian tubes should be discussed in all women uninterested in future reproduction, as these structures serve as the source of many ovarian malignancies *(LE 3, Strong recommendation).*

STATEMENT 26
Bilateral pelvic lymph node dissection (PLND) with removal, at a minimum, of the obturator, external iliac, and internal iliac lymph nodes should be performed in all patients *(LE 3, Strong recommendation).*

STATEMENT 27
Continent urinary diversion (orthotopic neobladder or heterotopic continent pouch) should be offered to all eligible patients as an alternative to an ileal conduit. An intraoperative frozen section evaluation of the urethral margin should be performed prior to creating an orthotopic diversion *(LE 3, Moderate recommendation).*

STATEMENT 28
Merits of urethrectomy should be discussed in men with high-grade or invasive urethral disease distal to the prostatic urethra, a positive urethral margin, or suspected prostatic stromal involvement in men and bladder neck tumors in women *(LE 3, Moderate recommendation).*

STATEMENT 29
The operative technique should be determined through shared decision-making with the patient, with open, robotic, and laparoscopic approaches all acceptable methods to perform RC *(LE 1, Strong recommendation).*

STATEMENT 30
Partial cystectomy for MIBC is discouraged and should only be considered in specific situations: unifocal, small tumor (e.g., <3 cm), dome location, good bladder capacity, no hydronephrosis, minimal to no concomitant CIS. Random bladder biopsies or blue light cystoscopy with directed biopsies (plus prostatic urethral biopsy) should be performed prior to partial cystectomy to rule out occult disease (CIS). PLND should be performed at the time of partial cystectomy *(LE 3, Moderate recommendation).*

RC is the standard surgical therapy for MIBC, with established, long-term oncologic outcomes.[52] Perioperative patient counseling regarding the extent of the operation and the associated sex-specific organs to be resected should be documented preoperatively. At a minimum, a standard PLND constituting the external iliac, obturator, and internal iliac lymph nodes should be removed for therapeutic and staging purposes.[53-57]

Many retrospective studies have suggested a survival benefit of extending the cystectomy lymph node dissection boundaries to a level as high as the inferior mesenteric artery;[58,59] however, two randomized trials comparing standard to extended lymph node dissection failed to demonstrate a survival advantage with an extended lymph node dissection despite increased nodal yield in the extended lymph node groups.[60,61] In the SWOG S1011 trial, extended lymph node dissection was associated with an increased adverse event profile, with 16% grade 3/4 adverse events compared to 8% in the standard lymph node dissection group, as well as an increased postoperative mortality (2.7% vs. 0.3% at 30 days and 6.5% vs. 2.4% at 90 days). These data support the role of a high-quality, standard PLND at the time of cystectomy, as the median number of lymph nodes removed in the control arms of the SWOG S1011 trial and the German LEA AUO AB 25/02 trial were 24 and 19, respectively.

At the time of cystectomy, routine intraoperative assessment of ureteral margins is not mandatory but may be considered, particularly in patients at high risk of ureteral disease (e.g., diffuse CIS, trigonal tumor, prior upper tract disease). If performed, ureteral margin frozen section analysis should be done with the goal of implanting ureters with negative margins. In the setting of a positive intraoperative margin with CIS, additional length of the ureter should be resected to achieve a negative margin. Reimplantation of a ureter with persistent CIS at the margin is not ideal but is reasonable if achieving a negative margin is not possible.

Nephroureterectomy should not be performed for a positive CIS margin given the low probability of progressive disease in this setting.[62,63] Intraoperative urethral margin analysis is mandatory in patients undergoing neobladder urinary diversion and may only be omitted if preoperative prostatic urethral biopsies are negative.[64,65]

Preoperative counseling on the risks of sexual dysfunction should occur for both men and women. Nerve-sparing cystectomy should be offered, when oncologically safe and feasible, for patients interested in preserving sexual function (i.e., in those where wide local excision of nerve bundles is not necessary). Although, as traditionally described, the reproductive organs and anterior vagina are removed during female RC, a female organ-sparing (i.e., uterus, ovaries, and/or vagina) operation can be offered to women interested in preserving sexual and/or reproductive function.

Growing evidence supports the role of ovarian preservation in female patients less than 50 years of age.[66]

Ovarian preservation has been associated with improved cardiovascular and bone health and oophorectomy in younger patients is associated with an increased risk of all-cause mortality, sexual dysfunction, and anxiety.[67] Thus, oophorectomy should primarily be discussed and offered to women >50 years of age (to decrease the risk of subsequent ovarian cancer) and in those predisposed to ovarian malignancy (*BRCA* carriers and strong family history of breast and ovarian cancer). Since the fallopian tubes are considered the source of many aggressive ovarian cancers, salpingectomy should be discussed with all women not interested in further reproduction.[68,69]

Treatment of MIBC can lead to short-term and long-term side effects that should be discussed with patients. In one of the largest series reporting on 90-day complications after cystectomy, approximately 64% of 1142 patients experienced one or more complications, with 83% of those deemed significant (Clavien 2–5 on the Clavien-Dindo classification system).[53]

Given the burden of treatment of RC, detailed perioperative planning should be undertaken to optimize outcomes.

Excessive delays from TURBT to cystectomy should be avoided in patients not receiving NAC.[70] Eligibility for continent diversion should be determined for all patients, and final decisions on the type of diversion should be made based on renal and hepatic function, comorbidity/performance status, patient preference, and tumor location, with the latter also guiding discussions regarding concomitant urethrectomy at the time of cystectomy. Growing data support ERAS protocols as a means of decreasing length of stay and postoperative complications with RC.[71,72]

Robot-assisted RC has been found to yield similar oncologic outcomes to open RC in numerous randomized trials.[73,74] Secondary non-cancer outcomes, however, are superior with robotic RC when compared to open RC in patients with MIBC. Specifically, robotic RC is associated with lower rates of blood transfusion and shorter lengths of stay in the hospital.[75]

With respect to the latter, a recent randomized trial performed in the U.K. assessed the median number of days alive and out of the hospital within 90 days of surgery with robotic compared to open RC as the primary outcome (robotic 82 days vs. open 80 days) Additionally, robotic surgery demonstrated lower rates of thromboembolic complications (1.9% vs. 8.3%; difference -6.5%, 95% CI -11.4% to -1.4%) and wound complications (5.6% vs. 16.0%; difference -11.7%, 95% CI -18.6% to -4.6%) compared to open surgery. Furthermore, participants undergoing open surgery reported worse QoL and greater disability at five weeks compared to those who underwent robotic surgery. Based on these findings, robot-assisted RC is a favorable alternative to open surgery for MIBC patients undergoing RC.[76]

Cystectomy pathology

■ STATEMENT 31

The final pathology report should contain the following elements: histology (including subtypes), stage, grade, presence of concomitant CIS, presence of LVI, surgical margin status, number of lymph nodes, and number of positive lymph nodes *(LE 3, Strong recommendation).*

■ STATEMENT 32

Assessment of accompanying reproductive organs (prostate, uterus, cervix, ovaries, vagina) should be performed to rule out occult secondary malignancy and for determination of final pathologic stage *(LE 3, Moderate recommendation).*

■ STATEMENT 33

Cystectomy pathology indicative of a high risk of recurrence (pT3/4 or pN1-3) should undergo fibroblast growth factor receptor (FGFR) testing *(LE 3, Moderate recommendation).*

An accurate assessment of the pathologic stage in cystectomy specimens is of utmost importance. Synoptic reporting of pathologic data is encouraged to standardize nomenclature across institutions. Pathology data generally guide discussions about prognosis, with worse outcomes expected in higher-stage disease or with concomitant CIS or LVI.[20,77] Receipt of adjuvant chemo- or immunotherapy is also dependent on accurate pathologic assessment and is generally recommended for patients with node-positive and/or pT3/4 disease, and ypT2-4 and/or ypN1-3 disease for immunotherapy.[48] Synoptic pathology reporting also provides data that serve as surgical quality indicators (e.g., margin status, number of nodes removed, dissection template, etc.).

Reflex testing for FGFR2/3 alterations at the time of the pathology diagnosis in MIBC is recommended. If not possible in the TURBT specimen (based on availability and jurisdiction), genomic assessment of high-risk tumors in cystectomy specimens is recommended. For example, Ontario Health/Cancer Care Ontario recommends reflex FGFR testing in all cystectomy specimens with pT3/4 or pN1-3 pathology.[78] This recom-

mendation is based on evidence demonstrating the impact of FGFR inhibitors on survival in patients with advanced disease,[79] thus allowing for early identification of patients who may benefit from downstream FGFR-targeted therapy.

Radiotherapy

■ STATEMENT 34

TMT (radical TURBT + external beam radiotherapy + concomitant chemotherapy) can be offered to patients wishing to preserve their bladder, those unfit for cystectomy, or those refusing cystectomy *(LE 2, Moderate recommendation).* **Ideal tumor and patient characteristics for TMT are as follows: small (<5 cm), unifocal, no multifocal or extensive CIS, no significant hydronephrosis (unilateral mild/moderate acceptable), good bladder function, compliant patient motivated for bladder preservation who is agreeable to regular cystoscopic followup.**

■ STATEMENT 35

With TMT, maximally safe TURBT should be performed to clear all visible tumor prior to initiation of chemoradiation *(LE 3, Moderate recommendation).*

■ STATEMENT 36

Radiotherapy should be offered in combination with concurrent radio-sensitizing chemotherapy, either cisplatin or 5-FU/MMC chemotherapy *(LE 1, Strong recommendation)* **or gemcitabine** *(LE 2, Strong recommendation).* **An alternative to chemotherapy for radiation sensitization is carbogen-nicotinamide (LE 1, Strong recommendation). Radiation monotherapy in the treatment of localized MIBC is only acceptable in patients who are ineligible for or refuse radio-sensitizing agents** *(Expert opinion).*

■ STATEMENT 37

Hypofractionated radiotherapy should be offered to patients as part of TMT *(LE 1, Strong recommendation).*

■ STATEMENT 38

Whole pelvis radiotherapy (WP) is preferred to bladder-only (BO) radiotherapy, as this approach will cover the pelvic lymph nodes. This is particularly encouraged in patients with high-risk MIBC (see text) and/or clinically positive lymph nodes *(LE 3, Moderate recommendation).*

■ STATEMENT 39

Without a well-defined role for neoadjuvant or adjuvant radiotherapy, this treatment should not be offered to patients with localized MIBC outside of a multidisciplinary discussion *(LE 3, Moderate recommendation).*

Although RC has long been considered the de facto gold-standard surgical therapy for MIBC, TMT efficacy has been supported by several trials and can also be safely offered to appropriately selected patients who seek bladder preservation. Optimal patient selection, with criteria as delineated above, and provision of care in a multidisciplinary setting will likely yield the most robust outcomes.

One report demonstrated that, in carefully selected patients, TMT offered in a multidisciplinary bladder cancer clinic had moderate-term DSS rates similar to that of RC (73% for RC, 77% for TMT).[12] In an updated and expanded multicenter matched analysis using statistical methods (propensity score analysis and inverse probability treatment weighting) to balance the groups, and which included patients who would have been eligible for both TMT and RC, no significant differences were again observed in metastases-free survival and CSS between propensity-score matched patients who underwent RC and those who received TMT.[80] The authors emphasized TMT as a viable option for all suitable patients and not only for patients who are poor candidates for surgery. TMT should be undertaken within a framework of multidisciplinary shared decision-making to ensure the best treatment choice for each individual patient.[80] Ultimately, only approximately 30% of surgically fit patients will meet the criteria for TMT bladder preservation.

In addition to TMT providing the opportunity for bladder preservation in select healthy, surgically fit patients, TMT offers the ability to extend treatment to patients who would otherwise go untreated. Population-based data demonstrate that many patients are poor surgical candidates, thus leading to the undertreatment of non-metastatic MIBC in approximately 50% of patients.[81] Often, TMT can safely be offered to patients unfit for surgical therapy, thus providing some benefit for these patients.[82]

Where possible, radiation should be administered with radio-sensitizing chemotherapy. Radiotherapy alone has been shown in a large, randomized controlled trial (BC2001) to be associated with inferior locoregional DFS compared with radiotherapy plus chemotherapy.[83] A smaller randomized NRG Oncology/Radiation

Therapy Oncology Group (RTOG) trial demonstrated similar three-year distant metastasis-free survival regardless of whether the chemotherapeutic regimen used was 5-FU-based or gemcitabine-based.[84]

An alternative to concurrent chemotherapy for radio-sensitization is inhaled carbogen and oral nicotinamide, which were demonstrated in a large randomized trial (BCON) to be superior to radiotherapy alone.[85] Updated data from this trial suggested that patients with hypoxic tumors were most likely to benefit from this approach.[86] Finally, an individual patient data meta-analysis of the BC2001 and BCON trials supports a hypofractionated dosing schedule of 55 Gy in 20 fractions.[87] This approach was non-inferior to 64 Gy in 32 fractions in terms of toxicity and was superior with regard to invasive locoregional control.

Although NAC confers a survival benefit in patients receiving radiotherapy alone for local management,[33,88] the role of NAC and AC in TMT is not currently supported by level 1 evidence. The concept of administering NAC prior to TMT is appealing and would provide the same theoretical benefits seen when given prior to RC. Specifically, treating micrometastatic disease and causing primary tumor involution may lead to improved outcomes. Supporting this concept, a recent large, Canadian, multicenter, retrospective cohort study involving 864 MIBC patients treated with curative intent radiotherapy revealed that the use of NAC was associated with significantly improved CSS and OS in multivariable analysis.[89]

Provision of NAC in the TMT setting may increase TMT eligibility by inducing significant local tumor regression in patients whose tumors are chemosensitive; however, NAC should not replace a complete TURBT, as the TMT efficacy data published to date are in patients with completely resected disease. Due to uncertainties in data, NAC is used heavily in some centers,[11,71] whereas other centers have adopted an AC approach.[90] The ideal method has yet to be determined. Furthermore, unlike in surgically resected MIBC, there is currently no role for adjuvant immunotherapy in TMT, as the reported adjuvant immunotherapy trials in localized MIBC did not include TMT patients.[49,91] Additional research on neoadjuvant and adjuvant systemic therapy in the TMT space is needed to establish the optimal approach.

Treatment of the pelvic lymph nodes is controversial with TMT. For example, in the three randomized studies evaluating radio-sensitizing agents with radiation for bladder cancer, the BC2001 and BCON studies did not include pelvic lymph nodes whereas the NCIC-CTG trial of radiotherapy with concurrent cisplatin did.[92] Another randomized study failed to detect a difference in any oncologic outcome by treating the pelvic nodes, but there have been some concerns with respect to the validity of this study.[93,94]

Other retrospective data have also failed to detect differences in outcomes with respect to WP vs. BO radiotherapy.[93,95] On the other hand, a recent Canadian, multicenter study by Kool et al demonstrated that while WP radiotherapy did not impact complete response rates post-RT (OR 1.14, p=0.526), it was associated with benefits in both CSS (HR 0.66, p=0.016) and OS (HR 0.68, p=0.002), independent of other prognostic factors.[96] As a result, treatment of the pelvic lymph nodes in addition to the bladder seems reasonable, especially in healthy patients with higher-risk disease (i.e., hydronephrosis, cT3/4, positive for LVI, and/or aggressive histologic subtype component) until further evidence becomes available to guide therapy.

Unresectable and oligometastatic disease

■ STATEMENT 40

Patients with non-metastatic, clinically unresectable cT4b or cN1-3 tumors should be offered enfortumab vedotin plus pembrolizumab (EV+P) or nivolumab plus GC (nivo+GC) over standard GC chemotherapy *(LE 1, Strong recommendation).*

■ STATEMENT 41

In jurisdictions where EV+P or nivo+GC are not available, induction (primary) cisplatin-based combination chemotherapy with either GC or dd-MVAC, if eligible, or a carboplatin-based combination regimen if cisplatin-ineligible, should be offered *(LE 1, Strong recommendation).* **Patients who are platinum-ineligible may be offered immunotherapy (if available), an alternative combination chemotherapy regimen, or enrolment in a clinical trial, if possible** *(LE 2, Moderate recommendation).*

■ STATEMENT 42

Consideration of consolidative local therapy (i.e., radiotherapy or cystectomy) for both locally advanced and/or oligometastatic disease in patients experiencing a complete (CR) or partial response (PR) to systemic therapy must be on a case-by-case basis after multidisciplinary tumor board discussion *(LE 4, Weak recommendation).*

STATEMENT 43

Maintenance avelumab immunotherapy should be provided to patients with unresectable, stable, cT4b or cN1-3 disease, PR, or CR after platinum-based chemotherapy if consolidative curative therapy is not pursued *(LE 1, Strong recommendation).*

STATEMENT 44

At present, there are insufficient data to support a role for resection of oligometastatic disease as part of primary therapy (synchronous) or as management of recurrent disease (metachronous) *(Expert opinion).*

Level 1 evidence supports the use of EV+P over standard GC chemotherapy in patients with unresectable or oligometastatic disease at presentation. In the EV-302/KEYNOTE-A39 study, patients with unresectable or metastatic disease experienced a significant survival advantage when treated with EV+P compared to standard GC (HR 0.47, 95% CI 0.38–0.58, p<0.00001; median OS 31.5 months vs. 16.1 months).[97] Likewise, in the Checkmate 901 trial, nivolumab combined with GC yielded improved survival outcomes compared to GC alone in the same setting (HR 0.78, 95% CI 0.63–0.96, p=0.02; median OS 21.7 months vs. 18.9 months).[98] These latter two regimens are currently Health Canada-approved and available via compassionate support programs but at the time of publication are not funded. With funding, they will supplant platinum-based combination chemotherapy in the first-line metastatic and unresectable setting.

If EV+P or nivo+GC are not available, patients with locally advanced, unresectable, or oligometastatic disease should be offered primary chemotherapy. Platinum-based chemotherapy has been the mainstay of treatment for locally advanced and metastatic urothelial carcinoma for decades, with cisplatin-based combinations as the optimal first-line therapy and carboplatin-based regimens reserved for those who are cisplatin-ineligible. If ineligible for platinum-based chemotherapy, immunotherapy should be considered in jurisdictions where such regimens are funded and approved.

No randomized data support oligometastectomy in the synchronous setting (i.e., RC plus resection of oligometastatic sites in one setting), yet retrospective data suggest that carefully selected patients who undergo resection of the primary lesion along with limited metastasectomy can achieve durable long-term survival rates of 10–20%.[99,100] Oligometastatic sites that have been resected include, most commonly, the retroperitoneal lymph nodes, lung metastases, and bone.[101] Factors to be considered prior to embarking on such extensive surgical consolidation include: 1) response to primary chemotherapy; 2) extent of disease; 3) feasibility of resection; 4) performance status; and 5) patient motivation.

In patients with locally advanced, non-metastatic, initially unresectable disease with an excellent response (CR or PR) to systemic platinum-based therapy, multidisciplinary cancer conference discussion regarding the role of consolidative therapy of the primary vs. maintenance avelumab should be undertaken. Regarding the latter, the Javelin 100 trial included patients with both metastatic urothelial carcinoma and cT4b and cN1-3 disease deemed locally advanced and unresectable, although the proportion of these latter patients was not reported. In this trial, patients with stable disease, PR, or CR after platinum-based chemotherapy received maintenance avelumab, which provided a survival benefit of approximately seven months over best supportive care.[102] As a result, switch maintenance with avelumab is the standard of care in patients with unresectable disease who respond to platinum-based chemotherapy.

Patients whose disease is resectable after systemic therapy may also be offered consolidative local therapy. Consolidative treatment options include RC with lymphadenectomy or radiotherapy and should be discussed in a multidisciplinary setting. Principles of consolidation should be considered prior to embarking on local therapy, including the response to primary chemotherapy, the extent of disease, the feasibility and safety of resection, performance status and patient motivation.

Local therapy enables control of the pelvis and may be curative in a subset of patients, particularly in the era of adjuvant immunotherapy. In the Checkmate 274 study of adjuvant nivolumab after cystectomy, patients with node-positive disease or advanced stage achieved long-term survival with adjuvant nivolumab.[50] Although the original clinical stage prior to enrollment was not reported, 47% of patients had pN+ disease, indirectly supporting benefit in patients who become resectable with node-positive disease. Retrospective data also demonstrate a five-year survival rate of up to 30–33% with local pelvic surgical control post-chemotherapy in locally advanced disease, further supporting a consolidative approach in advanced disease.[103]

The Javelin 100 study did not address the question of when to consolidate in patients with a PR or CR after chemotherapy. Data supporting consolidation after a period of stability with avelumab maintenance therapy are scant. The timeframe during which a patient should undergo consolidative therapy if eligible while

on avelumab is also currently unknown. Additional research is required to answer these questions but until then, these decisions require multidisciplinary tumor board discussion.

Followup and quality of life

STATEMENT 45

Followup schedules should be tailored to final pathologic tumor, node, metastasis (TNM) staging *(LE 3, Weak recommendation).*

STATEMENT 46

Followup visits after RC should include a metastatic survey, an investigation for upper tract recurrence, an assessment for hydronephrosis, and laboratory studies to detect metabolic complications of urinary diversion *(LE 3, Moderate recommendation).*

STATEMENT 47

In patients at high risk for urethral or upper tract recurrence, urethral washings ± urethroscopy and urine should be collected for cytologic examination at interval followup visits *(LE 3, Moderate recommendation).*

STATEMENT 48

Patients treated with bladder preservation (radiotherapy-based or partial cystectomy) should also receive, in addition to the same investigations performed for RC patients, long-term cystoscopic evaluation at each followup visit to survey the remaining urothelium *(LE 3, Strong recommendation).*

STATEMENT 49

Intravesical recurrences after bladder preservation may be managed as per primary bladder tumors based on pathologic assessment after TURBT *(LE 3, Weak recommendation).* **Careful consideration for RC should occur for high-risk recurrences.**

STATEMENT 50

Endoscopic biopsy is recommended following TMT to assess response *(LE 3, Moderate recommendation).*

STATEMENT 51

QoL in the form of a validated patient-reported outcome (PRO) measure or QoL instrument may be captured for all patient visits *(LE 3, Weak recommendation).*

Bladder cancer is known to have a significant impact on QoL.[104,105] Cystectomy patients are at risk of long-term sexual dysfunction, urinary complications (recurrent infections, uretero-enteric anastomotic strictures, stones, renal failure), and bowel dysfunction (diarrhea or constipation).[106-108] TMT patients may experience sexual dysfunction, as well as voiding and storage symptoms from urethral strictures or radiation cystitis, and bowel toxicity, such as radiation enteritis or proctitis.[109,110] They can also experience obstructive uropathy secondary to fibrosis and ureteral stricture disease. Downstream toxicity from perioperative chemotherapy may also occur (e.g., coronary artery disease, peripheral neuropathy, ototoxicity).[111] There are emerging data in the oncology literature supporting the need for QoL and PRO assessment in cancer patients, with some data suggesting improved survival in patients reporting PROs.[112]

In addition to monitoring for recurrent disease, surveillance regimens should incorporate testing to detect long-term complications. While no randomized data support a single surveillance protocol, a risk-adapted approach based on tumor stage (risk of urothelial recurrence) and comorbidity status (competing risk of death) may better tailor followup to maximize recurrence detection while minimizing the burden of surveillance.[113]

Currently, EAU and NCCN guidelines recommend surveillance strategies that incorporate the risk of recurrence, with more frequent followup CT scans, bloodwork, and cytology in the first two years, and continued surveillance to at least five years, with no definitive recommendations on cessation.[5,8] The Canadian Bladder Cancer Network has recommended a stage-based strategy to detect recurrences and delineates a stage-specific surveillance protocol.[114] Regardless of the followup regimen chosen, it should ideally be incorporated into a MIBC patient survivorship program.

Supportive and palliative care

STATEMENT 52

For patients with localized, non-metastatic MIBC who are unfit for radical intervention (RC or TMT), an aggressive endoscopic approach ("radical TURBT") can be performed to achieve local control. This may be combined with radiotherapy on a case-by-case basis *(LE 3, Weak recommendation).*

STATEMENT 53

Palliative care consultation should be requested early on in the care of incurable/unresectable patients *(LE 1, Strong recommendation).*

■ STATEMENT 54

Palliative cystectomy can be performed in select cases, with non-curative intent, for intractable hematuria or pelvic pain secondary to the bladder tumor *(LE 3, Weak recommendation).*

■ STATEMENT 55

Palliative radiotherapy may also be offered for symptom control, such as hematuria or bony pain *(LE 3, Moderate recommendation).*

Patients with unresectable or metastatic disease should be offered an early palliative care referral, as a number of oncology randomized controlled trials have demonstrated improvements in health-related QoL and symptom control with prompt referral.[115] Local options for patients with intact bladders include palliative TURBT for hematuria, palliative cystectomy or radiotherapy for intractable hematuria or pelvic pain, and site-directed palliative radiotherapy for painful metastatic lesions. Current systemic options are rapidly evolving and include palliative chemotherapy, immunotherapy, antibody-drug conjugates, and FGFR antagonists. A discussion on these therapies is outside of the scope of this document.

CONCLUSIONS

MIBC is a potentially lethal malignancy that requires intensive, multidisciplinary care to maximize cure while minimizing the burden and toxicity of treatment. This guideline establishes a Canadian perspective on the management of this difficult disease.

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