

Canadian Urological Association guideline: Muscle-invasive bladder cancer

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Introduction

On average, an estimated 9000 incident cases of bladder cancer are diagnosed in Canada annually.¹ Of these, approximately 25% will be muscle-invasive at presentation. Muscle-invasive bladder cancer (MIBC) possesses an aggressive biology that portends metastatic disease. Overall, the five-year mortality of patients diagnosed with localized MIBC is approximately 40–50%.^{2,3} In the setting of metastatic disease, long-term survival is rare. To help streamline treatment and optimize care, the Canadian Urological Association (CUA) commissioned the creation of a national guideline on MIBC.

Methods

All relevant articles on MIBC and metastatic bladder cancer were sought using a combination of Medline and EMBASE searches. The search strategy involved the following key words: “bladder cancer,” “urothelial carcinoma,” “invasive,” “muscle-invasive,” and “metastatic.” Filters included English language, human studies, and an index date between 2000 and 2017, 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,⁴ American Society of Clinical Oncology,⁵ American Urological Association,⁶ and the National Comprehensive Cancer Network⁷ were also considered for additional content.

An expert panel of academic clinicians with experience managing patients with MIBC and metastatic 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, and future directions. Final guideline 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.^{8,9} “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. A “weak” recommendation, on the contrary, represents the scenario where the level of evidence available is poor or where significant uncertainty in the guideline 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

- **MIBC patients should be assessed in a multidisciplinary manner whenever possible (LE 3, strong recommendation).**

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 Center for Evidence-Based Medicine⁹ RCT: randomized controlled trial; SR: systematic review.

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, 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.¹⁰⁻¹² 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, and radiotherapy may be determined. All patients should also be considered for appropriate clinical trials.

Diagnosis

- **MIBC should be diagnosed with a good-quality TURBT, including muscularis propria that confirms muscle invasion (LE 3, strong recommendation).**

The diagnosis of localized bladder cancer usually begins with a high-quality TURBT.¹³ Where possible, clearance of all macroscopic disease is recommended to ensure optimal pathological analysis and to render the patient clinically disease-free such that all treatment options, including bladder preservation with trimodal therapy, are available to the patient.¹⁴ Despite this goal, it is recognized that complete transurethral resection for particularly large tumors may be unsafe and thus impossible.

In the majority of cases, inadequate sampling of the muscularis propria of the bladder precludes a MIBC diagnosis. In these cases, repeat resection should be strongly considered. However, in those rare 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 procured to establish a bladder cancer diagnosis and determine final histology.

TURBT pathology

- **The histological type (i.e., urothelial, squamous cell, small cell carcinoma, etc.) of the tumor should be reported. For tumors displaying mixed histology, each histological type present in the sample should be noted (LE 3, strong recommendation).**
- **Additional pathological 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).**
- **Divergent differentiation of urothelial carcinoma (e.g., urothelial carcinoma with squamous, glandular, or sarcomatoid differentiation), including variant histology (i.e., micropapillary, plasmacytoid, nested variant, etc.), should be recorded, as well as an estimate of the proportion of variant histology (LE 3, strong recommendation).**
- **Pathology review by a second pathologist, preferably a dedicated genito-urinary pathologist, is recommended for all cases of variant histology (LE 3, moderate recommendation).**

While urothelial carcinoma comprises 90% of MIBC, 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 and thus carry a higher risk of recurrence and worse overall prognosis.¹⁵⁻¹⁷ 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 in patients with pT2 or less disease at RC.¹⁸ It has also been associated with radioresistance.¹⁹ Patients with LVI also have more aggressive disease and its documentation may reinforce the need for neoadjuvant chemotherapy (NAC).^{20,21}

Variant urothelial histology (i.e., micropapillary, nested/large nested, plasmacytoid, sarcomatoid, microcystic, small tubules, or lymphoepithelioma-type urothelial carcinoma) or extensive glandular/squamous differentiation also portend poorer outcomes and more advanced disease at presentation. Given reported evidence of significant interobserver variability in pathologists' abilities to discern variant histology, all tumors displaying variant histology should undergo pathological re-review, preferably by an expert genito-urinary pathologist.²²

Staging

- **Examination under anesthesia should be performed immediately after TURBT to accurately determine clinical stage and resectability** (LE 3, moderate recommendation).
- **Computed tomography (CT) of the chest, abdomen, and pelvis is the ideal treatment modality to stage localized MIBC and metastatic bladder cancer** (LE 3, moderate recommendation).
- **Magnetic resonance imaging (MRI) is an option to determine the local extent of disease** (LE 3, moderate recommendation).
- **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).
- **Currently, the role for 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 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 the determination of local extent of the disease, information that is required 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. Chest imaging (CT or x-ray) 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 most sensitivity to detect metastases. Currently, there is insufficient evidence to recommend routine use of PET CT imaging in bladder cancer

patients, although guidelines from other organizations have suggested its incorporation in the staging and followup of MIBC, albeit with lower levels of evidence.⁷

Treatment

Chemotherapy

- **All eligible patients with cT2-T4a N0 M0 urothelial carcinoma of the bladder should be encouraged to receive cisplatin-based combination chemotherapy (gemcitabine plus cisplatin [GC]; methotrexate, vinblastine, doxorubicin and cisplatin [MVAC]; or dose-intense [dd]-MVAC) as NAC prior to radical local therapy** (LE 1, strong recommendation).
- **Absolute contraindications to 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 (GFR) \leq 50 ml/min/1.73m². Relative contraindications for NAC include an eGFR between 50 and 60 ml/min/1.73m², a history of recurrent infection, and concomitant immunosuppression** (LE 2, strong recommendation).
- **Patients with contraindications to cisplatin-based NAC should proceed directly to radical local therapy** (LE 2, strong recommendation).
- **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).
- **After 2/4 cycles of GC or conventional MVAC NAC, restaging should be performed to ensure treatment response or stable disease during chemotherapy. In the event of non-metastatic progressive disease or significant toxicity to chemotherapy that precludes its delivery, NAC should be discontinued and cystectomy performed within 4–6 weeks of last chemotherapy. Patients receiving ddMVAC, given every two weeks, do not need restaging in the midst of chemotherapy, as the short course of treatment precludes the need for imaging** (Expert opinion).
- **Patients receiving NAC should ideally 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).
- **The role of neoadjuvant chemotherapy in pure non-urothelial carcinoma (squamous cell carcinoma, adenocarcinoma, etc.) is not defined and should not be used** (LE 3, strong recommendation).
- **In patients who do not receive NAC prior to cystectomy, adjuvant cisplatin-based combination chemotherapy (GC, MVAC, or dd-MVAC) should be offered to**

those eligible patients with pT3/T4 and/or N+ disease (LE 2, strong recommendation).

- **Patients with non-metastatic, clinically unresectable cT4b or cN+ tumors should be offered induction (primary) cisplatin-based combination chemotherapy if eligible or an alternative combination chemotherapy regimen if cisplatin-ineligible (e.g., gemcitabine/carboplatin), or enrolment in a clinical trial, if available. Consolidative radical therapy should be considered after induction chemotherapy, where possible, particularly in those with responsive or stable disease (LE 3, weak recommendation).**

Two large, phase 3 clinical trials have demonstrated a mortality benefit with the use of NAC prior to local radical treatment.^{23,24} 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% mortality relative risk reduction in patients receiving NAC.²⁵ 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.

Despite level 1 evidence supporting NAC, uptake has been poor, with recent data still demonstrating only a 27% compliance rate in the modern era.²⁶ Reasons posited for 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. 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% confidence interval [CI] 1.39–8.24),²⁷ death directly attributable to chemotherapy and any possible delays in radical therapy from NAC.²⁸

Even with the aforementioned potential shortcomings, the NAC meta-analysis nevertheless reported a survival benefit. A number of reports also suggest that NAC does not increase perioperative morbidity or complication rates, lending further support to its usage.^{29,30} Ample time (usually 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, as adopted by the Canadian Association of Genitourinary Medical Oncologists (CAGMO), is within 4–6 weeks, although a maximal window of 10 weeks has not been shown to compromise outcomes.^{31,32}

To date, there are no randomized trials comparing NAC to adjuvant chemotherapy (AC). While data do support use of AC, with an approximate 23% survival benefit (hazard ratio [HR] 0.77, 95% CI 0.59–0.99) based on meta-analyzed

data,³³ no single phase 3 trial has demonstrated an overall survival benefit with AC compared to observation. Even the most recent 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 overall survival benefit (HR 0.78; 95% CI 0.56–1.08).³⁴ The overall quality of evidence also favours 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.³⁵ Postoperative complications may also limit AC use, excluding approximately 30% of patients who may have been eligible from receiving necessary treatment.³⁶ 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 favouring a NAC approach.

Surgical management

- **The standard therapy for localized MIBC is RC (LE 1, strong recommendation).**
- **The optimal timing of RC where NAC has not been administered is within six weeks of TURBT (LE 3, moderate recommendation).**
- **Patients scheduled for RC are recommended to receive perioperative optimization according to endorsed Enhanced Recovery after Abdominal Surgery (ERAS) protocols (LE 2, moderate recommendation).**
- **In male patients, RC entails removal of the bladder and prostate en bloc. A nerve-sparing procedure can be safely offered to select patients interested in preserving sexual function (LE 3, moderate recommendation).**
- **In female patients, RC entails 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 function (LE 3, moderate recommendation).**
- **Bilateral pelvic lymph node dissection (PLND) with removal, at minimum, of the obturator, external iliac, and internal iliac lymph nodes should be performed in all patients (LE 3, strong recommendation).**
- **Orthotopic urinary diversion 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).**
- **Urethrectomy should be performed in men with high-grade or invasive urethral disease distal to the pros-**

- tatic urethra, a positive urethral margin, or suspected prostatic stromal involvement in men and bladder neck tumors in women (LE 3, moderate recommendation).
- Both laparoscopic/robotic and open approaches are acceptable methods to perform RC with comparable cancer outcomes (LE 1, strong recommendation).
 - Partial cystectomy for MIBC is discouraged and should only be considered in specific situations: unifocal, small tumor <2 cm, dome location, good bladder capacity, no hydronephrosis, minimal to no concomitant CIS. Random bladder biopsies (plus prostatic urethral biopsy) should be performed prior to partial cystectomy to rule out occult disease. 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 oncological outcomes.³⁷ Perioperative patient counselling regarding the extent of the operation and the associated gender-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.³⁸⁻⁴² 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^{43,44} and randomized controlled data that may definitively support this observation is pending maturity.⁴⁵

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).³⁸

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.⁴⁶ 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.^{47,48} Specifically, a CUA continuing professional development slide deck on the topic has been created to guide urologists' implementation of ERAS for cystectomy.⁴⁹

Cystectomy pathology

- The final pathology report should contain the following elements: histology (including variants), stage, grade, presence of concomitant CIS, presence of LVI, number

of lymph nodes, number of positive lymph nodes, and surgical margin status (LE 3, strong recommendation).

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

An accurate assessment of pathological stage in cystectomy specimens is of utmost importance. Synoptic reporting of pathological data is encouraged to standardize nomenclature across institutions. Pathology data generally guide discussions about prognosis, with worse outcomes expected with higher-stage disease or with concomitant CIS or LVI.^{18,50} Receipt of AC is also dependent on accurate pathological assessment and is generally recommended in patients with node-positive and/or pT3/4 disease.³⁶ Synoptic pathology reporting also provides data that can serve as surgical quality indicators (e.g., margin status, number of nodes removed, dissection template, etc.).

Radiotherapy

- Trimodal therapy (TMT; radical TURBT + external beam radiotherapy + concomitant chemotherapy) can be offered to select patients wishing to preserve their bladder, those unfit for cystectomy, or those refusing cystectomy (LE 3, moderate recommendation).
- Ideal tumor and patient characteristics for TMT are as follows: small (<5 cm), unifocal, no CIS, no hydronephrosis, good bladder function, patient motivated for bladder preservation (LE 3, moderate recommendation).
- With TMT, maximal/radical TURBT should be performed to clear all visible tumor prior to initiation of chemoradiation (LE 3, moderate recommendation).
- Radiotherapy as monotherapy in the treatment of localized MIBC is only acceptable in patients who are ineligible for both RC and chemotherapy. Otherwise, radiation should be offered in combination with either cisplatin or 5-FU/MMC chemotherapy (LE 1, strong recommendation) or gemcitabine (LE 2, strong recommendation).
- Currently, there is no well-defined role for neoadjuvant or adjuvant radiotherapy in the setting of localized MIBC (LE 3, moderate recommendation).

Although RC is the de facto gold standard surgical therapy for MIBC, TMT can also be offered to select patients who seek bladder preservation. Optimal patient selection is key in this setting, with criteria as delineated above and provision of care in a multidisciplinary setting likely yielding the most robust outcomes. A recent report demonstrated that, in carefully selected patients, TMT offered in a multidisciplinary bladder cancer clinic yielded moderate-term disease-specific survival rates rivalling that of RC (73% for RC, 77% for TMT).¹⁰ Ultimately, only approximately 20–25% 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 undertreatment of non-metastatic MIBC in approximately 50% of patients.⁵¹ TMT can safely be offered to patients unfit for surgical therapy, thus providing some benefit for these patients.⁵²

Where possible, radiation should be administered with radio-sensitizing chemotherapy. Radiotherapy alone as monotherapy has been shown in a large randomized control trial to be inferior to radiotherapy plus chemotherapy.⁵³ A smaller randomized NRG Oncology/Radiation Therapy Oncology Group (RTOG) trial demonstrated similar three-year distant metastases-free survival regardless of whether the chemotherapeutic regimen used was 5-FU-based or gemcitabine-based.⁵⁴

Unresectable and oligometastatic disease

- **First-line therapy for unresectable urothelial carcinoma is cisplatin-based combination chemotherapy with either GC, MVAC, or dd-MVAC. In cisplatin-ineligible patients (i.e., absolute contraindications to cisplatin; see section on NAC above), carboplatin combination chemotherapy or single-agent chemotherapy may be substituted as first-line therapy (LE 1, strong recommendation).**
- **At present, there is 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).**
- **Consideration of consolidative surgery (RC) combined with oligometastectomy in initially unresectable patients experiencing a significant complete response (CR) or partial response (PR) must be on a case-by-case basis after multidisciplinary tumor board discussion (LE 4, weak recommendation).**

Patients with unresectable or oligometastatic disease at presentation should undergo primary chemotherapy. In those with an excellent response (CR or PR), multidisciplinary cancer conference discussion regarding the role of consolidative therapy of the primary and metastatic lesion(s) should be undertaken. 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 along with limited metastectomy can achieve durable long-term survival rates of 10–20%.^{55,56} Oligometastatic sites that have been resected include most commonly the retroperitoneal lymph nodes, lung metastases, and bone.⁵⁷ 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.

Followup and quality of life

- **Quality of life (QoL) in the form of a validated patient-reported outcome (PRO) measure or QoL instrument should be captured for all patients at each visit (LE 3, weak recommendation).**
- **Followup schedules should be tailored to final pathological TNM staging (LE 3, weak recommendation).**
- **Followup visits after RC should include a metastatic survey, including an investigation for upper tract recurrence, assessment for hydronephrosis, and laboratory studies to detect metabolic complications of diversion (LE 3, moderate recommendation).**
- **In patients at high risk for urethral or upper tract recurrence, urethral washings +/- urethroscopy and urine should be collected for cytological examination at interval followup visits (LE 3, moderate recommendation).**
- **Patients treated with a bladder preservation approach (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).**
- **Intravesical recurrences after bladder preservation may be managed as per primary bladder tumors based on pathological assessment after TURBT (LE 3, weak recommendation). Careful consideration for RC should occur for high-risk recurrences.**
- **Endoscopic biopsy is recommended following TMT to assess response (LE 3, moderate recommendation).**

There are emerging data in the oncology literature supporting the need for QoL and PRO assessment in cancer patients, with a recent study suggesting improved survival in patients reporting PROs.⁵⁸ Bladder cancer is known to have a significant impact on QoL.^{59,60} 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).⁶¹⁻⁶³ TMT patients may experience sexual dysfunction, voiding and storage symptoms from urethral strictures or radiation cystitis, or bowel toxicity (radiation enteritis or proctitis).^{64,65} Downstream toxicity from perioperative chemotherapy may also occur (e.g., coronary artery disease, peripheral neuropathy, ototoxicity).⁶⁶

In addition to monitoring for recurrent disease, surveillance regimens should incorporate testing to detect such 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 fol-

lowup to maximize recurrence detection while minimizing the burden of surveillance.⁶⁷ Currently, EAU and NCCN guidelines recommend five years of risk-adapted by stage and two years of non-risk-adapted surveillance, respectively.^{4,7} The Canadian Bladder Cancer Network recommends a stage-based strategy to detect recurrences and delineates a stage-specific surveillance protocol.⁶⁸ Regardless of the followup regimen chosen, it should ideally be incorporated into a MIBC patient survivorship program.

Supportive and palliative care

- **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 (LE 3, weak recommendation).**
- **Palliative care consultation should be requested early on in the care of incurable/unresectable patients (LE 1, strong recommendation).**
- **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).**
- **Palliative radiotherapy may also be offered for intractable hematuria or bony pain secondary to metastatic disease (LE 3, moderate recommendation).**
- **Palliative chemotherapy (e.g., gemcitabine) may be offered to patients with unresectable or metastatic disease who are ineligible for or have failed platinum-based combination chemotherapy (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.⁶⁹ Local options for patients with intact bladders include palliative TURBT for hematuria, palliative cystectomy, or radiotherapy for intractable hematuria or pelvic pain and localized palliative radiotherapy for painful metastatic lesions. Systemic options include palliative chemotherapy with agents with minimal toxicity (e.g., gemcitabine monotherapy) or enrollment in a clinical trial if available.^{70,71}

Conclusions

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

Competing interests: Dr. Kulkarni has been an advisory board member for Ferring, Janssen, Merck, and Theralase; has received honoraria from Abbvie, Amgen, Astellas, Biosyent, Ferring, Janssen,

Merck, Roche, and TerSera; and has participated in clinical trials supported by Abbvie, Bristol Myers Squibb, Eleven Biotherapeutics, Merck, and Theralase. Dr. Black has been an advisory board member for AbbVie, Asieris, AstraZeneca, Astellas, Bayer, Biosyent, BMS, Janssen, Lilly, Merck, Roche, Sanofi, and Urogen; is a member of a speakers bureau for AbbVie, Biosyent, Janssen, Ferring, Pfizer, and TerSera; has received a grants/honoraria from Bayer, GenomeDx Biosciences, iProgen, and Sanofi; has participated in clinical trials supported by Astellas, Ferring, Genentech, Janssen, MDx Health, and Sirka; and shares a patent with GenomeDx. Dr. Sridhar has been an advisory board member for Astellas, Janssen, Pfizer, Roche, and Sanofi; has received grants/honoraria from Astellas, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Bayer, Janssen, and Roche. Dr. Kapoor has been an advisory board member for BMS, Eisai, Ipsen, Merck, Novartis, Pfizer, and Roche; a speakers' bureau member for Eisai, Ipsen, Novartis, and Roche; and has received honoraria from BMS, Eisai, Ipsen, Merck, Novartis, Pfizer, and Roche. Dr. Zlotta has been an advisory board member for Janssen, Sanofi, and Roche. Dr. Shayegan has received grants/honoraria from Abbvie, Astellas, Janssen, and Roche; and has participated in clinical trials supported by Astellas and Janssen. Dr. Rendon has been both an advisory board member and a speakers bureau member for and has received grants/honoraria from Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, and Sanofi Aventis. Dr. Chung has received grants/honoraria from Sanofi; and participated in a clinical trial supported by Abbvie. Dr. Alimohamed has received honoraria from Astellas and Bayer. Dr. Fradet has been an advisory board member for Astellas, Merck, Roche, and Sanofi; and has received a grant from Astellas. Dr. Kassoof has received honoraria from Astellas, AstraZeneca, Janssen, Merck, and Roche. Dr. van der Kwast reports no competing personal or financial conflicts related to this work.

This paper has been peer-reviewed.

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