Recommendations for the improvement of bladder cancer quality of care in Canada: A consensus document reviewed and endorsed by Bladder Cancer Canada (BCC), Canadian Urologic Oncology Group (CUOG), and Canadian Urological Association (CUA), December 2015

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Multidisciplinary consensus committee

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Introduction

This initiative was undertaken in response to concerns regarding the variation in management and in outcomes of patients with bladder cancer throughout centres and geographical areas in Canada. Population-based data have also revealed that real-life survival is lower than expected based on data from clinical trials and/or academic centres.

To address these perceived shortcomings and attempt to streamline and unify treatment approaches to bladder cancer in Canada, a multidisciplinary panel of expert clinicians was convened last fall for a two-day working group consensus meeting. The panelists included urologic oncologists, medical oncologists, radiation oncologists, patient representatives, a genitourinary pathologist, and an enterostomal therapy nurse. The following recommendations and summaries of supporting evidence represent the results of the presentations, debates, and discussions.

Methodology

Prior to the two-day consensus meeting, the steering committee assigned subtopics to individual experts who were asked to conduct a literature search on an assigned topic, identify knowledge gaps and limitations, and develop recommendation statements based on the best available evidence, taking into consideration the Canadian context. These recommendations were pre-circulated to the entire committee prior to the event. If evidence for any important clinical question was absent or inadequate, the topic experts were asked to provide their own opinions based on both their understanding of the biology of the disease and clinical experience.

During the consensus meetings, each topic expert presented his/her recommendation statements, as well as the published or presented evidence, where it existed, to support those recommendations. During and after each presentation, the participants' panel was asked to provide comments and to indicate whether they agreed with the recommendations or, if not, to propose revisions. In most cases, consensus was reached on the statements presented in this document. In those cases where consensus was not reached, this is clearly stated.

The levels of evidence and grades of recommendations used in this document are adapted from those of the Oxford Centre for Evidence-based Medicine.[1]

I. Hematuria: Workup, rapid access clinic, timelines, investigations

For the purposes of this document, the panel agreed that the term "gross hematuria" would be used rather than other interchangeable terms, such as visible hematuria or macroscopic hematuria. The panel also chose the term "microscopic hematuria" rather than non-visible hematuria. To be considered a positive specimen for microscopic hematuria, three or more red blood cells (RBCs) per field are required. Notably, however, the panelists acknowledged that when discussing hematuria with patients, it might be easier for many patients to understand "visible" and "non-visible" rather than the terminology used in this document.

There are a number of different clinical practice guidelines, consensus documents, and recommendations available dealing with microscopic hematuria.[2-6] The following is the consensus arrived at by the Canadian Working Group after synthesizing the existing recommendations and reviewing the available clinical trial evidence.

A. Recommended indications for evaluation by primary care physicians

i. Single episode of gross hematuria, in the absence of urinary tract infection (UTI) or other transient causes (Level III–Grade C).
ii. Single episode of symptomatic (e.g., hesitancy, frequency, urgency, dysuria) microscopic hematuria (in absence of UTI or other transient causes) (Level III–Grade C).
iii. Confirmed episode of asymptomatic, microscopic hematuria (in absence of UTI or other transient causes) (Level III–Grade C).
iv. A positive dipstick alone should prompt confirmation with a formal microscopic analysis, but not workup for hematuria (Level III–Grade C).
v. Use of anti-coagulation or anti-platelet agents do not exclude patients from undergoing hematuria evaluation (Level III–Grade C).
vi. Transient causes of hematuria, such as UTI, menstruation, trauma, instrumentation, exercise-induced hematuria, or myoglobinuria, should be excluded (Level III–Grade C).

Discussion

With respect to the requirements for evaluation — whether one needed confirmation of microscopic hematuria or if a single episode was sufficient — there was no consensus reached among the panelists. However, the evidence does suggest that one positive sample is sufficient to prompt an evaluation.[7-14]

It is also important to note that non-malignant causes of microhematuria (e.g., medical renal disease, bladder stones, urethral stricture) would also benefit from active management. Given that gross hematuria associated with serious conditions is most often intermittent, only one episode is required before prompting evaluation.

For microscopic hematuria, a dipstick test is a good positive predictor (91–100% sensitivity), but cannot be used to rule in hematuria, as there are many potential reasons for false-positives (e.g., myoglobinuria and oxidizing contaminants) and false-negatives (e.g., presence of reducing agents like ascorbic acid, urinary pH <5.1).[15]

B. Recommended elements of initial evaluation of hematuria in primary care

i. The assessment of the symptomatic or asymptomatic microscopic hematuria patient should include a careful history and physical examination, including measurement of blood pressure (Level III–Grade C).
ii. Laboratory blood work: Creatinine, blood urea nitrogen (BUN), calculated glomerular filtration rate (GFR) (Level III–Grade C).
iii. Urinalysis. The presence of dysmorphic RBCs, proteinuria, cellular casts, and/or renal insufficiency or any other clinical indicator suspicious for renal parenchymal disease warrants concurrent nephrologic workup, but does not preclude the need for urologic evaluation (Level III–Grade C).
iv. Urinary cytology is indicated in patients with gross and symptomatic microscopic hematuria; it is not indicated in patients with asymptomatic microscopic hematuria (Level III–Grade C).

Discussion

The recommended laboratory work (creatinine, BUN, calculated GFR) is critical, as abnormal renal function warrants evaluation to establish the etiology of renal dysfunction. The evaluation of renal function is also needed to consider the selection of the diagnostic imaging studies to be employed as part of the hematuria evaluation, particularly whether the patient can have a computed tomography (CT) with contrast.

With respect to the use of urinary cytology, a wide range of sensitivity and specificity has been reported in the literature (sensitivity 0–100%, specificity 62.5–100%).[2,16] Although we recommended that cytology be used for gross hematuria and symptomatic microscopic hematuria, we acknowledge that cytology has minimal application in ruling out malignancy or excluding patients from further investigation.

C. Recommended indications for referral to urology

i. All patients with a SINGLE episode of gross hematuria (any age) (Level III–Grade C).
ii. All patients with a SINGLE episode of symptomatic microscopic hematuria (any age) (Level III–Grade C).
iii. All patients with a CONFIRMED episode of asymptomatic microscopic hematuria aged ≥35 yrs (Level III–Grade C).
iv. Patients with asymptomatic microscopic hematuria aged <35 years and perceived high-risk factors (Level III–Grade C).

Discussion

Note that the threshold age among those with asymptomatic hematuria is 35 years. This threshold, recommended by the American Urological Association (AUA)-endorsed guidelines in 2012, was lowered from previous recommendations, which used 40 years as the threshold. This was motivated by a review of the literature, which showed that 95 of 98 (97%) patients diagnosed with a urinary tract malignancy in 17 screening studies[7-12,17-27] were older than 35 years; and 406 of 409 (99.3%) patients diagnosed with a urinary tract malignancy in the initial and further workup studies were older than 35 years.

Other high-risk factors include current or past tobacco use, history of pelvic irradiation, cyclophosphamide or other carcinogenic alkylating agent exposure, and exposure to occupational hazards such as dyes, benzenes, and aromatic amines. Among patients with these risk factors who present with microscopic hematuria, the incidence of malignancy has been reported to be as high as 25.8%.[12]

We recognize that our recommendations for referral may cast a broad net with a relatively low yield. A large, retrospective analysis of 156 691 patients with microhematuria (from the US Kaiser Permanente database) showed that the overall three-year incidence of bladder cancer among patients with hematuria was low, at 0.68%.[14] Some observers have interpreted these findings to suggest that criteria for referral should be more stringent than those that we suggest.[28]

D. Recommended indications for referral to nephrology

i. In addition to the urological evaluations, patients with the following findings should be considered for further renal function evaluation (Level III–Grade C):
   - Abnormal GFR.
   - Significant proteinuria.
   - Isolated hematuria (i.e., in the absence of significant proteinuria) with hypertension in those aged <40 years.
   - Gross hematuria coinciding with intercurrent (usually upper respiratory tract) infection.

E. Recommended urological investigations

i. All patients with an indication for referral to urology should undergo the following tests:
   - Cystoscopy (clinical principle).
   - Upper tract imaging (Level III–Grade C).
   - The use of urinary markers, including cytology, is not recommended as a part of the routine

evaluation of the patient with asymptomatic microhematuria; for those with gross hematuria or symptomatic microhematuria, cytology is recommended (Level III–Grade C).

Discussion

With respect to cystoscopy, there are many studies that have been published comparing the different modalities (conventional white-light cystoscopy [WLC] or blue-light cystoscopy with 5-aminolaevulinic acid [ALA] or hexyl aminolevlinate [HAL]).[29-46] The evidence remains inconclusive as to which modality is preferred, as the published sensitivities and specificities of each span broad ranges across the various studies.

For upper urinary tract imaging of patients with gross hematuria or symptomatic microscopic hematuria, multiphasic CT urography (with IV contrast), is the imaging procedure of choice because it has the highest sensitivity and specificity for imaging the upper tracts.[47,48] This modality should include sufficient phases to evaluate the renal parenchyma to rule out a renal mass and an excretory phase to evaluate the urothelium of the upper tracts. For patients with relative or absolute contraindications that preclude use of multi-phasic CT (such as renal insufficiency, iodinated contrast allergy, pregnancy), magnetic resonance urography (MRU) (without and with intravenous contrast) is an acceptable alternative imaging approach. For patients with relative or absolute contraindications that preclude use of both multi-phasic CT and MRI (such as presence of metal in the body) where collecting system detail is deemed necessary, combining non-contrast CT or renal ultrasound with retrograde pyelograms provides alternative evaluation of the entire upper tract.[49-51]

For patients with asymptomatic microscopic hematuria, imaging is still recommended, but the choice of modality is left to physician and patient preference on a case-by-case basis.

With respect to urinary markers, while they are not recommended as part of routine workup, there is published evidence from numerous studies that they can have predictive value.[52-63] For example, for the marker NMP22, sensitivities ranged from 6.0–100% and specificities from 62–92%. With BTA-stat, specificities were reported in the range of 69–73%; and in studies investigating UroVysion FISH, sensitivities ranged from 61–100% and specificities from 71.4–93%.

F. Recommendations for long-term monitoring in primary care (all recommendations Level IV–Grade D):

i. Patients not meeting criteria for referral to urology or nephrology, or who have had negative urological or nephrological investigations, need long-term monitoring due to the uncertainty of the underlying diagnosis. Patients should be monitored for the development of:
   - Voiding lower urinary tract symptoms (LUTS);
   - Gross hematuria;
   - Significant or increasing proteinuria;
   - Progressive renal impairment (falling eGFR); and/or
   - Hypertension.

ii. Annual urinalyses for three years for patients with gross hematuria, symptomatic microscopic hematuria, and persistent asymptomatic microscopic hematuria after negative urologic workup.

iii. If a patient with a history of persistent asymptomatic microscopic hematuria has two consecutive negative annual urinalyses (one per year for two years from the time of initial evaluation or beyond), then no further urinalyses for the purpose of evaluation of asymptomatic microscopic hematuria are necessary.

iv. Cytology is recommended yearly for three years following a negative workup in patients with risk factors for urothelial cell carcinoma.

v. For persistent or recurrent asymptomatic microscopic hematuria after initial negative urologic workup, repeat evaluation within three to five years should be considered.

vi. Changes in the clinical scenario, such as a substantial increase in the degree of microscopic hematuria, the detection of dysmorphic RBCs with concomitant hypertension and/or proteinuria, the development of gross hematuria, pain, or other new symptoms, may warrant earlier re-evaluation and/or referral to other practitioners, such as nephrologists.

Discussion

With respect to long-term monitoring for hypertension, one must keep in mind that the development of hypertension in older people may have no relation to the hematuria and, therefore, not increase the likelihood of underlying glomerular disease.

The recommendation for discontinuing monitoring for patients with asymptomatic microscopic hematuria after repeat evaluations is supported by the finding that among 234 men with negative evaluation, only two developed bladder cancer during 14 years of followup.[64] Another study involving 140 patients with microscopic hematuria reported that those individuals with fewer than five RBCs/HPF on three urinalyses may be followed conservatively, as they are unlikely to have significant pathology.[65]

G. Recommended timing of evaluation (all recommendations Level IV–Grade D)

i. Patients with gross hematuria or symptomatic microscopic hematuria should undergo complete urological evaluation, including cystoscopy, within four weeks.
ii. Patients with asymptomatic microscopic hematuria should undergo urological evaluation, including cystoscopy, within 12 weeks.

Discussion

Recent evidence shows that wait times for initial evaluation are variable. A retrospective cohort study using data from two provincial health databases in Quebec showed that the median delay before a first urologist visit was 32 days (mean: 72 days, SD: 96.8, interquartile range [IR]: 75).[66] The median waiting time was 45 days for women and 23 days for men. The median waiting time between the first urologist visit and the first cystoscopy was 22 days (mean: 69, SD: 103, IR:77).[66]

H. Recommendations for dissemination of guidelines and education

i. A public campaign is recommended to increase awareness at the patient level.
ii. Guidelines should be disseminated to primary care physicians and education provided to increase proper evaluation of patients with hematuria.

Discussion

These actions are recommended based on the understanding that patients do not often see their physician after an episode of hematuria[67] and that primary care practitioners have demonstrated poor adherence (approximately one-third adherent) to published guidelines.[68]

I. Recommended areas for research

i. We encourage the development of a multi-institutional registry to help investigate unmet needs with respect to hematuria.
ii. The creation of hematuria clinics is encouraged.

Discussion

The following are some of the potential unmet needs that may be investigated with a multi-institutional registry:

- Determination of true incidence of malignancy and other abnormalities found upon hematuria workup.
- Determination of location (upper vs. lower urinary tract) of abnormalities in order to help determine the most cost-efficient upper tract evaluation method.
- Validation of stratification of risk to dictate intensity of hematuria workup.
- Evaluation of cost-effectiveness of hematuria workup.
- Future role of urinary markers.

The creation of "one-stop" hematuria clinics in Australia has been demonstrated to facilitate the referral process from primary care physicians to urology and decrease the time required to complete assessment (up to 50% completion of assessment in one single visit).[69,70]

II. Optimizing outcomes in high-risk non-muscle-invasive bladder cancer (NMIBC)

A. Recommendations for transurethral resection of bladder tumour (TURBT) technique

i. All visible tumours should be resected if possible (Level III–Grade B).
ii. Re-resection should be performed for all T1 lesions when muscle has not been sampled (Level II–Grade B).
iii. In select situations where resection of a small T1 tumour with muscle performed by an experienced surgeon who is confident that the extent and depth of the resection is adequate, a re-resection may not be necessary (Level III–Grade C).
iv. Re-resection of TaHG lesions is not routinely recommended (Level IV–Grade C).

Discussion

The rate of recurrence at the first followup cystoscopy is highly variable, ranging from 3–46% in the literature.[71] Although differences in recurrence rates may in part be explained by differences in study populations, the authors of a combined analysis of studies investigating recurrence rates concluded that the quality of the transurethral resections (TURs) also has a very significant impact.[71]

Immediate postoperative instillation of intravesical chemotherapy does not compensate for poor surgical technique; complete responses (CRs) with this latter method are only in the range of 30–50%, and the recurrence rate for those who do not reach a CR is up to 80%.[72]

There are several reasons why the panel recommended re-resection in the above-mentioned populations (all T1 lesions where muscle has not been sampled, T1 lesions with muscle if uncertainty regarding the extent of resection exists [e.g., large lesions, multiple tumours, initial resection by non-bladder-cancer-focused surgeon], and/or for prognostic information). These include: improved staging, improved therapy, clearance of microscopic residual tumour, improved response to bacillus Calmette-Guérin (BCG), and more insight into the biology of the disease.[73,74]

A large, single-centre, retrospective study of 1021 patients treated with intravesical BCG for non-muscle invasive high-risk bladder cancer demonstrated that the recurrence rate at three months among those with re-resection was significantly lower than among those who did not have a second resection (9.6% vs. 44.3%).[75] Understaging after initial transurethral resection of a bladder tumour (TURBT) has been reported in 27–78% of cases.[76,77] Re-resection has been shown to lead to a change of therapy in approximately one-third of patients.[78]

Several retrospective series have demonstrated the benefits of re-resection on the rate of progression.[75,79,80] In addition, a single randomized, controlled trial has been published that demonstrated re-resection decreased recurrence of disease regardless of whether postoperative single intravesical instillation of chemotherapy was used or not. However, this study has several limitations due to its design (e.g., no blinding, no sample size justification, lack of definitions of endpoints).[81,82]

Although the value of re-resection is often stated, whether or not it leads to an actual improved response to BCG is not clear. The studies evaluating repeat vs. single TURBT in this regard[83,84] should not be considered conclusive.

While the evidence does support re-resection for most patients, the panel did note that there could be select situations, such as resection of a small T1 tumour with muscle by an experienced surgeon who is confident that the extent and depth of the resection is adequate, that re-resection may not be necessary. Research has shown that experienced surgeons are less likely to leave residual disease than their less experienced colleagues.[85]

With respect to TaHG tumours, there is a lack of consensus among guidelines. The European Association of Urology (EUA) guidelines assert that re-resection is the standard of care in this population;[86,87] the 2010 Canadian Urological Association (CUA) guidelines include a Grade C recommendation for re-resection in this population,[88] while the AUA makes no specific recommendation for this subgroup.[89] The lack of consensus reflects the scarcity of available data; most of the published research focuses on T1 disease.

B. Recommendations for induction BCG

i. First-line adjuvant treatment for T1HG disease should be BCG or BCG + electromotive drug administration (EDMA)/mitomycin C (MMC) (Level I–Grade A).
ii. Induction BCG should be reserved for high-risk (T1 or HG) tumours only (Level I–Grade B).
iii. Induction BCG as first-line therapy for intermediate risk disease should be used sparingly (Level IV–Grade C).
iv. Induction BCG should be administered at full dose when possible (Level I–Grade A).

Discussion

For induction therapy, BCG + TUR has been shown to be superior to TUR alone in terms of reducing recurrences and the risk of progression.[90,91] It has also been shown to be the best single agent to use in this setting, having demonstrated superiority in terms of recurrences[92,93] and progression[94] compared to intravesical MMC in meta-analyses of randomized, controlled trials. In a single European Organisation for Research and Treatment of Cancer (EORTC) study, BCG was also found to be superior to intravesical epirubicin.[95]

The optimal dosing, schedule and duration of BCG has not been conclusively demonstrated, but we recommend that it be used at full dose whenever possible. A recent randomized non-inferiority trial of full-dose vs. one-third dose BCG failed to prove non-inferiority of one-third BCG dosing compared to full dose.[96] However, for high-risk NMIBC, full-dose BCG for three years was superior to one-third dose BCG given for one year.

The cautious recommendation for intermediate-risk disease is based on the observation that there are no specific studies of BCG as first-line therapy in this population. However, in patients with low-grade Ta tumours, which are multifocal AND large (>3 cm) AND multi-recurrent (>1 per year), BCG induction is an appropriate option, as these patients should be treated as high-risk.

Notably, there are different strains of BCG available, with the potential for differences in efficacy between these strains.[97] This has not been well studied in the Canadian context.

One report has also shown that the use of sequential BCG and EMDA MMC is more effective than BCG alone in an Italian population.[98] Another study reported that EMDA MMC alone may have similar efficacy compare with BCG alone.[99] We acknowledge that at the time of writing, access to EMDA MMC is uneven across Canada and validation in a North American population has not been done.

C. Recommendations for maintenance BCG

i. Maintenance BCG should be provided, whenever possible (Level I).
ii. The optimal dose and duration of BCG maintenance is full dose for three years for high-risk disease (Level I–Grade A).
iii. In cases where BCG induction is used for intermediate-risk disease, BCG maintenance can be shortened to 12 months (Level II–Grade B).

Discussion

The recommendation in favour of maintenance BCG is based largely on the results of the SWOG 8507 trial, involving 384 patients with intermediate- and high-risk Ta, T1,

or Tis disease.[100] This trial showed that maintenance BCG was superior to no maintenance in terms of recurrence and progression. The difference between the study arms was not significant for overall survival.[100] It should be noted that this study has some substantial limitations, including that it was not blinded and used a composite endpoint instead of true progression. Although some studies have suggested that BCG dose reductions can improve compliance (via decreased toxicity), contemporary randomized trial results demonstrate >80% compliance rate regardless of dose.[101]

The optimal maintenance regimen for BCG among patients with high-risk disease has been defined as three years at full dose,[102] with administration at three, six, 12, 18, 24, 30, and 36 months (after initial therapy for six weeks).[103]

For intermediate-risk disease, full dose with one year maintenance was associated with efficacy similar to full dose with three years of maintenance therapy.[102] In patients in whom BCG is associated with significant side effects or there exist significant barriers to its administration (e.g., travel, drug shortage, poor tolerability, patient choice, etc.), maintenance therapy (dose and duration) can be modified to one year.

D. Recommendations for early cystectomy

i. Patients with T1 disease with concomitant high-risk features have the highest probability of progression. If multiple high-risk features are present, these patients should be counselled regarding the merits of early cystectomy (Level III–Grade C).

ii. Early cystectomy should be strongly considered for patients with T1 disease on a complete initial resection AND with persistent T1 on re-resection (Level IV–Grade C).

Discussion

With respect to the first recommendation, high-risk features include concomitant carcinoma in-situ (CIS), lymphovascular invasion (LVI), large/multiple tumour size (>3 cm), micropapillary features, and extensive (as opposed to focal) invasion. Research clearly shows that patients with T1 disease (either initially or upon restaging pathology) have a significantly higher risk of progression compared to patients with T0, Ta, or CIS.[73,104] Immediate cystectomy for these high-risk patients is a valid option, as surveillance may shorten survival if they are allowed to progress to muscle invasion.[105]

The majority of patients, regardless of age, will not want cystectomy. These individuals should receive education about the outcomes and pros/cons associated with early cystectomy. Notably, younger patients (<60 years) with T1HG and minimal to no comorbidities stand to benefit the most from immediate cystectomy. They have the most to lose from suboptimal treatment, both in terms of duration of life and quality of life.[106]

III. Salvage therapy in NMIBC

When considering the recommendations in this section, note that for selected patients with recurrent low-volume/low-grade disease, office fulguration is a potentially efficacious strategy that is often overlooked. Evidence suggests that patients with small papillary tumours who have only had TaLG previously can safely undergo office fulguration.[107]

It should be recognized that there are many definitions in the literature for BCG failures: BCG-refractory, BCG-intolerant, and BCG relapse. For the purposes of this discussion, we have elected to use the following definitions:

- BCG-refractory: Any T1HG at three months or failure to achieve a high-grade disease-free state after six months following BCG induction with one cycle of maintenance.[108]
- BCG-relapse: Recurrence of high-risk disease after being disease-free (complete response) at six months from TURBT following induction and maintenance BCG. Relapse is substratified as early (within 12 months) or late (>12 months) with respect to last dose of BCG. [108]
- BCG-intolerant: Tumour recurs after less than an adequate course of therapy due to a BCG-related adverse event.[108]

A new disease state is evolving in the context of clinical trial design that is referred to as BCG-unresponsive, which includes BCG-refractory disease along with BCG relapse within six months of last BCG dose.

A. General recommendations

i. Always consider extravesical location of disease or understaging as possible reason(s) for treatment failure.

ii. Optimization of first-line therapy will decrease the risk of failure and the need for subsequent salvage therapy.

iii. Smoking cessation interventions should be offered to all patients.

iv. Determine risk category to help determine the choice of salvage therapy.

Discussion

There are several potential reasons for treatment failure. Consideration of which is the most likely cause in each scenario will help determine the subsequent course of treat-

ment. For example, there may have been inadequate staging with more advanced disease than appreciated that will not respond to further intravesical therapy (e.g., already muscle-invasive or metastatic [especially nodes], or there is occult disease in upper tracts or prostate urethra that is not in contact with the intravesical agents). In a retrospective analysis of 110 patients with high-risk NMIBC repeatedly treated with intravesical BCG, the investigators found that 57 cases (52%) of recurrences had upper tract and/or urethral carcinoma.[109]

Alternatively, the tumour may be resistant to the intravesical agent, in which case, intravesical therapy with a different agent may still be considered.

Optimization of first-line therapy includes some of the following considerations:

1. Ensure high-quality TURBT with muscle present in the specimen;
2. Repeat the TURBT in patients with T1HG bladder cancer or if the first TURBT was incomplete;
3. Administer appropriate maintenance intravesical therapy in all patients;
4. Do not discontinue first-line therapy prematurely (i.e., at three months) in patients with TaHG or CIS; and
5. Consider immediate cystectomy in the highest-risk patients, especially those with LVI and/or variant histology.

In order to reduce the risk of failing MMC, administration of MMC needs to be optimized. In meta-analyses comparing BCG to MMC, MMC administration was not optimized and no maintenance therapy was administered.[91,92,94] MMC use should include pharmacokinetic manipulations to increase drug concentration (i.e., 40 mg in 20 mL), reduce subsequent dilution by urine (i.e., limit patient fluid intake before administration and ensure empty bladder at start of instillation), and alkalinization of the urine to stabilize the drug.[110] The benefit of maintenance intravesical chemotherapy has not been shown definitively, but limited evidence does support its use, including one prospective randomized trial comparing induction BCG in one arm to induction mitomycin in a second arm and induction mitomycin with three years of monthly maintenance in a third arm.[111]

Every patient should be asked if he/she is a smoker and, if so, referred to a smoking cessation program. There is evidence that cessation lowers risk of recurrence and, possibly, of progression.[112]

Patients being considered for salvage therapy can be stratified into three groups based on the stage/grade of tumour at the time of salvage therapy: intermediate-risk (TaLG), high-risk (TaHG, CIS) and very high-risk (T1HG).

B. Recommendations for intermediate-risk patients (recurrent or multifocal TaLG or size >3 cm)

i. Best salvage is often aggressive TURBT + postoperative mitomycin + close surveillance (cystoscopy every three months; office fulguration for small recurrences), especially if recurrences occur less than once per year. This avoids the overuse of intravesical therapy.
ii. If prior MMC, then use BCG for salvage (full dose with 12 months maintenance).
iii. If prior BCG, then use MMC for salvage (weekly for six weeks, then monthly up to 12 months).
iv. There is little evidence to guide the sequence of the other potential options in BCG-refractory patients. In no particular order of preference, these include: BCG re-induction and maintenance, BCG + interferon [IFN], EMDA/MMC + BCG, gemcitabine, docetaxel, epirubicin/doxorubicin, and MMC-hyperthermia.
v. If tumour continues to be resistant/refractory in this setting:
   - If patients continue to have recurrences, but less frequent and in lower numbers, it is still beneficial to continue therapy. We recommend waiting six months before changing therapy. Re-evaluate upper tracts.
   - If tumour relapses more than 12 months after finishing therapy, then re-treat with the same agent as last course.
   - If tumour relapses less than 12 months after finishing therapy, then re-treat with a different agent.
vi. Cystectomy should be considered in primarily unresectable or uncontrollable disease (e.g., multifocal tumours on every resection), or with other factors that make the patient high-risk (e.g., combination of large size, multiple, and frequent recurrences).

Discussion

Patients with recurrent/multifocal TaLG are at much lower risk of progression than TaHG, CIS, and T1 disease. According to the EORTC risk tables, the progression rate is in the range of 15–20%.[113]

The selection of salvage intravesical agents after BCG and MMC failure will depend primarily on the availability of treatments at different centers (e.g., EMDA) and the clinician's experience with different agents.

The efficacy of microwave hyperthermia in combination with intravesical chemotherapy has been demonstrated in several studies,[114-116] but this intervention is not currently available in Canada. Combination BCG/IFN α-2b has been shown to have potential for patients as an alternative to BCG alone (using a lower dose of BCG in the combination),[117] but its efficacy in BCG-refractory patients remains uncertain.[118,119] A recent prospective, randomized study reported in abstract form only indicated that BCG in combination with IFN may improve recurrence-free survival over BCG alone in BCG-naïve patients.[117]

There are no data on EMDA in the salvage setting. The recommendation to consider this agent is an extrapolation from its use as a primary adjuvant therapy.[98]

With respect to the recommendations for changing therapy, it should be noted that there is no consensus definition of treatment-resistant/refractory disease in the intermediate-risk setting. Also, the recommendation of a 12-month threshold for deciding whether or not to use the same agent or a different one is expert consensus that is based loosely on the findings of Joudi et al that BCG + IFN is as efficacious in patients who have failed BCG more than 12 months previously as it is in BCG-naïve patients.[119] Overall intermediate-risk patients are at relatively low risk of progression and there is little hurry to change therapy.

C. Recommendations for high-risk patients (TaHG and CIS)

i. Low-grade recurrences in patients receiving intravesical therapy for high-grade disease are not considered treatment failure.
ii. First-line therapy should always be BCG; persistence at three months should not lead to initiation of salvage therapy.
iii. BCG-refractory disease (persistence at six months) requires salvage therapy.
iv. Relapse within 12 months after last dose of BCG requires salvage therapy.
v. Relapse beyond 12 months after last dose of BCG should be treated with repeat induction and maintenance BCG or BCG/IFN.
vi. Radical cystectomy is recommended as the first-line salvage therapy for all patients with BCG-refractory high-risk bladder cancer or BCG-relapsing high-risk disease within 12 months of the last BCG dose.
vii. If a patient is ineligible for radical cystectomy or prefers an additional course of intravesical therapy, the following options can be considered (in no order of preference): BCG re-induction and maintenance, BCG + IFN, EMDA/MMC and BCG, gemcitabine, docetaxel, epirubicin/doxorubicin, and MMC-hyperthermia.
viii. The risk of progression rises with each subsequent course of salvage intravesical therapy, so that all eligible patients should be encouraged to reconsider radical cystectomy upon recurrence following one course of salvage therapy.

Discussion

If a patient with TaHG or CIS on BCG therapy and has persistent (but not progressive) disease at three months, maintenance therapy should be continued. CIS does not require re-biopsy at the three-month time point, but any papillary disease should be resected.

The recommended treatment for patients with BCG-refractory, high-risk disease is radical cystectomy. Any subsequent salvage intravesical therapy is associated with an increased risk of disease progression. However, some patients will be medically unfit for cystectomy, and others will prefer a course of salvage therapy despite the inherent risk. The risk of progression increases with every course of salvage intravesical therapy.[120] As such, one should avoid using more than one salvage therapy, unless cystectomy is not an option.

Furthermore, the patient and treating practitioner must recognize that the likelihood of remaining recurrence-free after one year of salvage intravesical therapy is only approximately 15–30%.

Patients with persistent disease at six months are at risk for progression, but the short-term risk is relatively low. Many practitioners delay cystectomy to provide one course of salvage intravesical therapy based on studies that suggest that progression and mortality rates do not start to rise until after one year.[121-123] In one analysis by Jäger et al involving 278 patients with high-risk NMIBC, the five-year rates of cancer-specific survival were 86% for those who underwent cystectomy during the first four months, 83% among those whose cystectomy was performed from month five to one year, and 72% for those whose cystectomy was performed after one year or more.[123]

With respect to the individual treatments listed, no level 1 evidence is available for any of these in the salvage setting, and the points discussed above apply here also.

Evaluation of the various options for BCG failures has shown that radical cystectomy leads to two-year recurrence-free survival rates (40–90%) that are higher than those reported for salvage intravesical therapies (8–55%).[124,125]

D. Recommendations for very high-risk patients (T1HG)

i. Recurrence or persistence of T1HG bladder cancer at any time on BCG therapy (including at the three-month time point after induction BCG) or within 12 months of the last BCG dose is an indication for radical cystectomy (Grade B).
ii. Re-TURBT and additional intravesical therapy should only be considered if the:
    - Patient is not suitable for cystectomy; or
    - Recurrence more than 12 months after last tumour (Grade C).

Discussion

The risk of progression is markedly higher in patients with BCG-refractory T1HG bladder cancer, and any delay for salvage intravesical therapy puts the patient at undue risk.[126,127]

Concomitant CIS or lymphovascular invasion (LVI) are additional adverse risk features that should encourage radi-

cal cystectomy in the first-line or subsequent salvage settings. The results from Joudi et al suggest that re-induction with BCG plus IFN is safe if a patient recurs more than 12 months after the last BCG dose,[119] but radical cystectomy also remains an important treatment option in these patients.

E. Recommendations for BCG-intolerant recurrent bladder cancer

i. Immediate cystectomy should be considered in all patients with BCG-intolerant very high-risk disease.
ii. EMDA-MMC was shown to be equivalent to intravesical BCG in one trial and should be considered a valid option if available.
iii. Radical cystectomy is recommended in patients failing EMDA-MMC.
iv. If a patient is ineligible for radical cystectomy or prefers an additional course of intravesical therapy, the following options can be considered (in no order of preference): MMC, gemcitabine, docetaxel, epirubicin/doxorubicin, and MMC-hyperthermia.

IV. Prostatic urethral disease

A. Recommendations for investigations

i. Consider prostatic urethral biopsy if: (Level III–Grade C)
   - Positive urine cytology with no visible bladder tumour.
   - Tumour at trigone/bladder neck or presence of bladder CIS or multiple high-risk bladder tumours.
ii. Obtain upper tract imaging to exclude upper tract urothelial carcinoma. (Level III–Grade C)
iii. Perform staging studies if invasion into prostatic ducts, acini, or stroma. (Level III–Grade C)

Discussion

The consideration of a prostatic urethral biopsy for patients with positive urine cytology with no visible bladder tumour is supported by a study involving 276 male patients with NMIBC (242 males), among whom 36 had recurrence in prostatic urethra (26 with macroscopic tumours and 10 with CIS).[128]

CIS in the prostatic urethra has been identified in 9–25% of patients with high-risk bladder tumours (stages Ta/T1).[129-131] Given that these can evolve into prostatic stromal disease if left undiagnosed and untreated, it is reasonable to consider TURP biopsy among these patients. Importantly, prostatic urethral involvement is associated with understaging in NMIBC. In one series, understaging was reported among 53% of those with prostatic urethral positivity compared to only 20% among those without involvement.[132] Staging studies are recommended if there is invasion into ducts, acini, or stroma, as it may alter the prognosis and management.[133-136]

B. Recommendations for management

i. TURP should be performed if BCG is administered (Level III–Grade C).
ii. Consider re-TURP post-BCG (Level IV). If P0 post-BCG induction, then maintenance BCG is recommended.
iii. Radical cystoprostatectomy and BCG are options for ductal involvement (Level III–Grade C).
   - Focal ductal – BCG recommended (Level IV).
   - Non-focal ductal – radical cystoprostatectomy recommended (Level IV).
   - Consider simultaneous urethrectomy if non-orthotopic diversion performed (Level IV)
     - If ductal or stromal disease – default should be urethrectomy.
   - Routine biopsies of prostatic urethra prior to radical cystoprostatectomy are not required (Level III).
iv. If prostate stromal involvement (cT4a) and the patient is a radical cystectomy candidate consider: (Level III–Grade C)
   - Perioperative systemic chemotherapy.
   - Concomitant urethrectomy.

Discussion

Performing a TURP opens the bladder neck to allow BCG contact with the prostate urethra, improves the accuracy of disease staging, and is preferred prior to BGC administration.[137] There is very limited evidence to guide recommendations for patients with ductal involvement; current evidence consists of small series of fewer than 10 patients each.[138-140] While TUR biopsies of the prostatic urethra can provide information to complement staging and support clinical decision-making prior to radical cystoprostatectomy, it does lack sensitivity and specificity and should not be considered mandatory. The pattern of invasion on TURP biopsy does not always correlate with cystectomy pathology in clinical studies.[141,142]

In patients undergoing radical cystectomy, involvement of the prostatic urethra with high-grade disease, including CIS, is associated with an increased risk of subsequent urethral recurrence. This risk does not necessarily prohibit orthotopic diversion, provided the urethral margin is free of disease, but it does suggest that urethrectomy should be performed in patients undergoing heterotopic diversion.

V. Immediate postoperative intravesical chemotherapy

A. Recommendations

i. Recurrence reduction is best for low-risk bladder tumours (Level IA–Grade A).
ii. Benefit is unclear for high-risk bladder tumours (Level IB–Grade A).
iii. MMC, epirubicin, and doxorubicin all show beneficial effect (Level IA–Grade A).
iv. Within six hours (and up to 24 hours), immediate instillation is optimal (Level III–Grade C).
v. Do not instill if there is suspected bladder perforation, extensive TUR, or resection of orifice (Level III–Grade C), as significant complications can occur.
vi. Weigh risks of single instillation vs. morbidity of small, low-risk tumour recurrences that can often be managed by office fulguration (Level III–Grade C).

Discussion

The first meta-analysis of postoperative intravesical chemotherapy research was published in 2004 and included seven randomized trials with recurrence data for a total of 1476 patients.[143] The conclusion of this analysis was that a single immediate postoperative instillation of chemotherapy decreases the risk of recurrence by 11.7%. An updated meta-analysis, published in 2013, included data from 13 studies and 2548 patients.[144] Overall, the key finding was that postoperative intravesical chemotherapy significantly prolonged the recurrence-free interval by 38% (HR: 0.62; 95% confidence interval [CI], 0.50–0.77; p<0.001). Based on these data, nine patients need to be treated to prevent one bladder tumour recurrence in the first year.[144] However, according to the authors of the recent meta-analysis, there was a high risk of bias in the studies included, which calls the clinical relevance of the statistical findings into question. The specific limitations included significant heterogeneity within studies, significant heterogeneity between studies, lack of individual patient data, and lack of quality control on TURBT. In a multicentre, randomized trial of 305 patients with primary and recurrent tumours with low- and intermediate-risk (pTa/T1, G1/2), patients received either epirubicin or no treatment.[145] Overall, there was significant benefit observed in favour of active treatment (HR for recurrence 0.56, p=0.002). However, subgroup analysis showed that the benefits were restricted to low-risk patients. Those with primary, solitary tumours derived substantial benefit, while no benefits were observed in patients with recurrent or multiple tumours. Similarly, patients with a low EORTC risk score (0–2) benefited significantly from epirubicin treatment, while those with a score of 3 or higher did not.

A recent individual randomized, placebo-controlled, multicentre, double-blinded trial of single-instillation gemcitabine among 328 patients with histologically confirmed NMIBC (pTa/pT1,G1-3) was recently published.[146] In this study, there was no observed difference in recurrence-free survival between the treatment and placebo arms. Another randomized study of 404 patients treated with single-instillation epirubicin or placebo following TURBT showed that active chemotherapy prevented only small recurrences (1–5 mm), with no significant impact on those larger than 5 mm.[147]

With respect to timing of instillation, an analysis of factors determining new recurrences observed that there was a greater than two-fold relative risk for a new recurrence if the first instillation of chemotherapy (MMC in this study) was given later than on day 0.[148]

For patients with recurrent disease, evidence to support the repeated administration of intravesical chemotherapy with every recurrence is lacking. However, for those with infrequent recurrences (less than one per year), one can consider retreating.

There is evidence arguing against the use of intravesical chemotherapy in patients planned for receiving BCG. In a trial comparing the use of postoperative intravesical epirubicin plus delayed instillation of BCG vs. delayed BCG alone (among 161 patients with NMIBC), there were no significant between-group differences in recurrence rates or time to recurrence.[149]

The efficacy and safety of postoperative intravesical chemotherapy has also been compared to continuous saline bladder irrigation (CSBI) in a retrospective, non-randomized analysis involving 238 patients.[150] In that study, there was no significant difference between groups in terms of tumour recurrence, while the CSBI treatment was associated with fewer local toxicities.

Postoperative instillation of chemotherapy has also been evaluated in a head-to-head study compared to preoperative EMDA MMC or to TURBT alone among 374 patients with primary intermediate- or high-risk NMIBC.[151] The preoperative EMDA MMC was associated with lower rates of recurrence and a higher disease-free interval compared to postoperative MMC instillation (passive diffusion).

The most common complications of intravesical chemotherapy are mild cystitis, frequency, urgency, mild hematuria, and skin irritation/rash.[144] While these are generally mild to moderate in severity, complications can be more severe for those individuals with unrecognized bladder perforation. Pelvic pain, urinary retention, and severe lower urinary tract symptoms can result from intravesical chemotherapy in these individuals.[152]

VI. Surveillance of NMIBC

A. Recommendations

i. Cystoscopy should be performed every three months for the first two years, every six months for the next two years, then annually thereafter (Level III–Grade C).
   1. For all cases, cystoscopy must be performed at three months.
   2. For low-risk disease, one may omit the six- and nine-month cystoscopies in the first year and schedule them annually thereafter.

ii. Image upper tract for high-risk NMIBC every one to two years (Level III–Grade C). CT urogram is the preferred modality for upper tract imaging (Level IIB).

iii. Urinary cytology is recommended with cystoscopy (Level IIB).

iv. It is unclear if urinary markers provide significant additional information to facilitate detection and management (Level III), but a positive urine marker test leads to a better quality cystoscopic examination (Level IB).

v. PDD may reduce tumour recurrences. The value of PDD with respect to long-term recurrence, progression, and survival has not been demonstrated, and costs must be considered (Levels IIA & III).

vi. Narrow-band imaging may improve cancer detection and tumour recurrence rates, but the value with respect to long-term recurrence, progression, and survival has not been demonstrated (Level II).

Discussion

The importance of the three-month cystoscopy has been demonstrated by several investigators.[153] A retrospective study of 414 patients with TaG1-2 disease demonstrated that if the three-month cystoscopy is negative, 80% remain free of recurrence.[154] Recurrence at three months has also been associated with a greater than three-fold risk of progression.[155] For patients with TaLG, evidence shows that there is low risk of recurrence at six and nine months when the three-month cystoscopy is normal (4.3% and 2.7% recurrence rates for six and nine months, respectively).[156] As there is a long-term, lifelong risk of recurrence[157,158] long-term followup should continue. After five years, adjunctive testing (e.g., microhematuria dipstick) can be considered as an alternative to cystoscopy for low-risk disease.

With respect to upper tract imaging, evidence shows that risk of upper tract tumour recurrences increases during followup in high-risk bladder tumours.[159] The time to recurrence has varied in published studies, from 43.5–87.6 months. The frequency of upper tract imaging for these high-risk patients should be at least every two years.[153] CT urogram is the test of choice for evaluation of the upper tract.[160] If this is not available, intravenous pyelogram is a reasonable alternative.

Urinary cytology has a specificity of greater than 90% in experienced hands, but has limited sensitivity.[161] Urinary bladder tumour markers could, in principle, be useful for monitoring bladder cancer recurrence, reducing the need for cystoscopies.[162,163] However, inadequate sensitivities and specificities of these tests have limited their clinical impact for this purpose.[164] Positive urine marker tests have been shown to lead to better quality cystoscopic examinations.[165]

Fluorescence cystoscopy (PDD) has a higher sensitivity and lower specificity compared to white-light cystoscopy; false positives can occur with inflammation, recent TUR or within 3 months of BCG.[166-169] Similarly, several randomized trials have evaluated narrow band imaging (NBI) and demonstrated improved cancer detection rate compared to WLC.[170-173] Both NBI and PDD have shown increased tumour detection and decreased recurrences compared to WLC TUR. However, impact on long-term recurrences and progression has not been demonstrated.

VII. Perioperative chemotherapy for muscle-invasive bladder cancer (MIBC)

A. Recommendations

i. Patients with MIBC who are eligible for neoadjuvant chemotherapy should be either referred preoperatively to medical oncology or discussed in a multidisciplinary setting for consideration of perioperative chemotherapy.

Discussion

Deaths from invasive urothelial carcinoma are generally a result of metastatic disease. Systemic therapy can play a key beneficial role in eradicating micrometastatic disease and improving cure rates. To date, the uptake of perioperative chemotherapy has been increasing, but remains underused in the setting of MIBC.[174] This may be due to a number of factors, including a perception that the benefits are inadequate to justify its use, patient comorbidities, a lack of available resources for timely consultation, and a lack of referrals from other professionals to medical oncology.

Candidates included in the neoadjuvant chemotherapy trials (based on the findings of a meta-analysis evaluating 11 trials of neoadjuvant chemotherapy involving more than 3000 patients[175]) are primarily those patients who are younger than 80 years, have adequate performance status (0–1), have adequate renal function (eGFR >60 mL/min/1.73 m^2), and

no comorbidities that preclude cisplatin use. Select centres still administer cisplatin-based neoadjuvant chemotherapy in patients with eGFR as low as 50 mL/min/1.73 m^2. Although all patients with MIBC can be offered neoadjuvant chemotherapy, eligible patients with high-risk features (presence of hydronephrosis, LVI, prostatic stromal invasion, or small cell/micropapillary features) have been found to derive the most benefit from neoadjuvant chemotherapy.[175,176] Some centres have recommended neoadjuvant chemotherapy for patients with MIBC regardless of risk features, while other centres have advocated neoadjuvant chemotherapy only in MIBC patients with high-risk features to avoid overtreatment and toxicity.

Lastly, it is important to ensure expedient evaluation and delivery of neoadjuvant chemotherapy; consultation with medical oncology should occur within two weeks of referral and chemotherapy should start within one to two weeks of consultation.[177]

ii. Neoadjuvant therapy is preferred to adjuvant therapy based on current evidence.

Discussion

The evidence in support of neoadjuvant therapy includes an international, multicentre trial of 967 patients randomized to three cycles of cisplatin, methotrexate, and vinblastine (CMV) therapy or no chemotherapy prior to definitive local management (either cystectomy or radiotherapy [RT]).[178] Mean followup was eight years. In this study, the 10-year overall survival was 36% for the neoadjuvant group and 30% for the control group ($p<0.05$).

A smaller (n=317) SWOG study involving 317 patients with T2 to T4a disease evaluated the effects of three cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) compared to no chemotherapy prior to cystectomy.[176] The median survival reported in this study was 77 months for the neoadjuvant group and 46 months for the group undergoing cystectomy alone ($p=0.06$).

There have also been three meta-analyses of neoadjuvant chemotherapy, each of which concluded that cisplatin-based combination therapies are efficacious for improving overall survival.[175,179,180]

There is also evidence of benefit of adjuvant chemotherapy. However, the data are not as compelling as those for neoadjuvant therapy, with evidence available only for trials involving smaller numbers of patients with varying chemotherapeutic regimens. Two trials have reported a survival benefit. The first included 91 patients with T3, T4, or node-positive disease.[181] Following cystectomy, they were randomized to four cycles of cisplatin, doxorubicin and cyclophosphamide, or observation. The median survival was 4.3 years for the adjuvant group vs. 2.4 years for observation ($p=0.006$). This trial may, however, have been limited by selection bias; only 91 of 498 patients screened were eligible to participate.

The second positive study included 49 high-risk patients randomized to adjuvant chemotherapy or placebo. The chemotherapy was either MVAC or methotrexate, vinblastine, epirubicin and cisplatin (MVEC).[182] This study was terminated early after an interim analysis showed significantly improved three-year survival (63% vs. 13%, $p=0.002$). A subsequent followup analysis showed that there is a persistent benefit of adjuvant chemotherapy, as the 10-year progression-free survival rates were 44% vs. 13% ($p=0.002$) and 10-year tumour-specific survival was 42% vs. 17% ($p=0.007$).[183] The 10-year overall survival difference was not significant (27% vs. 17%, $p=0.07$).

More recently, the EORTC 30994 study randomized 284 patients with T3, T4, or node-positive disease to adjuvant treatment or deferred chemotherapy only upon relapse.[184] After a median followup of seven years, the absolute mortality rates were 47% for the adjuvant treatment group and 57% for the delayed treatment group. However, the difference was not statistically significant (adjusted HR 0.78, 95% CI 0.56–1.08; $p=0.13$). There was, however, a significant improvement in progression-free survival (HR 054, 95% CI 0.4–0.73; $p<0.0001$). Five-year progression-free survival rates were 47.6% in the adjuvant group and 31.8% in the deferred group.[184]

A meta-analysis of nine adjuvant studies involving a total of 945 patients concluded that there was a significant benefit of adjuvant cisplatin-based therapy in terms of overall survival (hazard ratio [HR] 0.77, 95% CI 0.59–0.99) and disease-free survival (HR 0.66, 95% CI 0.45–0.91); however, the power of the meta-analysis was limited.[185] Based on the meta-analysis, the best candidates for adjuvant therapy would include T3/4 and those with node-positive disease.

With respect to timing, patients should be referred to medical oncology within two to four weeks post definitive local therapy and initiation of chemotherapy within 10–12 weeks from surgery.

iii. Chemotherapy should be cisplatin-based combination therapy for three to four cycles. Evidence on the benefit of neoadjuvant chemotherapy is primarily based on the MVAC regimen.

Discussion

There is no evidence to support the superiority of any particular regimen for perioperative chemotherapy. However, all of the existing positive evidence is for cisplatin-based combination regimens. If the patient is cisplatin-ineligible, carboplatin should not be substituted, as there is no evidence to suggest this would be an effective therapeutic choice.

The number of cycles will depend on the regimen chosen. The impact of treating with fewer than planned number of

cycles (e.g., cessation due to toxicity) is not known, although even one or two cycles may be expected to have some activity against micrometastatic disease. Some institutions have advocated for dense-dose MVAC due to its decreased toxicity and shorter duration to avoid significant delays to cystectomy. Dense-dose MVAC may be an optimal regimen in the neoadjuvant setting. Gemcitabine and cisplatin is a reasonable alternative. If the patient is not cisplatin-eligible, there is no evidence to support administration of an alternative regimen, which would have unproven efficacy and could negatively impact survival by delaying cystectomy.

iv. If a patient did not receive neoadjuvant chemotherapy but is eligible for cisplatin-based chemotherapy postoperatively, adjuvant therapy can then be considered based on pathologic parameters and patient status.

Discussion

The recent meta-analysis of adjuvant chemotherapy[185] supports this approach in those who did not receive neoadjuvant chemotherapy, but the strength of evidence is still better for neoadjuvant therapy. Patients with extravescial extension (pT3/4) and/or lymph node involvement (pN1-3) potentially benefit most from adjuvant chemotherapy.

VIII. Surgical quality and outcomes

A. Recommendations on extent of surgery

i. In males, standard open radical cystectomy includes removal of the tumour-bearing bladder, prostate, seminal vesicles, and distal ureters (Level III–Grade C).
ii. In females, standard open radical cystectomy involves anterior pelvic exenteration, including the removal of tumour-bearing bladder, entire urethra (except in patients undergoing orthotopic bladder substitution), anterior vagina, uterus, ovaries, and distal ureters (Level III–Grade C).
iii. In males with excellent preoperative erectile function and clinically organ-confined disease (i.e., ≤cT2N0M0), nerve-sparing radical cystectomy should be considered (Level III–Grade C).
iv. In males, technical variations on classic nerve-sparing approaches (i.e., prostate-sparing, apical-sparing) aimed at improving functional outcomes should not be performed due to oncologic risk (Level III–Grade C).
v. In general, reproductive organ preservation in females should not be performed due to oncologic risk (Level III–Grade D). However, in females with non-palpable, anteriorly located, clinically organ-confined disease (i.e., ≤cT2N0M0), reproductive organ preservation aimed at improving functional outcomes may be performed.
vi. Urethrectomy should be performed in patients with invasive carcinoma at the urethral margin at radical cystectomy (Level III–Grade B).

Discussion

These recommendations are largely based on the 2013 recommendations of the EUA[186] and an evidence-based review conducted by the International Consultation on Urological Diseases for the treatment of MIBC.[187]

With respect to nerve-sparing cystectomy in males, the evidence supporting this recommendation includes a retrospective analysis of 101 patients with clinically organ-confined bladder cancer.[188] In this study, the procedure was associated with acceptable cancer control and erectile functional preservation outcomes.

The recommendation not to use technical variations on classic nerve-sparing approaches for men is based on the observation that patients undergoing radical cystectomy for bladder cancer are at high risk for several other genitourinary (GU) cancers, including a 38% risk of prostate adenocarcinoma (including 8% risk of clinically significant prostate adenocarcinoma), prostatic urothelial carcinoma (21% risk) and high-grade prostatic intraepithelial neoplasia (51.2%).[189]

For women, the recommendation that reproductive organ preservation can be considered in selected patients only is based largely on a retrospective analysis of 411 female patients with urothelial carcinoma who underwent anterior pelvic exenteration.[190] In this cohort, the risk of female reproductive organ involvement was relatively low, at 7.5%. The preoperative clinical variables associated with reproductive organ involvement were hydronephrosis and a palpable mass.

In published analyses, the risk of urethral occurrence has ranged from 3.7–8.1% among men and 0.8–4.3% among women.[191-193] Frozen section analysis (FSA) of the urethral margin at radical cystectomy, despite its limitations, is the best predictive parameter (sensitivity and specificity, 100%), and is therefore suggested for men with a history of prostatic urethral disease who do not consent for urethrectomy.

B. Recommendation on alternative surgical approaches

i. Laparoscopic and robot-assisted radical cystectomy are alternative surgical options to open radical cystectomy. Current data have not demonstrated clear advantages or disadvantages in terms of cancer control and functional outcomes of these minimally invasive surgical approaches. (Level III–Grade C)

Discussion

To date, there have been only two published randomized studies evaluating robot-assisted radical cystectomy with extra-corporeal urinary diversion compared to open radical cystectomy.[194,195] No significant difference was found between groups with respect to postoperative complications or duration of hospital stay. At the time of publication, there were no oncologic or functional outcomes yet available.

C. Recommendations on extent of lymph node dissection (LND)

i. Increasing the extent of LND appears to be associated with better outcome and overall survival after radical cystectomy. (Level IIB/III–Grade B).
ii. Any type of LND provides cancer control benefit compared to no LND. However, a more extensive LND is associated with superior cancer control outcomes compared to lesser degrees of LND (Level III–Grade B).
iii. Extended LND should be performed to include nodes to at least where the ureter crosses the common iliac vessels. All lymphatic tissues in the common iliac, external iliac, internal iliac, obturator, and presacral regions should be removed (Level III–Grade B).
iv. Super-extended LND (up to the proximal boundary of the inferior mesenteric artery) should be considered optional, as it likely only benefits a small subset of radical cystectomy patients, if any (Level IIB–Grade B).

Discussion

In a systematic review of LND among patients undergoing radical cystectomy for bladder cancer, the authors observed that seven out of seven studies favored LND in terms of better cancer control outcomes.[196] With respect to the number of nodes dissected, in a secondary analysis of 268 patients who underwent radical cystectomy in the SWOG 8710 randomized trial of neoadjuvant M-VAC + surgery vs. surgery alone, removal of fewer than 10 nodes was independently associated with an increased risk of local recurrence and mortality compared to removal of 10 or more nodes.[197] In terms of the extent of dissection, there is some evidence that extended dissection is superior to standard dissection in terms of cancer outcomes.[198]

D. Recommendations on urinary diversion

i. The type of urinary diversion does not affect cancer control outcome (Level III–Grade C).
ii. An orthotopic bladder substitute should be offered to male and female patients who lack any contraindications and who have no tumour in the urethra (Level IIB/III–Grade B).

Discussion

Ileal conduit is the most common type of urinary diversion. Neobladder diversion is used more frequently at radical cystectomy centres of excellence. Continent cutaneous diversions are usually reserved for specific indications.[199-201]

Absolute contraindications to orthotopic bladder substitution are: disease at urethral margin, renal insufficiency (glomerular filtration rate <50 mL/min), and severe hepatic dysfunction.[202] Relative contraindications include: intestinal dysfunction, stress urinary incontinence, sphincter dysfunction, multiple/recurrent urethral strictures, and mental or physical impairment precluding ability to self-catheterize.[202]

E. Recommendation on surgical margin status

i. Surgeons performing radical cystectomy should achieve a positive soft tissue surgical margin rate of less than 10% (Level III–Grade C).

Discussion

Positive soft tissue surgical margins at radical cystectomy are independently associated with an increased risk of local recurrence and mortality. A secondary analysis of 268 patients who underwent radical cystectomy in the SWOG 8710 randomized trial of neoadjuvant M-VAC + surgery vs. surgery alone showed that positive soft tissue surgical margins were independently associated with an increased risk of local recurrence (odds ratio [OR] 11.2, 95% CI 3.3–37.8, p=0.0001) and mortality (OR 2.7, 95% CI 1.5–4.9, p=0.0007).[197]

Positive margin rates in published cohort studies and clinical trials from international centres of excellence have ranged from 1–10%,[197,200,203-206] informing our decision to strive for positive margin rates of <10%.

F. Recommendations on perioperative morbidity and mortality

i. Complications after radical cystectomy should be reported using the modified Clavien grading system (Level II–Grade B).
ii. The perioperative followup interval for reporting complications should be a minimum of 90 days (Level III–Grade C).
iii. Centres performing radical cystectomy should attempt to achieve an overall 90-day mortality rate <5% (Level III–Grade C).

Discussion

The Clavien grading system used to classify postoperative complications is as follows:[207]

0. No event observed.
1. Use of oral medications or bedside intervention.
2. Use of intravenous medications, total parenteral nutrition, enteral nutrition, or blood transfusion.
3. Interventional radiology, therapeutic endoscopy, intubation, angiograph, or operation.
4. Residual and lasting disability requiring major rehabilitation or organ resection.
5. Death of patient.

Overall, reported 90-day mortality rates in published cohort studies and clinical trials from international centres of excellence ranged from 2.7–4.2%.[203,206-208] Predictors of 90-day mortality include advanced chronologic age and higher comorbidity status.[209]

IX. Bladder preservation approaches with focus on trimodal therapy

A. Recommendation

i. In the management of urothelial MIBC, patients should be referred to a multidisciplinary centre or otherwise discussed in a multidisciplinary setting to ensure that curative treatment with TURBT followed by chemo-radiation is consistently considered for:
   1. Patients who are not suitable for cystectomy; and
   2. Patients who refuse cystectomy and request bladder conservation.

Discussion

The standard for the curative management of MIBC is neoadjuvant chemotherapy followed by radical cystectomy. An established alternative for patients unable or unwilling to undergo cystectomy, and who accept the possibility of a slightly lower survival probability is trimodal bladder-conserving therapy that includes TURBT, radiation, and chemotherapy. Bladder preservation with radiotherapy alone is clearly inferior to trimodal therapy with respect to cancer control and survival and should only be considered an option in patients ineligible for radiosensitizing chemotherapy. Five-year disease-specific survival with trimodal therapy in well-selected patients has been reported to be from 45–64%.[210-215] Most data are based on limited followup (<5 years).

The performance of a complete and thorough TURBT is known to improve treatment outcomes. In an analysis of 348 patients with cT2-4a disease, those with visibly complete TURBT had five- and 10-year survival rates of 57% and 39%, respectively, both significantly higher than the 43% and 29% five- and 10-year survival rates among those without visibly complete TURBT.[214] While it is likely that the extent of the TURBT is as much a reflection of the initial local tumour burden as it is of therapeutic benefit, sound oncological principles and the referenced data support carrying out maximal resection.

As with surgery, there are several important aspects of radiotherapy that combine to maximize tumour-free bladder preservation rates with reduced toxicity. These include target volumes (whole or partial bladder, extent of nodal irradiation), dose fractionation, and treatment delivery accuracy. While the available data to date do not demonstrate differences in survival or bladder preservation rates with limited or more extensive target volumes, the importance of nodal dissection in the context of cystectomy makes it prudent to strongly consider some degree of elective nodal irradiation.

The established role for chemotherapy in trimodal treatment is in the concurrent administration of drugs during radiotherapy for additive tumour cell kill and, more importantly, radiosensitization purposes. Two phase III trials have shown that concurrent cisplatin alone[216] or 5-FU plus MMC[212] during radiotherapy is superior to radiotherapy alone in initial tumour eradication and eventual reduction of bladder tumour recurrence, resulting in superior bladder preservation rates. Other agents that have been investigated concurrently with radiation include gemcitabine and paclitaxel. Neither neoadjuvant nor adjuvant chemotherapy have yet demonstrated a benefit to concurrent chemo-RT, and the potential increased toxicity of neoadjuvant/adjuvant treatment limits their utility based on the RTOG trials. Role of neoadjuvant/adjuvant chemotherapy warrants further evaluation in patients treated with trimodal therapy.

Patients participating in reported clinical trials of trimodality treatment have included many carefully selected, favourable-risk patients and the best outcomes are obtained in these appropriately chosen patients (T2 disease, visibly complete TURBT, bladder free of extensive CIS, and no hydronephrosis). However, patients either not suitable for or who decline cystectomy, may still derive some benefit from trimodal therapy even if they do not meet these favourable selection criteria. Five-year survival for patients with T3-T4 disease was shown to be 53% (compared to 74% for T2 disease) in a single-centre study.[217] Multifocal CIS patients are not good candidates for radiotherapy.

Published analyses of trimodal approaches demonstrate a low incidence of chronic GU and gastrointestinal (GI) grade 3 toxicities. In four trials conducted by the RTOG group, after a median followup of 5.4 years, grade 3 GI toxicity was observed in 1.9% of patients and grade 3 GU toxicity in 5.7% (severe frequency or dysuria, frequent hematuria, reduction in bladder capacity [<150 mL]).[215] In this analysis, there was no significant difference in toxicity noted between subgroups younger or older than 65 years. Patient satisfaction with bladder function is the ultimate

barometer, but there is additionally some limited objective evaluation of this function in the literature. In a 32-patient series, urodynamic evaluation following trimodality treatment demonstrated normal function in 24 of 32 patients, decreased bladder compliance in seven, and two patients had bladder hypersensitivity, involuntary detrusor contractions, and incontinence.

X. Perioperative management of cystectomy patients

A. Recommendations on preoperative preparation

i. All patients undergoing a radical cystectomy should be involved in a multidisciplinary planned pre/peri/postoperative program (Early Recovery After Surgery [ERAS], formal care plans, etc.) to minimize operative morbidity and complications (Level II–Grade C).

ii. Patients should receive routine dedicated preoperative counseling and education including (Level III–Grade A):
- Surgical details.
- Hospital stay and discharge criteria in oral and written form.
- Stoma education.
- Preoperative nutritional counseling.
- Potential risks and complications of surgery.

iii. All patients must be assessed and provided optimal preoperative optimization of medical conditions, including (Level IV):
- Consideration of preoperative evaluation, if necessary, by anesthesia, internal medicine, cardiology, and hematology.
- Correction of anemia should be considered.
- Preoperative nutritional support should be considered, especially for malnourished patients.
- Counseling of patients to reduce modifiable operative risk factors: (e.g., smoking cessation, reduction of alcohol intake four weeks prior to surgery, encourage physical activity with or without physiotherapy consultation).

iv. Bowel preparation can usually be safely omitted (Level I–Grade C).

v. Compressive stockings and intermittent pneumatic compression devices can further decrease the risk of thrombosis. Extended prophylaxis with low-molecular-weight heparin (LMWH) for four weeks should be carried out in eligible patients.

Discussion

Enhanced recovery protocols, such as ERAS[218] have proven to be effective, reducing postoperative morbidity, use of analgesics and time spent in the intermediate care unit, and improving quality of life.[219,220]

With respect to preoperative nutrition, up to 33% of urology patients undergoing surgery are at nutritional risk.[221] Preoperative malnutrition independently increases the mortality rate,[222] but its impact on morbidity has not been studied. Preoperative oral nutritional support is helpful in patients undergoing major GI procedures,[223] and its role in reducing morbidity and mortality in urology remains unknown. In general, however, preoperative carbohydrate loading should be administered to all non-diabetic patients.

Studies investigating the utility of bowel preparation found no significant benefits with respect to morbidity or length of hospital stay in those who received bowel preparation when compared to those who did not prior to radical cystectomy and ileal conduit.[224,225] While bowel preparation is not typically indicated, it is recommended prior to Indiana pouch procedures or other urinary diversions using colon.

The incidence of clinically significant deep vein thrombosis after cystectomy is approximately 5%.[226] For all major pelvic surgeries, thromboprophylaxis using low molecular weight or unfragmented heparin is recommended to reduce this risk.[227] Prolonged thromboprophylaxis for up to four weeks after oncological pelvic surgery significantly decreases the incidence of delayed-onset, symptomatic deep vein thrombosis when compared to in-hospital prophylaxis, without increasing the risk of bleeding complications. The addition of compressive stockings and intermittent pneumatic compression devices can further decrease the risk.[227]

With respect to nutrition, the literature from colorectal surgery show that preoperative carbohydrate loading has been associated with decreased thirst and insulin resistance and with helping to maintain lean body mass and muscle strength.[228] Carbohydrate loading in diabetic patients is safe, although the impact on glycemic control on outcome remains to be studied.

Solid food intake up to six hours and clear liquids up to two hour before induction is acceptable and recommended by European guidelines.[228]

B. Recommendations on perioperative management

i. A well-functioning thoracic epidural analgesia is superior to systemic opioids in relieving pain and should be continued for 72 hours after surgery (Level III–Grade B).

ii. Patients should receive antimicrobial prophylaxis one hour before skin incision (Level II–Grade A).

iii. Skin preparation with chlorhexidine-alcohol prevents/decreases surgical site infection (Level II–Grade A).

iv. A standard anesthetic protocol should be used to attenuate the surgical stress response, intraoperative maintenance of adequate hemodynamic control, central and peripheral oxygenation, muscle relaxa-

tion, depth of anesthesia, and appropriate analgesia (Level V–Grade D).

v. Fluid balance should be optimized by targeting cardiac output using the esophageal Doppler system or other systems for this purpose and by avoiding overhydration (Level V–Grade D).

Discussion

Thoracic epidural anesthesia at level Th9-11 until the third postoperative day has been associated with improved functional outcomes among patients undergoing radical cystectomy and intestinal urinary diversion.[229] Evidence in colorectal surgery also supports the use of epidurals to dampen the stress response, provide superior pain relief, hasten functional recovery, and to reduce cardiopulmonary complications.[230] In the colorectal setting, the optimal duration of epidurals is between 48 and 72 hours after surgery.[230] Given the similarities of colorectal and bladder surgery in terms of surgical trauma and postoperative pain, it seems justified to strongly recommend the use of thoracic epidural analgesia for 72 hours after cystectomy.

There is limited evidence to recommend an optimal choice and duration of antimicrobial prophylaxis. The AUA Best Practice Guidelines recommend choosing a second- or third-generation cephalosporin, aminoglycoside + metronidazole or clindamycin.[231] The American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) recommend using a first- or second-generation cephalosporin combined with metronidazole or a fluorquinoline/aminoglycoside and metronidazole or clindamycin.Treatments ideally should be started preoperatively within 60 minutes of incision. Although a single dose is probably sufficient, treatments may be re-dosed if the duration of the procedure exceeds two half-lives of the antimicrobial agent or there is excessive blood loss during the procedure.[232]

With respect to skin preparation, chlorhexidine-alcohol scrub has been associated with significantly lower rates of surgical-site infection compared to a povidone-iodine scrub and paint among 849 patients undergoing clean-contaminated surgery (9.5% vs. 16.1%; p=0.004; RR=0.59; 95% CI, 0.41–0.85).[233]

With respect to the fluid recommendation, it is thought that fluid excess or hypovolemia can provoke splanchnic hypoperfusion, which could then result in ileus, increased morbidity and length of stay. The recommendation to use goal directed fluid therapy (GDFT) with esophageal Doppler comes from evidence in rectal surgery;[234,235] there are little available data in cystectomy patients. One small study (n=66) among patients undergoing radical cystectomy demonstrated a reduced incidence of ileus and of nausea and vomiting at 24 and 48 hours.[236] Restrictive intraoperative fluid may also aid in the reduction of intraoperative blood, when combined with a low-dose continuous norepinephrine infusion. In a study of 166 patients, patients were randomized to receive continuous norepinephrine administration at 2 mcg/kg/hr and 1 mL/kg per hour of Ringer's maleate solution or 6 mL/kg bolus of Ringer's maleate solution given continuously. Patients receiving the combined norepinephrine infusion and restricted fluid administration had reduced blood loss (p<0.0001) and reduced need for blood transfusions (relative risk: 0.54; 95% CI, 0.38–0.77; p=0.0006).[237]

C. Recommendations on postoperative management

i. Postoperative nasogastric intubation should not be used routinely (Level I–Grade C).

ii. Consider using mu-opioid receptor inhibitors (i.e., alvimopan) when available, especially if radical cystectomy is performed without epidural analgesia (Level I–Grade C).

iii. A multimodal approach to optimize gut function and prevent postoperative ileus should involve gum chewing with or without metoclopramide (Level I–Grade C).

iv. Multimodal postoperative analgesia should include thoracic epidural analgesia or rectal sheath catheter with infusion of local anesthetic.

v. If possible, early mobilization should be encouraged two hours out of bed postoperative day (POD) 0 and six hours out of bed POD 1 (Level V–Grade D).

vi. Early oral nutrition may be started four hours after surgery (Level IV–Grade D).

Discussion

The recommendation to avoid routine postoperative nasogastric intubation is supported by a small (n=43) randomized, controlled trial among patients undergoing radical cystectomy with urinary diversion.[238] In this study, early removal (12 hours after the operation) was not correlated with ileus and was associated with improved patient comfort and earlier ambulation compared to standard removal of the tube after first flatus. The recommendation is also supported by a meta-analysis of patients undergoing major abdominal surgery, in which postoperative nasogastric intubation was associated with more postoperative complications and no benefits.[239]

A randomized, controlled trial evaluating the use of alvimopan among 280 patients after radical cystectomy demonstrated that, compared to placebo, patients administered alvimopan experienced earlier GI recovery (5.5 vs. 6.8 days; p<0.0001), shorter mean length of stay (7.4 vs. 10.1 days; p=0.0051), fewer episodes of postoperative, paralytic ileus-related morbidity (8.4% vs. 29.1%; p<0.001).[240] Alvimopan is expected to become available in Canada in 2016.

Gum chewing has been shown to improve bowel recovery times, but not length of stay.[241,242]

As a general measure, all patients should be routinely audited for protocol compliance and outcomes. The system should also be routinely audited for outcomes, cost-effectiveness, compliance, and changes in protocol (Level V).

XI. Perioperative stomal teaching and followup

A. Recommendations

i. Provide preoperative education and reference to appropriate resources to all patients and families requiring possible/actual urostomy surgery (Level IIB–Grade B).
ii. Explore the potential impact of urostomy surgery on intimacy and sexual functioning with patient/partner before and after surgery and during the rehabilitation phase (Level IV–Grade C).
iii. Offer the patient/family the opportunity to meet a person (ostomy lifestyle expert) with a urostomy through an ostomy association or support group (e.g., Ostomy Canada Society local chapter, Bladder Cancer Canada) (Level V–Grade D).
iv. Perform preoperative stoma site marking on all patients undergoing possible/actual urostomy and neobladder surgery (Level IV–Grade C).
v. Evaluate the patient for stoma site marking in the following positions (lying, sitting, bending, standing) and when consideration of an assistive device (e.g., wheelchair) is required (Level V–Grade D).
vi. Identify risk factors that influence stomal and peristomal complications (e.g., diabetes, renal disease) (Level IIIB–Grade B).
vii. Educate patient and family members to recognize complications affecting self-care management of the stoma and peristomal skin (Level IV–Grade C).
viii. Conduct followup assessments of the patient/family at one month, three months and then yearly after ostomy surgery to evaluate possible stoma and peristomal complications, psychological wellness, and to promote optimization of quality of life (Level IIB–Grade B).
ix. Coordinate the discharge plan of care for the patient/family with home care support and other resources as required (Level IIB–Grade C).

Discussion

Stoma education is more effective if given preoperatively, with the potential to reduce hospital stay and stoma-related interventions.[243,244] Preoperative education by an enterostomal therapy nurse (ETN) can also improve health-related quality of life and skill acquisition in the immediate postoperative period and long-term adjustment to an ostomy.[245]

With respect to sexuality, patients need to be made aware of the likely consequences of urostomy surgery. In men, erectile dysfunction occurs in most patients and in women, some form of sexual dysfunction (e.g., painful intercourse, decreased sexual desire, and/or vaginal dryness) are experienced by most.[246-248] Neobladder surgery may lead to fewer sexual function complications.

Contact with an individual from an ostomy association (e.g., Ostomy Canada Society[249]) can be arranged by physician or ETN request. An ostomy association-certified person with an ostomy visits the individual awaiting surgery to provide training and support.[249]

With respect to site marking, the joint position statement of the AUA and the Wound Ostomy Continence Nurse Society (WOCN) states, "All patients scheduled for ostomy surgery should have stoma marking done preoperatively by an experienced, educated, and competent clinician."[250] Stoma marking has been associated with reduction in complications and an improvement in quality of life.[251] Patients in wheelchairs or other assistive medical devices merit special consideration with respect to stoma marking, as traditional lower left or right abdominal quadrant sites may be suboptimal for self-care or visualization of stoma. These individuals should be marked in different positions (e.g., lying down, sitting in wheelchair).[252] Other devices (e.g., brace or special work attire) may also impact on stoma optimal positioning and should be considered preoperatively.

Factors that are known to place individuals at higher risk of stoma complications include: emergency surgery, stoma height, gender, age, obesity, and type of stoma.[250,253,254]

Postoperative followup, with home care if desired/required, is crucial for ostomy patients. Social isolation affects some adults with an ostomy and is associated with decreased levels of overall satisfaction and emotional support.[255] A lack of social connectivity may be identified by an ETN. The nurse may also identify complications that are overlooked by the patient.[250,256] Home care support can also help increase independence and quality of life.[250,257] Given that external stoma complications are the most frequent indication for re-operation after cystectomy,[258,259] but often go unrecognized, the recommendation to educate the patient and caregivers is also crucial.

XII. Variant histology

A. General recommendations

i. All pathology reported with variant histology should be reviewed by an expert GU pathologist.
ii. Patients with pure variant histology should be reviewed at a multidisciplinary centre or otherwise discussed in a multidisciplinary setting.

iii. Patients with mixed urothelial and either glandular, squamous, or sarcomatoid differentiation can be treated in the same manner as patients with pure urothelial carcinoma with the understanding that they may more likely have invasive and extravesical disease at the time of presentation.
iv. Lymphadenectomy for patients with either mixed or pure variant histology should be the same as performed for pure urothelial carcinoma.

B. Recommendations for variant pathologies

i. Pure squamous cell carcinoma (SCC)
   1. Upfront radical cystectomy should be considered in patients with invasive SCC of the bladder.
   2. There is no role for neoadjuvant chemotherapy in pure invasive, non-metastatic SCC of the bladder.

ii. Pure adenocarcinoma
   1. Steps should be taken to rule out direct extension/metastatic spread from other sites (prostate, colon, lung, breast, ovary, etc.).
   2. Select patients with urachal adenocarcinoma may be treated with partial cystectomy with en bloc excision of the urachus +/- umbilectomy. Intraoperative frozen sections are recommended to ensure negative margins.
   3. The remainder of patients with non-metastatic, resectable invasive disease should be considered for radical cystectomy.

iii. Sarcoma
   1. Patients with primary sarcomas of the bladder should be treated according to sarcoma protocols in a multidisciplinary setting. Radical cystectomy will generally be required as part of the treatment.

iv. Micropapillary disease
   1. Early cystectomy should be considered, as T1 micropapillary bladder cancer has a high risk of being under-staged. If repeat TUR shows no residual disease (T0), consideration of intravesical therapy with BCG is an alternative option.
   2. Neoadjuvant chemotherapy should be offered for muscle-invasive micropapillary bladder cancer, as it leads to comparable pT0 rates (up to 45%).

v. Small cell carcinoma
   1. Patients with any component of small cell carcinoma in their pathology should be treated with neuroendocrine-specific chemotherapy protocols, followed by consolidation with local therapy (radical cystectomy or radiotherapy).

Discussion

Two reviews provide succinct summaries on the above-mentioned variants and their impact on outcomes of bladder cancer treatment.[260,261]

XIII. Surveillance strategies post-radical cystectomy, partial cystectomy, trimodal therapy

A. General recommendation

i. There is no high-level evidence in the literature to support the notion that early detection of asymptomatic recurrences leads to improved outcomes.

B. Recommendations for surveillance following radical cystectomy

Note that the timing of the following surveillance methods needs to be customized according to risk stage. Table 1 shows the recommended stage-specific surveillance protocol developed by the Canadian Bladder Cancer Network (Bladder Cancer Canada).[262]

i. Office visits.
ii. Chest X-ray or CT of thorax.
iii. Laboratory studies: Complete blood count (CBC), B12 (if continent diversion utilizing terminal ileum), electrolytes, creatinine, and liver function tests to monitor for anemia, metabolic complications, and renal insufficiency.
iv. Triphasic CT of the abdomen pelvis to monitor for common recurrence sites (e.g., pelvis, retroperitoneum, liver).
v. For patients with risk of urethral recurrence, consider monitoring the urethra in asymptomatic patients (e.g., urethroscopy or voided urine cytology/washes).
vi. For patients with risk factors for upper tract disease, consider upper tract surveillance with urine cytology and ultrasound/CT scan.
vii. General health surveillance needs to be at least once yearly to monitor other important postoperative factors (e.g., fracture risk, renal insufficiency).

Discussion

For a more complete discussion of the rationale for the surveillance methods and their timing, refer to the Canadian Bladder Cancer Network paper on surveillance guidelines.[262]

Table 1. Recommended stage-specific surveillance protocol after radical cystectomy (adapted from Yafi et al[262])

≤pT2 N0														
Months	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Office visit	X	X		X				X		X		X		X
Chest X-ray				X				X		X		X		X
Lab studies	X	X		X				X		X		X		X
Triphasic CT abdomen/pelvis				X				X		X				X
Urine cytology*				X				X		X		X		X
pT3-4 N0														
Months	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Office visit	X	X		X		X		X		X		X		X
Chest X-ray		X		X		X		X		X		X		X
Lab studies	X	X		X		X		X		X		X		X
Triphasic CT abdomen/pelvis		X		X				X		X		X		X
Urine cytology*				X				X		X		X		X
pTx N+														
Months	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Office visit	X	X	X	X		X		X	X	X	X	X	X	X
Chest X-ray	X	X		X		X		X	X	X	X	X	X	X
Lab studies	X	X	X	X		X		X	X	X	X	X	X	X
Triphasic CT abdomen/pelvis	X	X		X		X		X		X		X		X
Urine cytology*				X				X		X		X		X

*Urine washings/cytology once a year is optional. Vitamin B12 is recommended when clinically indicated and upper tract imaging to assess the uretero-ileal anastomosis at 6–8 weeks from time of RC is recommended in all groups. Baseline CT abdomen/pelvis at 3–6 months following radical cystectomy may be considered for all patients. CT: computed tomography.

C. Recommendation for surveillance following partial cystectomy

i. Patients should be followed in a similar fashion to radical cystectomy patients, with the addition of regular cystoscopic surveillance, as per the recommendations for followup of high-risk NMIBC.

D. Recommendation for surveillance following trimodal therapy

i. Patients should be followed in a similar fashion to radical cystectomy patients, with the addition of regular life-long cystoscopic surveillance in a schedule similar to high-risk NMIBC.

XIV. Management of locally advanced/unresectable disease

A. Recommendation for palliative cystectomy

i. In rare patients with metastatic bladder cancer, palliative cystectomy without curative intent may be considered (Level V–Grade D).

Discussion

The indications for palliative cystectomy in patients with locally advanced and metastatic bladder cancer include:

- Pain and voiding symptoms causing significant reduction in quality of life in which other treatment alternatives (transurethral resection or external beam radiation) are not successful or contraindicated.
- Recurrent and retractable hematuria requiring blood transfusions.

Before considering palliative cystectomy and urinary diversion, the risks and morbidity associated with surgery must be weighed against the potential improvements in the quality of life anticipated with surgery.

B. Recommendations for patients with MIBC in whom the bladder is found to be unresectable at time of cystectomy

i. Consideration of urinary diversion without removal of bladder may be performed if doing so reduces symptoms, improves renal function, and improves quality of life (Level IV).

ii. Aborting the procedure may also be considered if the patient is a candidate for chemotherapy, especially if the patient did not receive neoadjuvant chemotherapy.

1. Consolidation cystectomy or radiation may be considered if there is a complete or significant partial response to chemotherapy (Level V).

Discussion

In a series of 35 patients with aborted cystectomy due to positive lymph nodes or locally advanced disease, only seven eventually received consolidation cystectomy.[263] There is a lack of evidence to promote cystectomy in this setting, but the prognosis is poor either way and surgery may have palliative benefits.

In another series of 31 patients with unresectable disease, those patients who had pelvic lymph node dissection demonstrated a trend towards an improved survival compared with those who did not (24 vs. 10 months; p=0.09).[264] Only two of these patients had salvage cystectomy; 11 (35%) had urinary diversion, which has the potential to improve renal function and reduce hematuria and clot retention.

There have been a number of trials demonstrating benefits of chemotherapy among patients with unresectable disease.[265-269]

C. Recommendation for patients in whom newly diagnosed bulky nodes are found at time of laparotomy

i. Consider pelvic node dissection, with frozen section of the larger lymph nodes.
ii. If nodes are positive for urothelial cancer, and patient has not received neoadjuvant chemotherapy, consider aborting the procedure and administer chemotherapy with later consolidation with cystectomy or radiation.
iii. Continuation of surgery even if pelvic nodes are positive may be considered, as a small percentage of these will have long-term disease control if adenopathy is restricted to the pelvis only.

Discussion

If the nodes are grossly positive for urothelial cancer, cystectomy may be aborted and patients may be considered for chemotherapy (if neoadjuvant chemotherapy was not given). All patients should be considered for chemotherapy. A significant percentage of patients in the node-positive group could be cured by the combination of multi-agent chemotherapy and surgery. More than half (58%) remained disease-free, with a median followup of 6.8 years. There are several other studies that have shown a benefit to pelvic node dissection for those with small-volume lymph node metastasis.[270-274] Radical cystectomy can also be considered for those with grossly positive nodes, as a small percentage of these patients will have long-term disease control with surgery.[275]

XV. Pathology reporting and role of re-review (NMIBC, MIBC)

A. Recommendation for mandatory fields to be included in TURB pathology reports

i. Histological type, including variant histology of urothelial carcinoma (squamous, micropapillary, sarcomatoid, small cell, etc.)
ii. Tumour grade.
iii. Tumour extension: Lamina propria, muscularis propria, indeterminate for muscularis propria invasion, prostatic urethra/prostatic glands, prostatic stroma.
iv. Extent of lamina propria invasion (qualitative description as a minimum: Superficial/deep, focal/extensive).
v. Presence/absence of muscularis propria (in T1 disease).
vi. Presence/absence of lymphovascular invasion.
vii. Presence/absence of urothelial CIS.

Discussion

There are currently no Canadian guidelines or consensus recommendations regarding mandatory fields to be reported in TURB pathology reports. However, there is a protocol endorsed by the College of American Pathologists (CAP; 2013),[276] and a similar checklist endorsed by the International Consultation on Urological Diseases and the EAU (2012).[277] The CAP endorses a synoptic reporting system, and such a report does exist for TURBT. Anecdotally in Canada, while compliance with synoptic reporting is good for cystectomy, this has not been the case for TURBTs.

The reporting of variants is recommended to provide important information about the disease, its prognosis and treatment. Pathologists should differentiate pure SCC from extensive squamous differentiation in urothelial carcinoma (UC) when possible. The extent of differentiation should be reported in addition to its presence. The pathologist should at least provide a qualitative description (focal vs. extensive); reporting the proportion of squamous differentiation is optional. Glandular differentiation, plasmacytoid UC, and sarcomatoid UC should each be reported, although reporting of their extent is optional, as there are no related data available in the literature. A distinction should be made between non-invasive micropapillary carcinoma and invasive micropapillary carcinoma , as the literature generally refers to the latter. Small cell carcinoma should be reported, as well as its extent within the tumour (pure vs. non-pure).

In T1 disease, the pathologist should at least provide a qualitative description of the extent of invasion (superficial vs. deep; focal vs. multifocal/extensive). Providing additional information about muscularis mucosa invasion, depth of invasion, and the diameter of invasive focus is optional.

LVI should be reported in TURBs; the use of immunohistochemistry is encouraged in challenging cases. Urothelial CIS should also be routinely reported.

B. Recommendation for pathology review

i. A review by a pathologist with GU expertise is recommended in TURB specimens reported as T1 or T2 bladder cancer.

Discussion

The recommendation for a second pathology review is based on the evidence showing the high frequency of reclassification consistently reported in the bladder cancer literature. For example, in a combined analysis of five EORTC trials involving 1400 patients with primary or recurrent Ta/T1 disease, reclassification occurred in a large proportion of patients, particularly those with T1 disease.[278] Among the 581 patients enrolled with stage T1, 52% were reclassified as Ta and 4.7% as T2. Of the757 patients enrolled with Ta stage, 9% were reclassified as T1 and 1.3% as T2. This analysis was published in 2000. More recent analyses[279-281] have reported considerably lower rates of reclassification. In addition, variant histology is often missed (or not reported) by pathologists without GU expertise. A study published in 2013 included 589 patients who underwent TURBT and had pathology performed in the community with subsequent mandatory central pathology review at a large referral hospital in the U.S.[282] The proportion with variant histology identified by the central review was 19.5%. Of these, only 44% had been reported by the community pathologists.

Although second review is recommended for those patients with higher-risk disease, it should not be considered mandatory for non-invasive lesions (Ta, Tis).

XVI. Different models for multidisciplinary management of bladder cancer and their impact

A. Recommendations

i. A multidisciplinary approach (e.g., GU tumour board or multidisciplinary team) leads to better patient care and improved outcomes.
ii. At a minimum, patients with MIBC should be discussed by a multidisciplinary team before initiating treatment. Assessment in a multidisciplinary clinic or presentation at a genitourinary tumour board is considered optimal.
iii. Requirements of a tumour board include the following:
    1. Held at least five times per quarter.
    2. Patient cases are prospectively reviewed.
    3. Coordinator is assigned.
    4. Chairperson is assigned.
    5. Each of the relevant specialists should be present for at least 75% of conferences. Specialists include: Surgeon, medical oncologist, pathologist, radiation oncologist, radiologist. Nursing attendance is preferred, though not required.

Discussion

Improvements in care and outcomes associated with multidisciplinary approaches have been attributed to enhanced clinical decision-making, coordination of investigations and clinical care, and an open discussion of available treatment options both within the multidisciplinary team and with the patient.[283,284] The multidisciplinary approach leads to improved collaboration and helps to support research endeavors, especially with respect to cross-disciplinary clinical trials.

Bladder cancer is an excellent discipline in which to use a multidisciplinary care model. Treatment protocols are complex, with many options and many ongoing clinical trials. Advances in surgical procedures, chemotherapy, computer technology, and targeted molecular and radiation therapies have all led to an increase in multimodality therapy, which increases the need for communication among cancer specialists for any patient. There is a need to follow guidelines, to standardize treatments, and to coordinate care among healthcare professionals. In addition, there is a need to monitor side effects of treatment, both physical and psychological, and followup on an ongoing basis over the long term. Timely management in a multidisciplinary environment is crucial and is dependent upon good communication between urologists, medical oncologists, and radiation oncologists. Communication breakdown can result in delayed treatment planning and implementation, unnecessary duplication of tests, incomplete followup, increased patient anxiety, decreased patient satisfaction, and declines in quality of life.

The exact definition and scope of multidisciplinary care varies and, as such, can be easily adapted according to the institution and available resources. Some centres may opt to discuss cases in multidisciplinary rounds, while other centres may have dedicated multidisciplinary clinics.[285]

The adopted model of multidisciplinary care in a given institution needs to be objectively reviewed/audited to ensure that recommendations are carried forward.[286,287] The quality of decision-making should be evaluated, assessing concordance between recommendations and plans. All models need to be continuously evaluated, considering advantages, disadvantages, which aspects are working, which are not,

and what modifications may be needed. As more centres adopt standardized approaches, cross-centre comparisons can also take place.

There are data supporting the implementation of multidisciplinary clinics in other malignancies. A systematic review of 21 studies evaluated the impact of multidisciplinary cancer care on patient survival.[288] Of the 21 studies, 12 reported a significant relationship between multidisciplinary care and survival.

A systematic review of 51 papers investigating multidisciplinary teams in oncology demonstrated that these teams are associated with changes in clinical diagnostic and treatment decision-making with respect to urological, pancreatic, gastro-esophageal, breast, melanoma, bladder, colorectal, prostate, head and neck, and gynecological cancer.[289]

XVII. Impact of cystectomy provider characteristics: Surgical wait times, volumes, surgeon characteristics

A. Recommendations

i. Hospitals with annual case volumes of less than five cystectomies for bladder cancer should discontinue providing this service (Level III–Grade B).
ii. Cystectomy should be centralized to higher-volume centres, with an annual case volume of greater than 20 per year (Level III–Grade B).
iii. Within the higher-volume centres, consideration should be given to coordinating surgical care to at least two surgeons with a sub-specialty focus in bladder cancer (Level III–Grade C), allowing individual case volumes to be maintained at six or more cases per year (Level III–Grade B).
iv. Strategies to establish and identify centres and individual providers with sub-specialty focus in higher-risk bladder cancer is important to facilitate timely referral to the multi-disciplinary team and prevent undue delay to definitive management (Level III–Grade C).
v. Wait time for cystectomy for bladder cancer should be minimized to four to six weeks after completion of neoadjuvant chemotherapy (time from last dose to surgery) (Level IV–Grade D).
vi. Wait time for cystectomy for bladder cancer should ideally be done within six weeks for patients not undergoing neoadjuvant chemotherapy (time from TURBT/first urology visit to surgery) (Level IV–Grade D).

Discussion

It is illustrative in this discussion to provide details of the Canadian context with respect to delivery of bladder cancer care.

Higher surgeon volume has also been shown to correlate with improved outcomes in Canadian analyses.[290,291] Findings from other researchers has shown superior outcomes for surgeries performed by urologic oncologists (compared to urologists); in academic centres (vs. non-academic centres); and by bladder-cancer-focused surgeons (vs. non-bladder-cancer-focused).[292,293]

Thirty- and 90-day postoperative morality rates in academic centres in Canada have been reported to be 1.3% and 3.2%, respectively, with five-year overall survival of 57%.[294] This five-year survival rate is markedly higher than reported population-based outcomes across Canada, which have ranged from 30–43%.[290,291,295]

With respect to cystectomies, 42.6% of procedures were performed in hospitals with a case volume of fewer than 10 cystectomies per year.[291] Only 23.1% of cystectomies were performed in hospitals with case volumes of more than 25 per year. Statistics for individual surgeons were even further skewed towards less experienced practitioners. Almost 70% of cystectomies were performed by surgeons who perform fewer than five cystectomies per year.

The likely reasons higher-volume centres consistently perform better is not only surgeon experience (see above), but also appropriate infrastructure, nursing, and other support staff. When one considers that the lower-volume centres likely handle less complicated cases, the fact that they continue to be outperformed by higher volume centres is of concern.

Wait times for surgery in NMIBC (time from decision to OR completion) in Canada have ranged from 33–64 days.[295-298] In MIBC, published wait times from TURBT to cystectomy ranged from 33–50 days.[299] Median overall delay from primary care visit to cystectomy in Quebec was 116 days for the period of 2000–2009.[66]

In terms of outcomes research, there have been two systematic reviews investigating the impact of cystectomy wait times on survival. They reported inconsistent evidence of effect on survival.[300,301] Individual studies have produced conflicting results. One retrospective study of 592 patients at Johns Hopkins Hospital found that a delay of three months or longer to radical cystectomy was not associated with a lower overall survival compared to a delay of less than three months.[302] However, an analysis of data from 1633 patients in Quebec did find a significant correlation between wait time and survival,[303] as did an analysis of data from 2535 patients in Ontario.[299]

With respect to provider cystectomy volumes, a systematic review of eight studies relating hospital cystectomy volumes to outcomes showed that each of the studies demonstrated improvement in at least one outcome with higher compared to lower volume.[304] Analyses of Canadian data have also consistently demonstrated that higher volume of cases correlates with better outcomes, including lower mortality risk.[290,291,305]

There are also some data informing the timing of cystectomy following neoadjuvant chemotherapy. In a cohort of 153 patients with MIBC who received neoadjuvant chemotherapy and subsequently underwent radical cystectomy, the timing of cystectomy following the termination of chemotherapy did not significantly alter the risk of survival in the multivariate analysis.[306]

XVIII. Definition of bladder cancer centres of excellence

A. Recommendations

i. A level 1 centre of excellence in bladder cancer in Canada is best defined as a healthcare institution that provides comprehensive clinical care for patients diagnosed with all stages of bladder cancer, with the following requirements:
   1. Availability of a team of health professionals dedicated to bladder cancer (dedicated defined as postgraduate training, majority of practice, or academic focus), including one or more of each of the following:
      a. Urologic oncologist.
      b. Radiation oncologist.
      c. Medical oncologist.
      d. Genitourinary pathologist.
      e. Genitourinary radiologist.
      f. Interventional radiologist.
      g. Nurse practitioner or pivot nurse.

With availability of the following professional services:

      h. Colorectal, vascular, gynecologic, and plastic surgeons with expertise in reconstruction.
      i. Intensive/critical care.
      j. Stoma therapy.
      k. Clinical psychology/sexology.
      l. Social work.
      m. Supportive and palliative care.
   2. Provides guidance and support to a regional network of primary and secondary care urologists and other physicians.
   3. Serves as a referral centre for complex genitourinary cancer patient care.
   4. Provides care in an interdisciplinary fashion.
   5. Establishes or adopts, and adheres to evidenced-based standards of practice and guidelines.
   6. Conducts regular multidisciplinary tumour boards or conferences.
   7. Provides timely access to state-of-the-art imaging.
   8. Conducts clinical trial research in bladder cancer.
   9. Publishes clinical and/or laboratory-based research in bladder cancer.
   10. Measures and reports several indicators of clinical performance, including outcomes, compliance to guidelines, etc. that can be benchmarked.
   11. Provides education to trainees, nurses, and continued medical education.
   12. Promotes bladder cancer public awareness, early diagnosis, and prevention.
   13. Actively participates in a nationwide network of bladder or genitourinary cancer centres of excellence and in patient groups.
   14. The centre manages greater than the annual minimum caseload in the following:
      a. Radical cystectomy: 25.
      b. Continent urinary diversion: 5.
      c. Radiation-based definitive treatment: 5.

Discussion

Although there are no specific data to cite to support the formation of bladder or genitourinary cancer centres of excellence in particular, there was consensus amongst participants on the general criteria listed above. In addition, the criteria were validated by two independent, international clinical and academic experts in the field of bladder cancer.

The literature on this subject has focused mainly on the relationship of surgical volumes and clinical outcomes. There are some published Canadian data from other disciplines that help provide a rationale for regionalization of care. In thoracic surgery, it has been observed that centres with higher volumes of pulmonary lobectomies have better outcomes compared to those with smaller volumes.[307] An increase of 20 cases per year in this observational study was associated with a significant 15% relative risk reduction in in-hospital mortality (95% CI 9–19%; $p<0.0001$), as well as a 5% relative decrease (95% CI, 3–7%; $p<0.001$) in duration of stay.

Similar findings were reported in an observational Canadian study on esophagectomy,[308] where an increase of 10 cases per year was associated with a 15% decrease in in-hospital mortality (95% CI, 6–23%, $p=0.001$).

There are also some data from an American observational study showing a mortality benefit from regionalization of lung cancer resections.[309] Mortality rates associated with these procedures were 3.2% in teaching hospitals and 4.0% in non-teaching hospitals ($p<0.001$).

With respect to genitourinary cancer surgery and regionalization, a recent publication regarding prostate cancer surgery in the U.K. illustrates the clinical advantages of such an approach.[310]

One of the most important aspects of the centre of excellence concept is that these centres exist not to drive patients

away from other capable institutions, but rather to place them as the hubs of networks of centres that work together to provide the best standards of care.

More importantly, the elements listed above as criteria must be further defined with detailed methodology for assessment and continuous evaluation. A network-based scorecard to evaluate indicators of clinical and academic performance, which are benchmarked against leading centres around the world, is required to ensure centres maintain high standards.

XIX. Quality indicators in the management of bladder cancer across Canada

A. Recommendation

i. To optimize bladder cancer quality of care in Canada, we recommend performing a Delphi process to establish a set of quality indicators across important categories of bladder cancer care which may include:
   1. Diagnosis
      a. Consultation with urologist.
      b. Time from date of consultation to urology visit:
         - For gross hematuria.
         - For microhematuria.
      c. Time from urology visit to completion of hematuria workup:
         - For gross hematuria.
         - For microhematuria.
   2. TURBT
      a. Complete radiologic assessment for staging.
      b. Documentation of completeness of resection, depth of resection, and EUA findings.
      c. Documentation of presence of detrusor muscle in pathology report.
      d. Restaging TUR when detrusor muscle is absent in T1 disease.
      e. Pathology review of T1-2 tumours by a GU pathologist.
   3. Therapy
      a. Time from TURBT to pathology report.
      b. Time from TURBT to pathology report known by patient.
      c. Time from last TURBT to radical cystectomy.
      d. Time from TURBT to 1st cycle of chemotherapy.
      e. Time from TURBT to 1st dose of radiation.
      f. Complete radiologic assessment for staging.
   4. NMIBC
      a. Completeness of pathology report.
      b. Postoperative instillation of intravesical chemotherapy.
      c. BCG induction course with minimum one-year maintenance for high-risk NMIBC.
      d. Cystoscopy by four months following TURBT.
   5. MIBC
      a. Consultation with a medical oncologist perioperatively/postoperatively.
      b. Followed using a multidisciplinary approach.
      c. Among patients receiving neoadjuvant chemotherapy, % receiving cisplatin-based combination therapy.
      d. % of nonmetastatic MIBC receiving any definitive therapy.
   6. Radical cystectomy
      a. 90-day mortality rate.
      b. Length of stay.
      c. Quality of pelvic lymph node dissection (e.g., number of nodes, extent of dissection).
      d. Soft tissue positive margin.
      e. Use of surgical safety checklist.
      f. Use of thrombosis prophylaxis.
      g. Use of pneumatic compression devices intraoperatively.
      h. Perioperative pharmacologic prophylaxis.
      i. Post-discharge prophylaxis for four weeks.
      j. 90-day complication rate (stratified using standardized tools) with all modalities.
      k. Reoperation within 90 days.
      l. Cystoscopy after trimodality therapy in surgical candidates.
      m. % of patients monitored for complications and mortality.
      n. Use of perioperative standardized care pathways.
   7. Urinary diversion
      a. % of patients receiving neobladder (by age group).
      b. % with consultation with enterostomal therapist preoperatively.
      c. % with followup with enterostomal therapist post discharge among patients with ileal conduit.
   8. Providers.
      a. Hospital volumes.
         - Radical cystectomy.
         - Radiation-based definitive treatment.
         - Neobladders.

b. Surgeon volumes.
   - Radical cystectomy.
   - Neobladders.

Discussion

The establishment of benchmarks for a number of quality indicators in bladder cancer care is an important component of the overall delivery of care. Benchmarks provide tangible goals for healthcare professionals and their patients, as well as a means of assessing to what extent we are achieving our goals. Tracking and reporting of quality measures for localized bladder cancer has been shown to improve patient outcomes and safety and identify barriers to high-quality care.[311]

The process of establishing goals, times, and benchmarks was deemed to be beyond the scope of the consensus conference that has shaped the above recommendations. However, the participants at this meeting agreed that this is a worthwhile endeavor to be explored by a similar multidisciplinary group with expertise across all aspects of bladder cancer care and establish quality indicators via a Delphi process.

Competing interests:

Dr. Kassouf is/has received grants/honoraria from Amgen, Astellas, and Janssen. Dr. Kassouf is also the recipient of a Research Scholar Award from the FRSQ.

Dr. Aprikian has received grants/honoraria from Abbvie, Amgen, Astellas, and Janssen; and has participated or is participating in clinical trials for Astellas.

Dr. Black is/has been an Advisory Board member for Abbvie, Amgen, Astellas, Biocancell, Cubist, Janssen, Novartis, and Sitka; is/has been on Speaker Bureaus for Abbvie, Janssen, Ferring, Novartis, and Red Leaf Medical; has received grants/honoraria from Pendopharm; has participated or is participating in clinical trials for Amgen, Astellas, Ferring, Janssen, and Roche; and has received research funding from GenomeDx, iProgen, Lilly, and New B Innovation.

Dr. Izawa has received grants/honoraria from Abbott, AstraZeneca, Astellas, Janssen, Sanofi, and Pfizer.

Dr. Eapen has received grants/honoraria from Abbott and AstraZeneca; and has participated or is participating in numerous clinical trials.

Dr. So is/has been on Speaker Bureaus for Amgen, Astellas, and Janssen.

Dr. North is/has been an Advisory Board member for Astellas; has received grants/honoraria from Astellas, Janssen, and Sanofi; and has participated or is participating in clinical trials for Astellas, Janssen, and Sanofi.

Dr. Rendon is/has been an Advisory Board member and on Speaker Bureaus for Amgen, Astellas, Ferring, and Janssen.

Dr. Sridhar is/has been an Advisory Board member for Astellas; has received grants/honoraria from Astellas, Janssen, and Sanofi; and has participated or is participating in clinical trials for Agenisys, Imclone, OGX, Roche, and Sanofi Aventis.

Dr. Chin is/has been an Advisory Board member for Profound Medical Inc.

Dr. Chung has received grants/honoraria from Sanofi.

Dr. Fradet is/has been an Advisory Boards member for Amgen, Astellas, AstraZeneca, DiagnoCure, and Janssen; has received grants/honoraria from Amgen, Astellas, AstraZeneca, GammaDynacare, and Janssen; and has participated or is participating in clinical trials for Abbott.

Dr. Jewett is/has been an Advisory Board member for Novartis, Pfizer, and Theralase Inc; has received grants/honoraria from Novartis, and Pfizer; holds investments in Theralase Inc; and has participated or is participating in clinical trials GSK, Novartis, and Pfizer.

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Dr. Gotto is/has been an Advisory Board member for Amgen, Astellas, and Janssen; has received honoraria from Amgen, Astellas, Janssen, and Novartis; and is or has participated in clinical trials SPARTAN, ENZAMET, and COSMiC.

Dr. Siemens has participated or is participating in clinical trials for Amgen, Astellas, Ferring, and Janssen.

Dr. Saad, Dr. Fairey, Dr. Kulkarni, Dr. Brimo, Dr. Blais, Dr. Booth, Dr. Shayegan, Dr. Drachenberg, Dr. Fleshner, and Mr. Alam declare no competing financial or personal interests.

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