Guideline Resource Unit
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Non-muscle Invasive Bladder Cancer

Effective Date: September 2024

Background

Bladder cancer is the fifth most common cancer in Canada. It is the fourth most common cancer for men. Bladder cancer is less common among women (ranked eleventh). In 2024, an estimated 12,300 Canadians will have be diagnosed with bladder cancer and 2,600 Canadians will die from bladder cancer [link].

Though amenable to surgery, early bladder cancer can recur frequently.[1] The risk of recurrence is affected by factors such as size, number, T category, tumour grade, concomitant CIS, and prior recurrence.[2] Following curative surgery, adjuvant therapy to prevent recurrences is an important aspect of bladder cancer treatment. Several agents have been studied in the adjuvant setting with outcomes of progression-free survival and disease-free survival as the primary endpoints; these agents include epirubicin, doxorubicin, interferon (IFN)-α2b, mitomycin C (MMC), and bacillus calmette-guerin (BCG). The purpose of this guideline is to establish best practice for the surgical management of patients with nonmuscle invasive bladder cancer, as well as to describe patient selection criteria for adjuvant therapy, appropriate agents, dosing, and duration of therapy.

Guideline Questions

1. What is the appropriate primary therapy for patients with non-muscle invasive bladder cancer?
2. Which patients are appropriate for adjuvant therapy?
3. Which agents are most efficacious in preventing bladder tumour recurrences?
4. What is the appropriate dosing and duration of adjuvant therapy?
5. How often are follow-up examinations required and for what duration?

Search Strategy

For this update, the Pubmed database was queried for phase III trials published between May 2015-2020. An evidence table is available upon request.

Target Population

The following recommendations apply to adult patients with a diagnosis or suspicion of non-muscle invasive bladder cancer.

Recommendations

American Joint Committee on Cancer (AJCC) staging definitions for bladder cancer are included in Appendix A (page 14).

Management of Ta

Staging
Complete resection, including muscularis propria, is recommended.

Aside from the bladder, the urethra should be examined as well.
Upper tract imaging should be performed in the initial evaluation of a patient with bladder cancer.
For patients with T1HG bladder cancer on TURBT, a re-resection TURBT is recommended, particularly if muscularis propria is not sampled.

Risk Stratification
Low risk solitary, primary, low grade Ta, <3cm, no CIS.
Intermediate risk multiple or recurrent, large (>3cm), low grade Ta, or solitary primary small (<3cm) TaHG.
High risk T1, CIS, High grade or variant histology (micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid). Or TaHG that is large (>3cm), recurrent, and/or multifocal.[3]

Adjuvant Therapy
Post-TURBT single-dose chemotherapy instillation should be considered for all risk categories of pTa patients, especially for low risk patients, as these patients benefit most in terms of recurrence rates at 2 years.
A. The standard of care is adjuvant-immediate chemotherapy instillation post-TUR, unless the bladder is perforated with TUR or if there is a significant risk of vesico-ureteral reflux. Chemotherapy should consist of: epirubicin (50 mg/50 mL) or mitomycin C (MMC; 40 mg/40 mL) or Gemcitabine (2 g in 100 mL of saline).
B. The role of single-dose postoperative chemotherapy is unclear for patients with high risk NMIBC planned for subsequent intravesical BCG.

Induction and Maintenance Therapy
Induction and maintenance therapy is recommended for intermediate and high risk patients, including those with multifocal tumours or frequent recurrences.
A. BCG: induction therapy for 6 weeks then 3-weekly injections at 3-month intervals; continue for 12-36 months, if patient is disease-free at three months.
B. MMC: 40 mg/ mL monthly; continue for 12-24 months.
C. Gemcitabine (1g in 50ml) + Docetaxel (37.5mg in 50ml) induction (weekly x 6 weeks), followed by maintenance x 2 years (monthly x 12-24months).
D. For intermediate risk, up to 1 year of maintenance is sufficient. For high risk, 3 years of maintenance BCG is recommended.

Management of Recurrences
TURBT is recommended for resection and pathologic assessment of recurrences in most patients
In patients with suspected TaLG recurrences, cystoscopy, biopsy +/- fulgurization under local anesthesia is an alternative

BCG Unresponsive Bladder Cancer is defined as any of the following

A. T1HG at the first 3-month cystoscopy following induction.
B. Recurrent T1HG/TaHG within 6 months of completion of adequate BCG.
C. Recurrent CIS (+/- T1HG/TaHG) within 12 months of completion of adequate BCG.
(Adequate BCG is defined as at least 5/6 weekly induction courses plus either at least 2/3 weekly maintenance courses or 2/6 weekly courses of a second induction cycle)

Management of BCG unresponsive bladder cancer

A. Radical cystectomy, pelvic lymphadenectomy, and urinary diversion is the standard of care in surgically fit patients
B. In patients ineligible or refusing cystectomy, salvage therapies include:
- **i.** Intravesical Gemcitabine (1g in 50ml) + Docetaxel (37.5mg in 50ml) induction (weekly x 6 weeks), followed by maintenance x 2 years (monthly x 12-24months)
- **ii.** Intravesical Mitomycin C: administer intravesically at a dose of 40 mg weekly for 4 weeks
- **iii.** Pembrolizumab 200 mg intravenously q3 weekly for a maximum 35 cycles. This approach is Health Canada approved but not funded in Alberta.[4, 5]

Management of BCG relapse not meeting definition for BCG unresponsive bladder cancer

A. Consider rechallenge with a 2nd induction course of BCG

BCG Administration

A. Start date must be at least 3 weeks after last TURBT.
B. No liquids x 4 hours prior, and no caffeine the day of treatment.
C. Catheterize patient to ensure bladder is empty.
D. BCG (Merck 1 vial; Verity 2 vials) diluted in 50 mL normal saline instilled via catheter weekly x 6 weeks.
E. Patient should hold BCG x 2 hours, prior to voiding (sitting) into toilet.
F. After voiding add 1 cup of household bleach (5.25-6.15% sodium hypochlorite) to the toilet, put the lid down and wait 20 minutes prior to flushing one time.
G. Cystoscopy to be performed within 6 weeks of induction

Risk Adjusted Follow-up

Initial cystoscopy post first resection at 3-4 months post-operatively, as clinically indicated.

If initial cystoscopy is negative for malignancy

Low risk

A. Cystoscopy annually for 5 years then in the absence of recurrence further surveillance at discretion of patient and urologist.

B. If asymptomatic, routine upper tract imaging not required

Intermediate risk
A. Cystoscopy q3-6 months for 2 years, then q 6-12 months for the 3rd year, then annually.
High risk
A. Cystoscopic evaluation q 3-4 months for the first 2 years, then q 6 months for 2 years then annually for 10 years.
B. Consider upper tract imaging q 1-2 years.

Discussion

The management of Ta and T1 bladder cancer includes resection plus adjuvant-immediate chemotherapy, consisting of epirubicin or mitomycin C.[6, 7] Recurrences are common in bladder cancer [3] and management consists of bacillus calmette-guerin therapy (BCG). In intermediate to high risk patients, the addition of prulifloxacin has not been shown to improve recurrence rates at six months (21.6 vs. 23.0%);[8] however, in another study, the addition of gemcitabine to BCG therapy increased the time to recurrence by 4.3 months (24.1 vs. 19.8 months; P<.05).[9] An EORTC trial (Sylvester, et al. 2010) showed that in intermediate and high risk patients (n=820), BCG significantly reduced the rate of recurrence (36.7 versus 52.7% epirubicin; P<.05) and increased the rate of overall survival (70.1 versus 62.0%; P<.05), with a median follow-up of 110 months.[10] Another smaller study (n=89 Ta/T1 patients) showed that, after a median follow-up of 102 months, BCG resulted in a significantly lower recurrence rate versus mitomycin-C (59.1 versus 80%; P<.05); disease-free survival was also higher in patients treated with BCG (90.9 versus 80.0%).[11]

For Ta disease, in the event of a failure on BCG therapy, options include salvage surgery, BCG therapy plus alpha-2b interferon, or mitomycin C.[6] Gemcitabine has also demonstrated efficacy: overall survival rate was approximately 20% higher (approximately 70 versus 50%; P<.05) versus mitomycin-C at a median follow-up of 36 months;[12] recurrence rate was 35% lower (52.5 versus 87.5%; P<.05) versus BCG;[13] and recurrence free survival rate was approximately 16% higher (19 versus 3%; P<.05) versus BCG (median follow-up of 12 months).[13] However, in a smaller study of high risk patients, BCG was more efficacious than gemcitabine, in terms of recurrence rate (28.1 versus 53.1%; P<.05).[14] Larger trials with gemcitabine are required and currently BCG plus alpha-2b interferon or mitomycin-C remains the standard of care for first-line treatment of recurrent disease.

For Tis disease, in the event of a failure on BCG therapy, and for T1 high-grade disease, BCG therapy followed by repeat TURBT or discussion of immediate cystectomy is mandatory.[6] Adjuvant therapy consists of immediate instillation with epirubicin. Maintenance therapy consists of BCG with alpha-2b interferon, if the patient is disease free at first cystoscopy. In patients with stage Ta or T1 bladder cancer (n=115) given one of the following three treatments, post-TURBT: (1) maintenance

therapy with BCG (81 mg, intravesically) once weekly for 6 weeks followed by three once-weekly instillations at 3, 6, 12 and 18 months; (2) BCG (81 mg, intravesically) once weekly for 6 weeks; or (3) epirubicin (40 mg, intravesically) instilled nine times, the recurrence-free survival rates after two years of follow-up were 84.6%, 65.4%, and 27.7%, respectively.[7] Maintenance therapy with BCG is an important component of care in this setting.

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Appendix A: AJCC 8th Edition

Primary Tumour (T)

Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
Ta: Non-invasive papillary carcinoma
Tis: Carcinoma *in situ*: “flat tumour”
T1: Tumour invades subepithelial connective tissue
T2: Tumour invades muscularis propria

- pT2a: Tumour invades superficial muscularis propria (inner half)
- pT2b : Tumour invades deep muscularis propria (outer half)

T3 : Tumour invades perivesical tissue

- pT3a : Microscopically
- pT3b : Macroscopically (extra vesical mass)

T4: Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall

- T4a: Tumour invades prostatic stroma, uterus, vagina
- T4b : Tumour invades pelvic wall, abdominal wall

Regional Lymph Nodes (N)

Nx: Lymph nodes cannot be assessed
N0: No lymph node metastasis
N1: Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2: Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N3: Lymph node metastases to the common iliac lymph nodes

Distant Metastasis (M)

M0: No distant metastasis
M1: Distant metastasis

- M1a: Distant metastasis limited to lymph nodes beyond the common iliacs
- M1b: Non-lymph-node distant metastases

T	N	M	Stage
Ta	N0	M0	0a
Tis	N0	M0	0is
T1	N0	M0	I
T2a	N0	M0	II
T2b	N0	M0	II
T3a, T3b, T4a	N0	M0	IIIA
T1-T4a	N1	M0	IIIA
T1-T4a	N2, N3	M0	IIIB
T4b	Any N	M0	IVA
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial GU Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial GU Tumour Team who were not involved in the guideline's development, including urologist, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2013.

Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; AJCC, American Joint Committee on Cancer; AUC, Area under the curve; BCG, Bacillus Calmette-Guerin; CBC, Complete blood count; CCA, Cancer Care Alberta; CIS Carcinoma in situ; CMV, Cisplatin, methotrexate, vinblastine; Cr, Creatinine.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GU Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

Conflict of Interest Statements

Dr. Bimal Bhindi* has been an advisory board member for Verity Pharmaceuticals; and has received speaker honoraria from Merck; and consultancy for Ferring.

Derek Tilley has nothing to disclose.

*Lead

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