



PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

GENITOURINARY

UROTHELIAL CANCER

GU Site Group – Urothelial Cancer

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1. INTRODUCTION

Urothelial cancers arise in the urothelium of the renal collecting systems, the ureters, bladder, prostate and urethra. The bladder is the most frequent site of disease accounting in Canada for 5.8% of new cancers and 3.3% of cancer deaths in males, and 2.1% of new cancers and 1.5% of cancer deaths in females (Canadian Cancer Statistics 2008). This difference in incidence is attributed in part to the smoking patterns seen between Canadian men and women. The most common histology is transitional cell carcinoma (TCC). An important feature of transitional cell malignancy is the propensity to behave as a field defect with multifocal disease in primary and recurrent presentations. Consequently the entire transitional urothelium is considered as a single functional unit at risk for purposes of investigation and follow-up of patients with transitional cell malignancy.

2. PREVENTION

The most effective prevention strategy for urothelial cancer is tobacco control, with avoidance of smoking or smoking cessation. All consenting smokers should be referred for smoking cessation programs. Other possible strategies to prevent urothelial cancer include reducing occupational exposure to smoke and other carcinogenic substances.

3. SCREENING AND EARLY DETECTION

There is no formal screening system for urothelial cancer. Patients at highest risk for TCC include current and former smokers, and patients with a history of TCC. The latter should participate in a long-term follow-up program that includes regular cystoscopy. Smokers without a diagnosis of TCC should undergo urinalysis for occult blood as a part of routine annual health assessment. Any individual with sterile gross hematuria should be referred to an urologist for formal assessment.

4. DIAGNOSIS

Diagnosis of TCC may be made with positive urinary cytology in some cases. Formal assessment requires thorough cystoscopic and radiologic inspection of the urothelium with biopsy of suspicious areas. Differential upper tract urinary cytology and cytological brushings of suspicious upper urinary tract lesions may be required in specific instances. Random biopsies of the bladder and prostatic urethra are required for invasive and high grade superficial disease. Staging and grading of bladder TCC is necessary for treatment and requires transurethral resection of bladder tumor (TURBT). Non-TCC urothelial bladder tumors may only be diagnosed through TURBT.

At the initial assessment, patients (particularly those with potentially curable cancers requiring multimodality input and/or treatment) should be assessed in a multidisciplinary environment.

Clinical Evaluation:

- Complete history in all patients
- Record of lower urinary symptomatology and bladder function
- Quantitative documentation of tobacco use, occupational carcinogen exposure
- Social & personal history (secondary exposure to smoke, carcinogens)
- Co-morbid conditions (previous cancers, heart disease, cerebrovascular disease, liver disease, diabetes, renal dysfunction)
- Family history of cancer
- Prior treatment of cancer, if any
- Complete physical examination in all patients.

Oncologic Imaging and Laboratory Evaluations:

Evaluation of local extent of disease:

Low grade superficial TCC: Urinary cytology and complete cystoscopic inspection of the bladder. Biopsy suspicious lesions.

High grade superficial and invasive TCC: Urinary cytology and complete cystoscopic inspection of the bladder. Biopsy suspicious lesions. Random biopsies of bladder and prostatic urethra. TURBT bladder tumor to include detrusor muscle. If there is no detrusor muscle in the specimen, the procedure should be repeated 4-6 weeks later.

Assessment of upper tracts: CT urogram or retrograde urograms. Cytologic brushing of suspicious lesions where possible. Differential ureteral cytology required in situation of positive cytology and no visible urothelial tumor.

Image guided needle biopsy of renal pelvic lesions in specific situations: All patients should have an MRI of the pelvis to complement systemic staging CT scans to optimally evaluate local and nodal disease extent for patients with muscle invasive bladder disease. If ordered following TURBT, imaging should be delayed until the acute surgical reaction has resolved.

Metastatic Workup: Imaging is undertaken for patients to determine the presence of nodal, visceral or skeletal metastases in high-risk individuals, or in those with signs or symptoms suggestive of metastatic disease.

- A contrast-enhanced CT of the abdomen and pelvis to detect metastases in pelvic or abdominal lymph-nodes or liver is limited to patients with superficially invasive or invasive high-grade disease. Metastases may be detected in the imaged skeleton, and these should be confirmed with a nuclear medicine bone scan.
- A nuclear medicine bone scan to detect metastases in the skeleton is limited to patients with invasive high grade disease.
- CT of the chest to detect lung metastases or concurrent lung primary in smokers is limited to patients with invasive high grade disease.

Laboratory Tests:

- CBC, electrolytes, calcium, creatinine, liver function studies

Other Investigations:

- CT or ultrasound guided aspiration biopsy to confirm malignancy in nodal, visceral or skeletal lesions suspicious on imaging.

5. PATHOLOGY

All patients should have documentation of the tumor histology and its subtype (See WHO Classification for prostate cancer in Appendix I).

Pathology reports in urothelial cancer should specify histological subtype and grade, the presence or absence of muscle tissue in TURBT specimens, and the presence or absence of muscle infiltration with tumor. Random biopsy specimens should report geographic location of disease.

In surgically resected specimens(e.g radical cystectomy), reports on type of specimen, tumor extensions, depth of invasion, whether there is muscle involvement, lymph node status and resection margins status must also be provided so that an accurate pathological staging of the tumor can be rendered.

All current and previous specimens from community hospitals should be obtained for expert uropathology review to accurately document the grade, stage and the patient's personal natural history of disease.

The 2002 WHO classification is the official classification system used for diagnosis, and is provided in Appendix I. Non-muscle invasive TCC is classified according to the Canadian Urological Association (CUA) management guidelines risk stratification (Appendix II).

Staging is according to the Joint UICC & AJCC Staging Seventh Edition, 2010. The following is a brief summary of the clinically relevant TN classification of bladder cancer:

Ta	Noninvasive, papillary
Tis	In-situ: "flat tumor"
T1	Subepithelial connective tissues
T2	Muscularis
T3	Beyond muscularis
T4	Prostate, seminal vesicle, uterus, vagina, pelvic side wall, abdominal wall
N1	Single
N2	Multiple
N3	Common iliac

More detailed description of urothelial staging is provided in Appendix II

6. MANAGEMENT

6.1 Bladder Cancer

Management strategies for newly diagnosed patients are based on assigned histology, stage (See appendix II), grade, urothelial disease pattern and patient factors such as serious co-morbidities, anticipated life-span and patient choice.

Curative treatment options include superficial therapy (TURBT + intravesical therapy); bladder conservation surgery; radical cystoprostatectomy; bladder conservation using radical radiotherapy.

Chemotherapy is used as primary, neoadjuvant, concomitant, or adjuvant therapy, in selected cases.

6.1.1 Primary presentation non-muscle invasive bladder disease (Ta, Tis, T1)

Low risk (Ta, low grade)

Complete TURBT of all known and suspected areas of disease.

Routine use of induction or maintenance intravesical therapy is not recommended.

Intermediate risk (Tis, T1 low grade)

Complete TURBT of all known and suspected areas of disease.

Intravesical therapy commencing 2-4 weeks following TURBT: Induction with 6 weekly courses of BCG and maintenance with 3 weekly cycles at 3 months and 6 months, then every 6 months up to 36 months.

High risk (T1 high grade)

Complete TURBT of all known and suspected areas of disease and repeat TURBT in 4-6 weeks

Intravesical therapy commencing 2-4 weeks following TURBT: Induction with 6 weekly courses of BCG and maintenance with 3 weekly cycles at 3 months and 6 months, then every 6 months up to 36 months.

Chemotherapy

There is no role for intravenous systemic chemotherapy in patients with non muscle invasive disease

Radiotherapy

Radiotherapy is not recommended for treatment of primary or recurrent carcinoma-in-situ.

6.1.2 Recurrent presentation non-muscle invasive bladder disease

Ta, low grade

Unifocal recurrence: Complete TURBT of all known and suspected areas of disease.

Routine use of induction or maintenance intravesical therapy is not recommended

Multifocal recurrence: Complete TURBT of all known and suspected areas of disease.

Intravesical BCG therapy commencing 2-4 weeks following TURBT as described in

6.1.1

Multifocal recurrence after BCG: Intravesical chemotherapy (mitomycin, epirubicin, adriamycin).

Failure of 2nd line therapy: Cystectomy or consider clinical trial.

Tis or T1 low grade

If BCG naïve: Complete TURBT of all known and suspected areas of disease.

Intravesical BCG therapy commencing 2-4 weeks following TURBT as described in

6.1.1

Prior BCG: 2nd induction with BCG for partial responders in reasonable. Intravesical chemotherapy (mitomycin, epirubicin, adriamycin) an option as well.

Failure of 2nd and 3rd line therapies: Cystectomy or drugs on clinical trial.

T1 high grade

If BCG naïve: Complete TURBT of all known and suspected areas of disease.

Intravesical BCG therapy commencing 2-4 weeks following TURBT as described in 6.1.1

Prior BCG: If reasonable prior response, a second induction course of BCG is reasonable

Failure of BCG: Cystectomy or consider clinical trial.

Chemotherapy

There is no role for intravenous systemic chemotherapy in patients with non muscle invasive disease

Radiotherapy

Radiotherapy is not recommended for treatment of primary or recurrent carcinoma-in-situ.

6.1.3 Muscle invasive bladder disease (T2-T4a, N1-3,NX, M0)

This may either represent newly diagnosed cancer or progression from non-muscle invasive disease. All cases of muscle invasive disease need to be discussed in a multidisciplinary manner (urologist, medical oncologist, and radiation oncologist). Standard treatment of muscle invasive bladder cancer consists of two possible approaches depending on tumor, physician and patient factors as indicated below.

Option 1

Cystectomy, lymphadenectomy and perioperative cisplatin-based chemotherapy. Chemotherapy can be administered either before surgery (neoadjuvant chemotherapy) or after surgery (adjuvant chemotherapy) but needs to be offered, because the risk of recurrence despite adequate surgery and lymphadenectomy approaches 50%..

a. **Surgery:**

Cystoprostatectomy with pelvic lymphadenectomy

- Radical cystoprostatectomy with urinary diversion
- En-bloc resection of involved structures if feasible
- Bilateral pelvic lymphadenectomy should be performed and include a minimum common, internal and external ilial and obturator lymph nodes

b. Chemotherapy:

There is Level 1 evidence to recommend neoadjuvant chemotherapy. For patients with adequate performance status and creatinine clearance >50, perioperative chemotherapy should be offered.

Chemotherapy regimens can include:

Gemcitabine and Cisplatin: Day 1,8, (21 day cycle) for 4 cycles or

Dose Dense MVAC: q2wkly for 4 cycles or

MVAC: q3 wkly for 4 cycles

Staging should be repeated after 2 cycles for Gem/Cis or MVAC. If there is response, complete 4 cycles of GC or MVAC. No midway staging is required for ddMVAC. If no response, then proceed to surgery when counts recover (3-4 weeks). Patients with T4a disease or bulky pelvic nodal disease who have responded after 2-3 cycles can complete 4-6 cycles before proceeding to definitive surgery or radiotherapy.

All patients not receiving neoadjuvant chemotherapy, should be offered adjuvant chemotherapy for which there is evidence of a benefit in terms of reducing risk of recurrence. Any of the regimens above can be considered.

Option 2

Patients who are agreeable to intense cystoscopic followup (every 3 months) and MRI imaging; or patients wanting a bladder sparing approach or patients who are not surgical candidates, can be offered maximum TURBT, followed by concurrent chemotherapy and radiation. These patients require cystoscopies every 3 months, and if a recurrence is detected need to be considered for salvage cystectomy.

Radiation Therapy:

Adequate bladder function

Evidence of no or limited CIS

No contraindication to pelvic radiotherapy

Treatment technique for EBRT

Daily image-guided intensity modulated radiotherapy (IMRT)

GTV will be identified with implanted fiducial marking if soft-tissue image guidance is not employed.

GTV: bladder tumor

CTV: bladder plus 1 cm margin around GTV

Dose to CTV: 60 Gy in 30 fractions over 6 weeks

Dose to GTV: Bladder boost of 6 Gy in 2 Gy fractions if normal tissue constraints permit. Pelvic lymph nodes will be treated in an initial treatment phase to 46 Gy in 23 fractions in 4.5 weeks.

Chemotherapy:

Creatinine clearance >50 ml/min

Intravenous cisplatin 40mg/m² IV once weekly

CBC, electrolytes, urea creatinine done weekly before chemotherapy.

Other chemotherapy agents (e.g. Gemcitabine) may be considered in the setting of poor renal function.

Followup:

Patients will undergo cystoscopic evaluation and an MRI abdomen and pelvis 8 weeks after treatment. After consultations between the urologist and radiation oncologist, those patients with persistent disease will undergo salvage cystectomy no later than 16 weeks after completing radiotherapy. Those with a complete response will enter the follow-up program described below.

Patients will undergo cystoscopic evaluation 12 weeks after treatment. Those with persistent disease will undergo salvage cystectomy. Those with a complete response will continue to be followed with clinical evaluation, cystoscopic evaluation and MRI abdomen and pelvis q 3-6 months for 1-2 years.

T4b (involving pelvic side-wall or abdominal wall) NOM0

Primary management is with chemotherapy, then depending on response to treatment, consolidation therapy with surgery or radiotherapy can be considered. Selection factors for type and use of consolidation treatment include volume and extent of disease, response to chemotherapy, patient preference. In some cases with bulky disease tri-modality therapy with chemotherapy, radiotherapy and surgery is an option if response to initial chemotherapy is suboptimal.

Patients not fit for primary chemotherapy may be treated with primary radiotherapy alone +/- low-dose chemotherapy.

Metastatic disease (M1)

Patients presenting with clinical evidence of metastatic disease in lymph nodes viscera or bone are treated with primary chemotherapy (regimens described below). Patients who achieve complete response in sites of metastatic disease may be considered for consolidation therapy to the primary tumor with surgery or radiotherapy.

Asymptomatic patients deemed incurable after multidisciplinary assessment may be treated with deferred chemotherapy when symptomatic.

Symptomatic patients not fit for chemotherapy are treated with palliative radiotherapy or best supportive care.

6.1.4 Metastatic TCC

Chemotherapy for symptomatic and/or high volume metastatic disease

Patient performance status 0-2, adequate renal function

1st line therapy: 6 cycles GC (restage after 3 cycles) or Gemcitabine/Carboplatin (if renal function compromised) or single agent gemcitabine (if likely to have poor tolerance of platinum agents) or MVAC

If disease progression is identified > 6 months after cisplatin (cisplatin refractory) consider retreatment or

2nd line therapy: For patients progressing < 6 months of neoadjuvant/adjuvant cisplatin, or < 6 months of first line chemotherapy, second line chemotherapy should be considered. Although there is no standard regimen, paclitaxel IV weekly or every 3 weeks is commonly used. These patients should be considered for clinical trials..

6.1.5 Management of progression after initial therapy

Superficial disease

Management of recurrent superficial disease is described in section 6.1.2

Muscle invasive disease

Bladder recurrence after radical radiotherapy

Management of superficial disease is outlined in 6.1.1

Muscle invasive disease: Cystoprostatectomy with urinary diversion.

Consider adjuvant chemotherapy if high-risk features identified (see 6.1.3)

Bladder recurrence after partial cystectomy

Management of superficial disease is outlined in 6.1.1

Muscle invasive disease: cystoprostatectomy with urinary diversion.

Consider adjuvant chemotherapy if high-risk features identified (see 6.1.3)

Pelvic soft-tissue recurrence after cystectomy

Patients may be considered for radical radiotherapy or immediate or deferred chemotherapy.

Selection factors for radical radiotherapy include ability to meet dose constraints on small bowel, no contraindication to pelvic radiotherapy.

Radiation dose and technique will be dictated by local anatomic factors.

Chemotherapy using a regimen described in 6.1.4 for patients not suitable for pelvic radiotherapy. Select patients may be considered for consolidative radiotherapy following chemotherapy.

Nodal recurrence after cystectomy

Patients may be considered for immediate or deferred chemotherapy using regimens described in 6.1.4.

Bone or visceral recurrence after cystectomy

Patients may be considered for immediate or deferred chemotherapy using a regimen described in 6.1.4.

6.1.6 Extravesical TCC

non- invasive extravesical disease

Carcinoma-in-situ prostatic urethra

Complete TURBT of all known and suspected areas of disease.

Intravesical BCG therapy to include resected prostatic urethra commencing 2-4 weeks following TURBT as described in 6.1.1

Carcinoma-in-situ ureter and renal pelvis

CIS is uncommonly diagnosed in these anatomic locations due to the difficulty in obtaining diagnostic biopsy specimens. Confirmed cases may be treated in selected cases with intraureteric and intrapelvic BCG therapy as described in 6.1.1 for intravesical disease. If this is not technically feasible then patients should undergo nephroureterectomy with cuff of bladder.

Invasive extravesical disease

Male urethra

Surgery:

Prostatic or penile urethra: Radical prostatectomy and urethrectomy.

Penile urethra: Penectomy and bilateral superficial inguinal node sampling.

Radiotherapy:

Prostatic and penile urethra: EBRT with daily image guided IMRT. Treatment volume and dose to be determined by local anatomic factors. Regional lymph nodes will be treated (inguinal for penile urethra,

Pelvic for prostatic urethra

Chemotherapy:

Neoadjuvant chemotherapy as described in 6.1.4 for bulky disease, or limited volume metastatic disease. Concomitant chemotherapy with radical radiotherapy. Adjuvant chemotherapy as described in 6.1.4 for those with high risk disease following surgery. Immediate or delayed chemotherapy for patients with non-curable disease.

Prostate ductal TCC

Surgery:

Radical prostatectomy and urethrectomy.

Radiotherapy:

EBRT with daily image guided IMRT.

GTV: Gross disease identified on pelvic imaging.

CTV: prostate and seminal vesicles + 5 mm expansion beyond GTV

PTV: 10 mm beyond CTV

Dose to CTV: 60-66Gy in 2Gy daily fractions, respecting dose constraints to bladder and rectum, and in consideration of any neoadjuvant anthracycline chemotherapy given

Regional pelvic lymph nodes will be treated to 46Gy in 23 fractions to 4.5 weeks

Chemotherapy:

Neoadjuvant chemotherapy as described in 6.1.4 for bulky disease, or limited volume metastatic disease. Concomitant chemotherapy with radical radiotherapy. Adjuvant chemotherapy as described in 6.1.4 for those with high risk disease following surgery. Immediate or delayed chemotherapy for patients with non-curable disease.

Female urethra

Surgery:

- Cystourethrectomy and partial vaginectomy with urinary diversion

Radiotherapy:

Perineal implant using high-dose rate or pulsed dose rate brachytherapy. Selection factors include no involvement of bladder neck and patient preference.

Chemotherapy:

Neoadjuvant chemotherapy as described in 6.1.4 for bulky disease, or limited volume metastatic disease. Adjuvant chemotherapy as described in 6.1.4 for those with high risk disease following surgery. Immediate or delayed chemotherapy for patients with non-curable disease

Renal pelvis and ureter

Surgery:

Nephroureterectomy with cuff of bladder
paraortic node sampling/dissection in selected individuals.

Chemotherapy:

Neoadjuvant chemotherapy as described in 6.1.4 for bulky disease, or limited volume metastatic disease. Adjuvant chemotherapy as described in 6.1.4 for those with high risk disease following surgery. Immediate or delayed chemotherapy for patients with non-curable disease

Radiotherapy:

Radical, neoadjuvant or adjuvant radiotherapy is not employed.

6.1.7 Adenocarcinoma of the bladder

Adenocarcinoma of the bladder can arise from the urachal remnant. Consequently disease is anatomically situated in the dome of the bladder, and may extend along the anterior abdominal wall towards the umbilicus. Stage classification and staging investigations are as outlined in section 6.1 for bladder cancer. There is no urothelial field defect associated with adenocarcinoma and evaluation for multifocal disease is not required.

Surgery:

Partial or total cystectomy depending on extent of disease. Resection of anterior abdominal wall if involved. Urachal remnants should be identified and resected.

Radiotherapy:

Radical radiotherapy is not employed.

Chemotherapy:

Neoadjuvant or adjuvant chemotherapy is not employed. Immediate or deferred chemotherapy is offered for non-curable disease. There is no standard regimen, but GI based regimens, for eg. FOLFOX, have shown the greatest benefit, over standard bladder regimens, from case reports in the literature.

6.8 Oncology Nursing Practice

Refer to [general oncology nursing practices](#)

7. SUPPORTIVE CARE**7.1 Patient Education**

Patient education is an integral aspect of cancer management in the GU site group. In addition to one-on-one education specific to the patient situation, written educational materials are provided to patients. The specific educational content is provided depending on the patient's diagnosis and management options. In addition, there is a library with resources available to the patient. Patients are encouraged to participate in prostate cancer support groups. These groups provide important peer support and education to recently diagnosed men and their families.

7.2 Psychosocial Care

Refer to [general psychosocial oncology care guidelines](#)

7.3 Symptom Management

Patients with urothelial cancer may have a multitude of physical and emotional symptoms related to their disease, treatment and co-morbid condition. DART and ESAS (Distress Assessment and Response Tool and Edmonton Symptom Assessment System) are the screening tools used to identify the symptoms of most concern to the patient. They add to the clinical assessment of the patient made by the clinician at an individual attendance, but are also recorded serially at each attendance, to observe outcomes of interventions used. Patients answers are reviewed by the nurse and oncologists, symptom management guides are used in response to this screening and patients with significant burden of symptoms can be referred to appropriate services (eg palliative care, social work etc).

7.4 Clinical Nutrition

Written materials on nutrition and health and access to a dietician are made available to patients with urothelial cancer.

7.5 Palliative Care

Refer to [general oncology palliative care guidelines](#)

8. FOLLOW-UP

Bladder TCC: Patients treated with curative radiotherapy or surgery

Follow-up is individualized during the acute period following radiotherapy or surgery.

All patients with bladder in-situ

Year 1: 3-monthly cystoscopy and urinary cytology. Biopsy of suspicious lesions

Year 2-5: 6 monthly cystoscopy and urinary cytology. Biopsy of suspicious lesions

Beyond year 5: Follow with annual urinary cytology.

Patients who are treated for relapse revert to year one follow-up protocol.

All patients post cystectomy

Year 1: Complete physical examination. 4-monthly Chest X-ray, CT abdomen and pelvis, CBC and liver function studies.

Year 2-5: Complete physical examination. 6-monthly Chest X-ray, CT abdomen and pelvis, CBC and liver function studies.

Beyond year 5: Follow-up is at discretion of treating oncologist.

All patients post radical radiotherapy

Week 8 post-treatment: MRI and cystoscopy

Years 1-2: q3-monthly cystoscopy and urinary cytology. Biopsy of suspicious lesions. q6-monthly MRI, chest X-ray, CT abdomen and pelvis, CBC and liver function studies.

Year 2-5: q6 monthly cystoscopy and urinary cytology. Biopsy of suspicious lesions. Annual MRI

Beyond year 5: Annual cystoscopy and urinary cytology.

Patients who are treated for relapse revert to year one follow-up protocol for post-cystectomy or post-chemotherapy

Extravesical TCC: Patients treated with curative radiotherapy or surgery

Renal pelvis and ureter TCC

Year 1: Complete physical examination. 4-monthly Chest X-ray, CT abdomen and pelvis, CBC and liver function studies. Urinary cytology.

Year 2-5: Complete physical examination. 6-monthly Chest X-ray, CT abdomen and pelvis, CBC and liver function studies. Urinary cytology.

Beyond year 5: Follow-up is at discretion of treating oncologist.

Prostate ductal TCC

Non-invasive (Tispsd)

Year 1: 6-monthly physical examination including DRE. Urinary cytology

Year 2-5: Annual physical examination including DRE. Urinary cytology

Invasive:

Year 1: 4-monthly complete physical examination including DRE (prostate in-situ only), Chest X-ray, CT abdomen and pelvis, CBC and liver function studies. Urinary cytology.

Year 2-5: 6-monthly complete physical examination including DRE (prostate in-situ only), Chest X-ray, CT abdomen and pelvis, CBC and liver function studies. Urinary cytology.

Beyond year 5: Follow-up is at discretion of treating oncologist.

Urethral TCC

Year 1: Complete physical examination. 4-monthly Chest X-ray, CT abdomen and pelvis, CBC and liver function studies. Urinary cytology.

Year 2-5: Complete physical examination. 6-monthly Chest X-ray, CT abdomen and pelvis, CBC and liver function studies. Urinary cytology.

Beyond year 5: Follow-up is at discretion of treating oncologist.

Adenocarcinoma of bladder

Year 1: 4-monthly complete physical examination, Chest X-ray, CT abdomen and pelvis, CBC and liver function studies.

Year 2-5: 6-monthly complete physical examination, Chest X-ray, CT abdomen and pelvis, CBC and liver function studies

Beyond year 5: Follow-up is at discretion of treating oncologist.

Patients treated with non-curative intent

Follow-up interval and investigations are individualized to the type of treatment employed, symptoms present and pace of disease.

APPENDIX I – PATHOLOGICAL CLASSIFICATION OF UROTHELIAL CANCER

2002 WHO Classification for urothelial cancer:

Normal Urothelium

- Normal urothelium consists of a flat mucosa lined by less than approximately seven layers of urothelial cells covered by an umbrella cell layer. There is no need to count the number of cell layers in order to distinguish normal urothelium from flat urothelial hyperplasia. Rather, only overt thickening should be designated as hyperplasia. The size of normal urothelial cells is approximately 3 times the size of lymphocytes, which can almost always be found in the underlying lamina propria. Flat lesions with benign cytology and minimal disorder should not be designated as mild dysplasia but rather as normal urothelium. Atypia in umbrella cells should not be overdiagnosed as dysplasia or CIS.

Papillary Hyperplasia

- Papillary hyperplasia is characterized by slight “tenting”, undulating, or an elevated configuration of the urothelium of varying thickness, lacking nuclear atypia. The lesion often has one or a few small, dilated capillaries at its base but it lacks a well-developed fibrovascular core.

Urothelial Papilloma

- Urothelial papilloma is defined as discrete papillary growth with a central fibrovascular cores lined by urothelium of normal thickness and cytology. There is no need for counting the number of cell layers.

Papillary Urothelial Neoplasm of Low Malignant Potential

- Papillary urothelial neoplasm of low malignant potential is a papillary urothelial lesion with an orderly arrangement of cells within papillae with minimal architectural abnormalities and minimal nuclear atypia irrespective of the number of cell layers. The urothelium in papillary urothelial neoplasms of low malignant potential is much thicker than in papillomas and/or the nuclei are significantly enlarged and somewhat hyperchromatic. Mitotic figures are infrequent in papillary urothelial neoplasms of low malignant potential, and usually confined to the basal layer.

Low-grade Papillary Urothelial Carcinoma

- Low-grade papillary urothelial carcinomas are characterized by an overall orderly appearance but with easily recognizable variation of architectural and or cytologic features even at scanning magnification. Variation of polarity and nuclear size, shape, and chromatin texture comprise the minimal but definitive cytologic atypia. Mitotic figures are infrequent and usually seen in the lower half, but may be seen at any level of the urothelium. It is important to recognize that there may be a spectrum of cytologic and architectural abnormalities within a single lesion, such that the entire lesion should be examined, with the highest grade of abnormality noted.

High-grade Papillary Urothelial Carcinoma

- High-grade papillary urothelial carcinomas are characterized by a predominantly or totally disorderly appearance at low magnification. The disorder results from both architectural and cytologic abnormalities. Architecturally, cells appear irregularly clustered and the epithelium is disorganized. Cytologically, there is a spectrum of pleomorphism ranging from moderate to marked. The nuclear chromatin tends to be clumped and nucleoli may be prominent. Mitotic figures, including atypical forms, are frequently seen at all levels of the urothelium. There is an option in the diagnosis of high-grade papillary urothelial carcinoma to comment on whether there is marked nuclear anaplasia.

Flat Urothelial Hyperplasia

- Flat urothelial hyperplasia consists of a markedly thickened mucosa without cytological atypia. Rather than requiring a specific number of cell layers, marked thickening is needed to diagnose flat hyperplasia. This lesion may be seen in the flat mucosa adjacent to low-grade papillary urothelial lesions. When seen by itself there is no data suggesting that it has any premalignant potential.

Reactive Urothelial Atypia

- Reactive (inflammatory) atypia consists of nuclear abnormalities occurring in acutely or chronically inflamed urothelium. In reactive atypia, nuclei are uniformly enlarged and vesicular, with central prominent nucleoli. Mitotic figures may be frequent. A history of instrumentation, stones, or therapy is often present. In the absence of appreciable nuclear hyperchromasia, pleomorphism, and irregularity in the chromatin pattern, the lesion should not be considered neoplastic.

Urothelial Atypia of Unknown Significance

- In some cases it is difficult to differentiate between reactive and neoplastic atypia. There may be a greater degree of pleomorphism and/or hyperchromatism out of proportion to the extent of the inflammation, such that dysplasia can not be ruled out with certainty. These cases should be designated as "atypia of unknown significance" so that the patients may be followed more closely and re-evaluated once the inflammation subsides.

Dysplasia

- Dysplastic urothelium has appreciable cytologic and architectural changes felt to be preneoplastic, yet falling short of the diagnostic threshold for carcinoma in situ.

Carcinoma in situ

- Carcinoma in situ is a flat lesion of the urothelium that is a documented precursor of invasive cancer in some cases. The lesion is characterized by the presence of cells with large, irregular, hyperchromatic nuclei that may be either present in the entire thickness of the epithelium or only part of it. Mitotic activity is frequently

observed, often in the mid to upper urothelium. Carcinoma in situ encompasses lesions which in the past were designated as severe dysplasia or marked atypia.

APPENDIX II – BLADDER CANCER STAGING (Joint UICC & AJCC Staging Seventh Edition, 2010):

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Ta Noninvasive, papillary
- Tis In-situ: “flat tumor”
- T1 Tumor invades subepithelial connective tissues
- T2 Tumor invades muscle
- T2a Tumor invades superficial muscle (inner half)
- T2b Tumor invades deep muscle (outer half)
- T3 Tumor invades perivesical tissue
- T3a Microscopically
- T3b Macroscopically (extravesical mass)
- T4 Tumor invades any of the following: prostate stroma, seminal vesicles uterus, vagina, pelvic side wall, abdominal wall
- T4a Tumor invades prostate stroma, seminal vesicles, uterus, vagina
- T4b Tumor invades pelvic side wall, abdominal wall

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastases
- N1: Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)
- N2: Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)
- N3: Metastasis in a common iliac lymph node(s)

Distant Metastasis (M)

- M0 No distant metastasis
- M1: Distant metastasis

Stage Groupings

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a,T2b	N0	M0
Stage III	T3a,b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1,N2,N3	M0
	Any T	Any N	M1

RISK CLASSIFICATION FOR NON-MUSCLE INVASIVE DISEASE

(Canadian Urological Association practice guidelines)

Low risk: Ta, low grade

Intermediate risk: Tis, T1 low grade

High risk: T1 high grade

RENAL PELVIS AND URETER STAGING (Joint UICC & AJCC Staging Seventh Edition, 2010):

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Ta Noninvasive, papillary tumor
- Tis Carcinoma in-situ
- T1 Tumor invades subepithelial connective tissues
- T2 Tumor invades muscularis
- T3 (Renal pelvis) Tumor invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumor invades beyond muscularis into periureteric fat.
- T4 Tumor invades adjacent organs or through the kidney into perinephric fat.

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastases
- N1: Metastasis in a single lymph node 2 cm or less in greatest dimension
- N2: Metastasis in a single lymph node more than 2 cm but more than 5 cm in greatest dimension, or multiple lymph nodes none more than 5 cm in greatest dimension.
- N3: Metastasis in a lymph node more than 5 cm in greatest dimension.

Distant Metastasis (M)

- M0 No distant metastasis
- M1: Distant metastasis

Stage Groupings

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IV	T4	N0	M0
	Any T	N1,N2,N3	M0
	Any T	Any N	M1

URETHRA STAGING (Joint UICC & AJCC Staging Seventh Edition, 2010):

Urethra male and female

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Ta Noninvasive, papillary, polypoid or verrucous carcinoma.
- Tis Carcinoma in-situ
- T1 Tumor invades subepithelial connective tissues
- T2 Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
- T3 Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
- T4 Tumor invades other adjacent organs (invasion of bladder).

Urothelial (Transitional cell) carcinoma of the prostate

- Tis pu Carcinoma in-situ, involvement of prostatic urethra
- Tis pd Carcinoma in-situ, involvement of prostatic ducts
- T1 Tumor invades subepithelial connective tissues
(for tumors involving prostatic urethra only)
- T2 Tumor invades any of the following: corpus spongiosum, periurethral muscle
- T3 Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
- T4 Tumor invades other adjacent organs (invasion of bladder).

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastases
- N1: Metastasis in a single lymph node 2 cm or less in greatest dimension
- N2: Metastasis in a single lymph node more than 2 cm in greatest dimension, or multiple lymph nodes.

Distant Metastasis (M)

- M0 No distant metastasis
- M1: Distant metastasis

Stage Groupings

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
	Tispu	N0	M0
	Tispd	N0	M0
	T1	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1,2	N1	M0
	T3	N0,N1	M0
Stage IV	T4	N0,N1	M0
	Any T	N2	M0
	Any T	Any N	M1