Guideline Resource Unit
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Upper Tract Urothelial Tumours

Effective Date: October 2024

Background

Bladder cancer is the fourth most common cancer among men and accounts for 8% of all new male cancer cases. Urinary bladder cancer is less common among women (ranked 11th) and accounts for less than 3% of all new female cancer cases. Statistics Canada estimates that in Canada in 2024 there will be approximately 12,300 new cases of bladder cancer and 2,600 deaths associated with bladder cancer [link]. Upper tract disease represents approximately 5-10% of all urothelial malignancies.[1]

Upper tract tumours can be graded, in order to distinguish those with a low risk of recurrence from those with a high risk. The grading system was developed by the World Health Organization (WHO) in 2004.[2] Papillary urothelial neoplasms of low malignant potential (PUNLMP) have a low rate of recurrence (36%) and stage progression (3.7%) as compared to low grade papillary urothelial carcinomas (50% and 10%, respectively). High grade papillary urothelial carcinomas have a high rate of recurrence and stage progression. The progression rate ranges from 15 to 40%.[3, 4]

Guideline Questions

1. What staging investigations are required for patients with upper tract tumours?
2. What are the appropriate treatment options (i.e., surgery, systemic therapy, etc.) for patients with upper tract tumours?
3. What is a reasonable follow-up strategy for patients who have completed treatment for upper tract tumours?

Search Strategy

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, urologists, pathologists, nurses, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Unit Handbook.

Target Population

These guideline recommendations apply to adult patients with transitional cell carcinoma (urothelial carcinoma) of the ureter and/or renal pelvis.

Recommendations

Staging

A. Laboratory Investigations

i. Urine cytology.

ii. Complete blood count.

iii. Basic metabolic panel (renal function).

B. Imaging studies

i. CT urography, CT abdomen/pelvis and chest imaging.

ii. Retrograde pyelogram, cystoscopy, +/- uteroscopy with tissue biopsy.

iii. Renal scan (optional).

iv. Bone scan if abnormal enzymes or if bone signs/symptoms.

Surgical Treatment

A. Primary Therapy for the Renal Pelvis

i. Low Grade (WHO Classification)

a. Nephroureterectomy with cuff of bladder is considered standard of care.

b. Endoscopic ablation in select situations.

ii. High Grade (WHO Classification) or Parenchymal Invasion

a. Nephroureterectomy with cuff of bladder.

b. Regional lymph node dissection.

B. Primary Therapy for the Urothelial Carcinoma of the Ureter

i. Low Grade (WHO Classification)

a. Nephroureterectomy with cuff of bladder.

b. Endoscopic resection.

c. Excision and ureteroureterostomy (low-grade mid-ureter).

d. Distal ureterectomy (distal-ureter).

ii. High Grade (WHO Classification)

a. Nephroureterectomy with cuff of bladder.

b. Endoscopic resection.

c. Excision and ureteroureterostomy (low-grade mid-ureter).

d. Distal ureterectomy (distal-ureter).

e. Regional lymph node dissection.

Neoadjuvant Chemotherapy

A. Neoadjuvant chemotherapy should be considered if the degree of disease invasiveness can be established prior to surgery.

i. Neoadjuvant chemotherapy should be cisplatin-based combination therapy. Options include cisplatin-gemcitabine or dose-dense MVAC. A total of 4 cycles should be planned. A standard dosing option for each regimen is provided below:

ii. Cisplatin-gemcitabine (21-day cycle): cisplatin 70 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8 (total dose per cycle = 2500 mg/m^2).

iii. ddMVAC (14-day cycle): methotrexate 30 mg/m^2 day 1, cisplatin 70 mg/m^2 day 2, vinblastine 3 mg/m^2 day 2, doxorubicin 30 mg/m^2 day 2, plus GCSF support.

iv. Consideration for split-dose cisplatin (cisplatin dose divided over 2 separate days) can be considered for patients who are otherwise good candidates for neoadjuvant chemotherapy but

have a creatinine clearance between 45-60 mL/min. Standard dosing options for split-dose regimens are provided below:

a. Split-dose cisplatin-gemcitabine (21-day cycle): cisplatin 35 mg/m^2 days 1 and 8, gemcitabine 1250 mg/m^2 days 1 and 8 (total dose per cycle = 2500 mg/m^2).

b. Split-dose ddMVAC (14-day cycle): methotrexate 30 mg/m^2 day 1, cisplatin 35 mg/m^2 days 1 and 2, vinblastine 3 mg/m^2 day 2, doxorubicin 30 mg/m^2 day 2, plus GCSF support.

v. Patients with contraindications to cisplatin should proceed directly to definitive locoregional therapy – routine use of carboplatin-based neoadjuvant combinations is not advised.

vi. For patients receiving cisplatin-gemcitabine, a CT scan of abdomen and pelvis should be performed after 2 cycles to exclude progression. If disease progression has occurred, then neoadjuvant chemotherapy should be abandoned and the patient should be taken to surgery if feasible. Imaging should also be performed prior to surgery.

Adjuvant Therapy

A. The decision as to whether to give adjuvant therapy is based on the pathologic stage of disease. For staging, refer to the Appendix.

i. pT0-1 Disease

a. No adjuvant therapy is recommended.

ii. pT2-4, OR N+ Disease

a. Adjuvant chemotherapy is recommended for eligible patients with pT2-4NxM0 or pTxN1-3M0 disease who have not received neoadjuvant chemotherapy. This is supported by Level 1 evidence. [22]

1. Chemotherapy is platinum-based combination therapy (e.g. cisplatin 70 mg/m2 day 1 or carboplatin, AUC 4.5-5, and gemcitabine, 1000-1250 mg/m2 day 1 and 8 q 21 days for 4 cycles. Adjuvant chemotherapy is not recommended for patients who have received NAC.

b. Adjuvant immunotherapy can be considered for high-risk patients. The Phase III Checkmate 274 trial demonstrated an improvement in disease-free survival in patients with urothelial carcinoma with high-risk muscle-invasive disease after surgery with one-year of adjuvant nivolumab compared to placebo.[5] Extended follow-up data presented at the European Urology Association meeting reported that adjuvant nivolumab demonstrated improvements in overall survival [link]. Eligibility criteria included:

1. Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy OR

2. Patients with pT3-4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin-based chemotherapy

3. Radical surgery within the past 120 days

4. Disease-free status within 4 weeks of dosing

- Nivolumab was delivered as 240mg IV q2weekly x 1 year in the Checkmate 274 study
- Nivolumab is Health Canada approved for this indication and is currently funded and available in Alberta. Dosing can be 240 mg q2weekly or 480 mg q4weekly.

Primary Therapy for Metastatic Urothelial Carcinoma

A. Chemotherapy is recommended for metastatic upper tract tumours. Please refer to the Alberta Health Services, Cancer Care guidelines on metastatic bladder cancers [link] for treatment options.

Follow-up

Table 1. Recommended protocol for follow-up after surgery (adapted from CUA Guideline[23])

Pathology	Investigations	No. months after surgery								
		3	6	12	18	24	30	36	48	60
LG pT<2,Nx/0										
	Hx and PE	x	x	x	x	x		x	x	x
	Blood work	x	x	x	x	x		x	x	x
	Urine cytology	x	x	x	x	x		x	x	x
	Cystoscopy	x	x	x	x	x		x	x	x
	CxR			x		x		x	x	x
	CTU			x		x		x	x	x
	±Ureteroscopy*	x	x	x	x	x		x	x	x
HG pT<2 Nx/0 or LG pT2 Nx/0										
	Hx and PE	x	x	x	x	x		x	x	x
	Blood work	x	x	x	x	x		x	x	x
	Urine cytology	x	x	x	x	x		x	x	x
	Cystoscopy	x	x	x	x	x		x	x	x
	CxR		x	x	x	x		x	x	
	CTU		x	x	x	x		x	x	
	±Ureteroscopy*	x	x	x	x	x		x	x	x
LG/HG pT>2 or pN+										
	Hx and PE	x	x	x	x	x		x	x	x
	Blood work	x	x	x	x	x		x	x	x
	Urine cytology	x	x	x	x	x		x	x	x
	Cystoscopy	x	x	x	x	x		x	x	x
	CxR	x	x	x	x	x	x	x	x	x
	CTU	x	x	x	x	x	x	x	x	x
	±Ureteroscopy*	x	x	x	x	x		x	x	x

Discussion

Due to the small number of patients that present with primary transitional cell carcinoma (TCC) of the ureter and renal pelvis, there is a lack of high level evidence (i.e., randomized controlled trials) to inform the treatment strategies for this disease. For this reason, many of the recommendations are based on findings from studies involving patients with TCC of the bladder. Physicians should take into account specific clinical characteristics of each patient with regard to renal function, comorbidities, tumour location, stage and grade when determining the optimal treatment for their patients.[6]

Surgery

If the tumour is operable, surgical excision is recommended. Nephroureterectomy with cuff of bladder excision is recommended, or if possible, a nephron-sparing procedure for low-grade disease. Lymph node dissection is recommended in high-grade cases. An analysis of the SEER database compared the cancer-specific mortality of patients with pT1-4 (any N, M0) disease who underwent a nephroureterectomy with a bladder cuff excision versus those who had a nephroureterectomy alone. The results indicated that the cancer-specific mortality was higher at 2 and 5 years among patients in the nephroureterectomy only group (17.7% and 28.1% versus 12.2% and 22.4%). However, patients that underwent bladder cuff excision were significantly younger.[7] A single institution retrospective study, comparing outcomes associated with nephroureterectomy versus nephron-sparing endoscopic surgery, among 96 patients with upper tract TCC, showed that the 5-year overall survival rate was comparable between treatment groups (i.e., 72% for nephroureterectomy and 75% for nephron-sparing approach). Patients with low grade disease treated with a nephron-sparing approach had a higher 5-year metastases-free survival (94% versus 88%) and 5-year cancer-specific survival (100% versus 89%), along with a lower complication rate (9.3% versus 29%). The authors concluded that endoscopic management provides cancer related and overall survival equivalent to that of nephroureterectomy in patients with low-grade disease.[8] An abstract presented at the American Urological Association meeting in May 2012 analyzed the outcomes of 1029 patients with upper tract TCC from the Canadian UTUC database.[9] In multivariate analyses, no differences were found in overall survival or disease-specific survival based on surgical approach (extravesical management, open bladder cuff excision or endoscopic management). Furthermore, open bladder cuff excision was found to reduce tumour recurrence compared with extravesical management (HR=0.628, 95% CI 0.491-0.801, p=0.0002).[9]

Neoadjuvant Therapy

Cases in which systemic therapy is being considered should be brought to and discussed at local tumour board meetings. Neoadjuvant chemotherapy can be considered in high grade patients, if the degree of invasiveness can be established prior to surgery. There is no strong evidence that neoadjuvant chemotherapy is effective in the treatment of TCC of the renal pelvis and ureter due to the rarity of the disease and lack of literature.[6, 10] A retrospective comparative study comparing patients with biopsy-proven high-grade disease who received neoadjuvant chemotherapy followed by nephrouterectomy with patients who underwent initial nephroureterectomy (N=150) demonstrated

significant downstaging with neoadjuvant chemotherapy (p =.004). The incidence of tumors classified as pathologic T2 (pT2) or as pT3 or higher was significantly lower in the study group (pT2, 65.4% vs 48.8%; P = .043; pT3 or higher, 47.7% vs 27.9%; P = .029).[11] Based on this data, the European Guidelines on Upper Tract Urothelial Carcinomas recommend this strategy.[11] Furthermore, because of the comparable etiology between TCC of the bladder and that of the upper tract, findings from studies involving patients with invasive bladder cancer can be extrapolated to patients with high-grade upper tract urothelial carcinoma.[12, 13] A meta-analysis by the Advanced Bladder Cancer (ABC) Meta-analysis Collaboration (2005) of 11 trials (N=3005) found a significant survival benefit with platinum-based combination chemotherapy (HR=0.86, 95% CI 0.77-0.95, p=.003), equivalent to a 5% absolute improvement in survival at 5 years. A significant disease-free survival benefit was also noted in those patients that received neoadjuvant platinum-based chemotherapy (HR=0.78, 95% CI 0.71-0.86, p<.0001).[14] Another meta-analysis of eight trials of neoadjuvant cisplatinum-based combination chemo-therapy for TCC of the bladder published similar results; the pooled HR was 0.87 (95%, CI 0.78-0.96, p=.006), consistent with an absolute overall survival benefit of 6.5%.[15] A more recent retrospective study that included patients with upper tract TCC who received neoadjuvant chemotherapy following by laparoscopic nephroureterectomy showed that, as compared to nephroureterectomy alone, neoadjuvant chemotherapy was associated with a significantly higher complete response rate (15% versus 1.7%); however, complications were higher in the neoadjuvant chemotherapy group (58% versus 45%).[16] Similar results have been reported elsewhere.[17]

Adjuvant Therapy

The open-label phase 3 POUT trial compared adjuvant chemotherapy to surveillance after nephroureterectomy with curative intent in UTUC patients. Chemotherapy was cisplatin or carboplatin (for GFR <50 mL/min) plus gemcitabine. A total of N=261 patients were enrolled from 57 sites. Adjuvant chemotherapy significantly improved disease-free survival (HR: 0.45; 95%CI: 0.330-0.68; p<0.001) after a median follow-up of 30.3 months. Treatment associated adverse events were reported in 44% of patients who underwent chemotherapy.[18]

The phase III double-blind CheckMate 274[19] randomized (N=709) patients with muscle-invasive urothelial carcinoma who had undergone radical surgery (1:1) to receive nivolumab or placebo every 2 weeks for up to 1 year (cisplatin-based chemotherapy before trial entry was allowed). After a median follow-up of 20.9 months, median DFS was 20.8 months with nivolumab vs 10.8 months with placebo HR: 0.70 (95%CI: 0.55-0.90; p<0.001). The percentage of patients who were alive and free from recurrence at 6 months was 77.0% with nivolumab and 62.7% with placebo HR: 0.72 (95%CI: 0.59-0.89); those with PD-L1 expression level of 1% or more was 75.3% and 56.7%, respectively HR: 0.55 (95%CI: 0.39-0.79). Treatment-associated grade ≥3 adverse events were 17.9% in the nivolumab group and 7.2% in the placebo group. A presentation at the European Urology Association annual meeting reported overall survival data after additional follow-up and found that nivolumab improved overall survival in the entire population (median 69.5 months vs 50.1 months) HR: 0.76 (95%CI: 0.61-0.95) and in the PD-L1 >1% population HR: 0.56 (95%CI: 0.36-0.86) [link].

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Appendix A: Bladder Cancer TNM Staging AJCC 8th edition[20]

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Urothelial carcinoma in situ: "Flat tumor"
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical soft tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Extravesical tumor directly invades any of the following: Prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades directly into prostatic stroma, seminal vesicles, uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall
Regional lymph nodes (N)	
N category	**N criteria**
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non-lymph-node distant metastases

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

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 surgical oncologists, radiation oncologists, medical oncologists, urologists, 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 2025. 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; CCA, Cancer Care Alberta; CI, Confidence Interval; HR, Hazard Ratio; MVAC, Methotrexate Vinblastine Doxorubicin and Cisplatin; TCC, Transitional Cell Carcinoma; UTUC, Upper Tract Urothelial Carcinoma

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. Nimira Alimohamed reports receiving grants from Astellas, AstraZeneca, Janssen, Merck, and Pfizer.

Derek Tilley has nothing to disclose.

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