UPPER TRACT UROTHELIAL TUMOURS

Effective Date: April 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team 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.
BACKGROUND

There were an estimated 429 new cases of kidney cancer and 315 new cases of bladder cancer in Alberta in 2009. However, upper tract urothelial carcinoma (i.e., cancer of the renal pelvis and ureters) is far rarer, accounting for only 10% of all renal tumors and only 5% of all urothelial tumors of the urinary tract. Most of these tumors occur in the renal pelvis. The majority (i.e., 95%) of upper tract tumors are transitional cell carcinoma (TCC). Patients with primary TCC of the bladder have a lifetime risk of 2 to 4% of developing a tumor in the upper tract; whereas patients with primary TCC of the upper tract have a risk of developing bladder cancer between 25 and 75%.

Upper tract tumors can be graded, in order to distinguish those with a low risk or recurrence from those with a high risk. The grading system was developed by the World Health Organization (WHO) in 2004. 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%.

GUIDELINE QUESTIONS

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

DEVELOPMENT AND REVISION HISTORY

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 Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

The PubMed database was searched for relevant literature using the following search terms: (renal pelvis AND neoplasm) OR (ureter AND neoplasm) AND transitional cell carcinoma. Results were limited to clinical trials, practice guidelines, systematic reviews, and meta analyses published from 1991 through 2012 March. The Medline database was also searched using the MeSH terms “Carcinoma, Transitional Cell” with subheadings drug therapy, radiotherapy, surgery and therapy, combined with the MeSH terms “Kidney Pelvis” and “Urinary Bladder Neoplasms.” Results were limited to literature published between 1990 and 2012 March. Based on feedback from the working group, the Medline database was searched subsequently using the MeSH terms “Carcinoma, Transitional Cell” AND “Neoadjuvant therapy” with
subheading drug therapy. Results were limited to literature published from 1990 through 2012 July. Non-relevant publications were excluded, as well as any publications that did not report survival outcomes.

The National Comprehensive Cancer Network (NCCN), British Columbia Cancer Agency (BCCA), European Society of Medical Oncology (ESMO), National Institutes of Health and Clinical Excellence (NICE), American Society of Clinical Oncology (ASCO), Scottish Intercollegial Guidelines Network (SIGN), Cancer Council Australia (CCA), and Cancer Care Ontario (CCO) websites were searched for guidelines on the management of upper tract tumours. A total of three guidelines, one meta-analysis, and 22 clinical studies (i.e., retrospective case series, prospective cohort studies, phase II-III trials) were included.

TARGET POPULATION

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

RECOMMENDATIONS

Work-up for:

Laboratory investigations
- urine cytology
- complete blood count
- basic metabolic panel (renal function)

Imaging studies
- IVP, CT urography, retrograde pyelogram, uroscopy, or MRI urogram (upper tract collecting system)
- cystoscopy
- chest x-ray
- renal scan (optional)
- bone scan if abnormal enzymes or if bone signs/symptoms

Treatment:

Primary Therapy for the Renal Pelvis

Low Grade (WHO Classification)
- Nephroureterectomy with cuff of bladder or nephron-sparing procedure, if necessary, due to renal impairment and/or comorbidities.

High Grade (WHO Classification) or Parenchymal Invasion
- Nephroureterectomy with cuff of bladder.
- Regional lymph node dissection.
- Neoadjuvant chemotherapy can be considered, if the degree of disease invasiveness can be established prior to surgery.
Chemotherapy is usually given as cisplatinum-based combination therapy (e.g. cisplatinum, 70 mg/m² day 1 and gemcitabine, 1000-1250 mg/m² day 1 and 8 q 21 days).

Neoadjuvant therapy should be given only when renal function is optimal.

Patients with contraindications to cisplatinum should proceed directly to definitive therapy, as the routine use of carboplatinum-based neoadjuvant combinations cannot be advised.

Following neoadjuvant chemotherapy patients should have a CT scan of abdomen and pelvis, prior to the cystectomy.

Primary Therapy for the Urothelial Carcinoma of the Ureter

Low Grade (WHO Classification)
- Nephroureterectomy with cuff of bladder or nephron-sparing procedure, if necessary, due to renal impairment and/or comorbidities.

High Grade (WHO Classification)
- Excision options:
  - Nephroureterectomy with cuff of bladder.
  - Endoscopic resection.
  - Excision and ureteroureterostomy (low-grade mid-ureter).
  - Distal ureterectomy (distal-ureter)
- Regional lymph node dissection.

Neoadjuvant chemotherapy should be considered in selected patients with proven high-grade disease or imaging suggesting invasive disease.

Chemotherapy is usually given as cisplatinum-based combination therapy (e.g. cisplatinum, 70 mg/m² day 1 and gemcitabine, 1000-1250 mg/m² day 1 and 8 q 21 days).

Neoadjuvant therapy should be given only when renal function is optimal.

Patients with contraindications to cisplatinum should proceed directly to definitive therapy, as the routine use of carboplatinum-based neoadjuvant combinations cannot be advised.

Following neoadjuvant chemotherapy patients should have a CT scan of abdomen and pelvis, prior to the cystectomy.

Primary Therapy for Metastatic Urothelial Carcinoma

Chemotherapy is recommended for metastatic upper tract tumours. Please refer to the Alberta Health Services, Cancer Care guideline, Bladder Cancer (www.albertahealthservices.ca/hp/if-hp-cancer-guide-gu002-bladder.pdf) for treatment options.

Adjuvant Therapy

The decision as to whether to give adjuvant therapy is based on the pathologic stage of disease. For staging, refer to the Appendix.
pT0-1 Disease
- No adjuvant therapy is recommended.

T2-4, N+ Disease
- Adjuvant chemotherapy can be considered.
  - Chemotherapy is usually given as cisplatinum-based combination therapy (e.g. cisplatinum, 70 mg/m² day 1 and gemcitabine, 1000-1250 mg/m² day 1 and 8 q 21 days).
  - Adjuvant therapy should be given when renal function is optimal.
  - Patients who are ineligible for cisplatinum based combination therapy in the adjuvant setting should not routinely receive carboplatin-based regimens as there is no evidence for benefit.

Follow-up:
- Cystoscopic evaluation every 3 months for the first year, then at every 6 months up to 2 years, then annually for 10 years.
- Chest x-ray as clinically indicated, then at increasing intervals (i.e., decreasing frequency).
- Radiological evaluation of lymph nodes and contra lateral upper tract, as clinically indicated.
- Duration as clinically indicated.

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.  

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.  

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. 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. 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).

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. A retrospective comparative study comparing patients with biopsy-proven high-grade disease who received neoadjuvant chemotherapy followed by nephroureterectomy 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). Based on this data, the European Guidelines on Upper Tract Urothelial Carcinomas recommend this strategy. 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. 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). 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%. 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%). Similar results have been reported elsewhere.

Adjuvant Therapy

For pT2-4, node positive disease, adjuvant chemotherapy can be considered; cisplatin combined with gemcitabine is recommended. This recommendation is again extrapolated from literature on TCC of the bladder. The ABC Meta-analysis Collaboration (2006) conducted a meta-analysis of data from 491 patients from 16 trials of adjuvant platinum-based chemotherapy in invasive bladder cancer. Trials were included if they randomized patients with biopsy proven stage T2-4a TCC and if patients received local definitive treatment, with or without adjuvant chemotherapy. The HR for overall survival was 0.75 (95% CI 0.60-0.96, p=.019). A limitation of this analysis is that some of the trials were closed early and included patients that did not receive the prescribed treatments. A retrospective case series, including patients with pT3N0M0 upper tract tumours, compared radical nephroureterectomy and lymphadenectomy followed by
MVAC chemotherapy with radical nephroureterectomy and lymphadenectomy alone (no MVAC chemotherapy). The five-year recurrence-free and disease-free survival rates were similar between both groups (68.2% versus 62.3%; p=.794 and 62.3% versus 70.7%; p=.783). A similar case series reviewed the outcomes of patients with upper tract TCC (pT3-4, any N; N=542) who underwent radical nephroureterectomy either with or without adjuvant chemotherapy (59% patients received MVAC). The median overall survival in the MVAC group was 24 months, as compared to 26 months among those patients who underwent only radical nephroureterectomy.

GLOSSARY OF ABBREVIATIONS

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<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>confidence interval</td>
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<td>HR</td>
<td>hazard ratio</td>
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<td>MVAC</td>
<td>methotrexate, vinblastine, doxorubicin, cisplatin</td>
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<td>TCC</td>
<td>transitional cell carcinoma</td>
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<td>UTUC</td>
<td>upper tract urothelial carcinoma</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
REFERENCES


APPENDIX

American Joint Committee on Cancer (AJCC)
TNM Staging for Renal Pelvis and Ureter Cancer (7th ed., 2010)

Primary Tumour (T)
Tx: Primary tumour cannot be assessed
T0: No evidence of primary tumour
Ta: Papillary noninvasive carcinoma
Tis: Carcinoma in situ
T1: Tumour invades the subepithelial connective tissue
T2: Tumour invades the muscularis
T3: (For renal pelvis only) Tumour invades beyond the muscularis into peripelvic fat or renal parenchyma
(For ureter only) Tumour invades beyond the muscularis into periureteric fat
T4: Tumour 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: Metastases in a single lymph node, 2 cm or less in the greatest dimension
N2: Metastases in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3: Metastases in a lymph node, more than 5 cm in greatest dimension

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Histological Grade (G)
For urothelial histologies, a low- and high-grade designation is used to match the current World Health Organization/ International Society of Urologic Pathology (WHO/ISUP) recommended grading system:
LG: Low grade
HG: High grade