Canadian guidelines for postoperative surveillance of upper urinary tract urothelial carcinoma

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Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a rare malignancy, accounting for 5% of urothelial tumours.[1] The gold standard management for non-metastatic UTUC is radical nephroureterectomy with bladder cuff excision.[2] Nephron-sparing procedures, including segmental ureterectomy and endoscopic ablation or resection, are often employed in select patients.[3] Postoperative recurrences are common. The primary aims of postoperative surveillance for UTUC are to identify urothelial recurrences, de novo tumours of the urinary tract, and distant metastases at early stages when they may be amenable to treatment. The rarity of the disease, as well as the heterogeneity of treatments, complicates the task of developing a standard follow-up protocol.

Multiple studies report on postoperative recurrence and prognosis for UTUC. By performing a systematic literature review, we generated an evidence-based consensus protocol for the surveillance of patients after surgery for UTUC based on the predictors, timing and locations of recurrences reported in the literature. The decision to provide neoadjuvant or adjuvant treatments is beyond the scope of this guideline and will not be reviewed. Wherever possible, the levels of evidence and grades of recommendation are noted using the modified Oxford Centre for Evidence-based Medicine system.

Methods

A systematic literature review of the electronic databases Embase, Medline and Cochrane was performed using the following search terms, their synonyms, related terms and relevant exploded terms: upper tract, urothelial carcinoma, transitional cell carcinoma, nephrouretectomy, ureterectomy, endoscopy, ureteroscopy, nephroscopy, percutaneous, follow-up, surveillance, recurrence, outcomes and prognosis. No language restrictions were implemented. Citations from included articles and review articles were manually searched.

The inclusion and exclusion criteria were defined a priori. We included studies which reported rates and/or patterns of recurrence after surgery (nephroureterectomy or nephron-sparing procedures) for UTUC. Nephron-sparing procedures include segmental ureterectomy and endoscopic (retrograde or antegrade) ablation or resection. Non-observational studies were excluded. No sample size limitations were applied to prospective studies. For retrospective studies, minimum sample sizes for nephroureterectomy series and nephron-sparing series were 100 and 20 respectively, with exceptions for special reasons by author consensus and with explanation. When multiple studies reporting on the same patient population were identified, we attempted to include only the most relevant study. Studies with major design flaws were excluded by author consensus and with explanation. For recurrence/metastases rates, weighted means across all relevant studies were calculated when possible; these are reported as "mean (range of means)." Where applicable, the weighted mean of follow-up duration is also included within parentheses.

Results

In total, 59 studies satisfied the inclusion criteria, of which 33 pertained to nephroureterectomy[4-36] and 26 to nephron-sparing procedures (Fig. 1).[37-62] One prospective study was included;[26] the rest are retrospective case-series, including several large multicentre series. One retrospective study of patients after nephroureterectomy with a sample size <100 was included by author consensus because of its large sample of pT3 tumours.[27] No studies were excluded for major

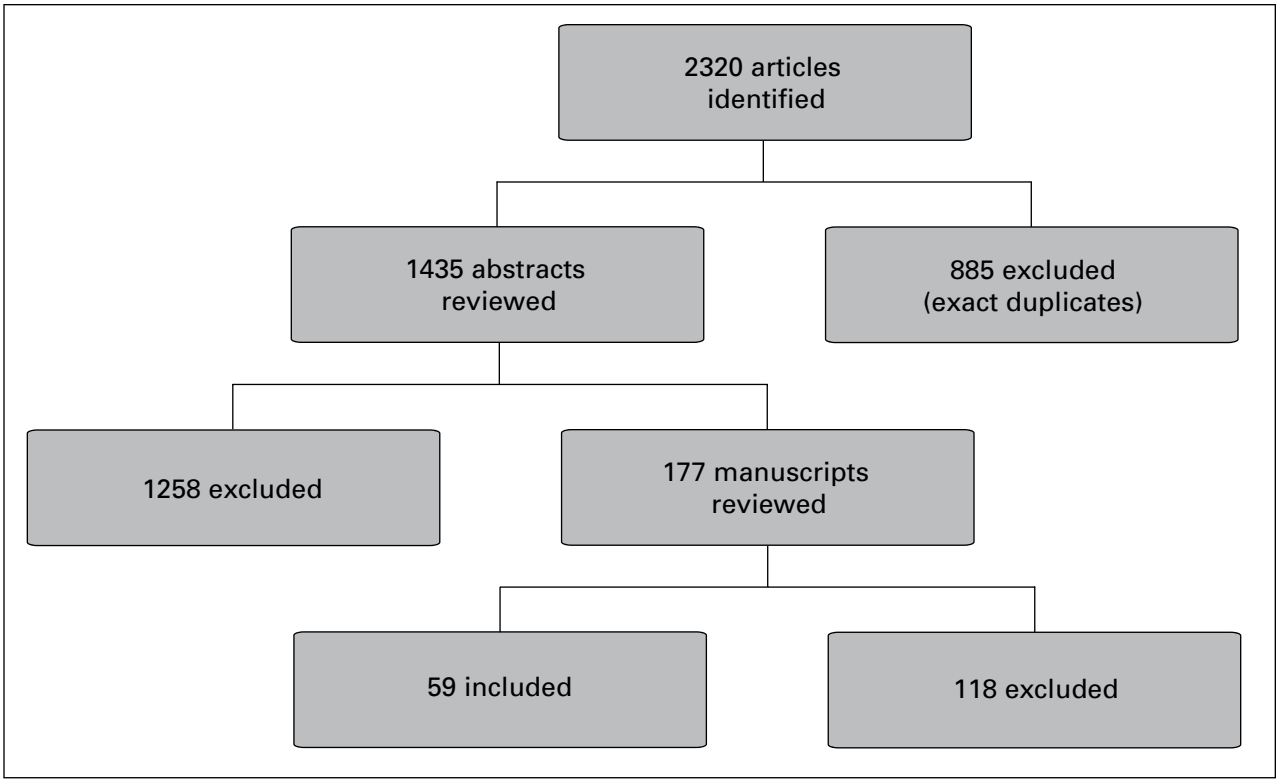

Fig. 1. Results of systematic literature search.

design flaws. In virtually all series, formal lymphadenectomy was not performed and methods of bladder cuff excision were not standardized. All studies report relatively high rates of postoperative recurrence.

Prognostic variables

Many studies report variables which are predictive of post-nephroureterectomy recurrence on multivariate analyses. The most commonly cited variable is tumour stage. In a retrospective series of 301 patients who underwent nephroureterectomy, Li and colleagues reported 5-year recurrence-free survival for patients with pTa/pTis/pT1, pT2, pT3, and pT4 tumours of 76.6%, 65.4%, 41.2%, and 0%, respectively.[16] In a large retrospective multicentre series of 1363 patients, Margulis and colleagues reported 5-year extravesical recurrence-free survival for pTa/pTis, pT1, pT2, pT3, and pT4 tumours of 91.8%, 88%, 71%, 48%, and 4.7%, respectively.[19] Additionally, tumour grade is associated with oncologic outcomes. While there is correlation between stage and grade,[44,63] each independently predicts postoperative recurrence.[19]

Although lymphadenectomy is seldom performed for clinically node-negative disease,[64] pathologic lymph node status is a strong predictor of post-nephroureterectomy recurrence.[19,21] Among 1363 patients, those with pathologically positive lymph nodes (N+) had 5-year recurrence-free survival of 29% compared to 73% in patients with negative (N0) or unknown (Nx) lymph node status.[19] In a large retrospective multicentre Canadian series, 5-year overall survival rates for Nx, N0, and N+ patients were 66.1%, 66.0% and 29.8%, respectively.[31]

Other prognostic variables following nephroureterectomy include lymphovascular invasion, concomitant carcinoma in situ (CIS), positive surgical margins, ureteral tumour location (as opposed to renal pelvis), previous or concomitant bladder tumours, tumour multifocality, and lack of postoperative intravesical mitomycin C instillation.[4,6,7,10-12,14-19,21-24,26,28-36,65-69] The rates of recurrence stratified by these variables are seldom reported.

Owing to the small sample sizes of most studies, multivariate analyses examining the predictors of recurrence after nephron-sparing procedures are lacking. Tumour grade is associated with recurrence; in a retrospective series of 40 patients, 75% of patients with high-grade disease had recurrence by 2 months and ultimately underwent nephroureterectomy.[43] Similarly, among 60 patients with a mean follow-up of 51 months, disease-specific survival for patients with grades 1, 2, and 3 tumours was 100%, 94%, and 62%, respectively.[54] Additionally, tumour stage and multifocality correlate with recurrence after nephron-sparing procedures.[44,47,52,56] Due to a lack of adequately powered studies, additional prognostic factors following nephron-sparing procedures are presently unknown.

Bladder recurrences

Among all patients with available data, bladder recurrences occurred following nephroureterectomy in 29.0% (22%-47%; 35.9 months). In a retrospective series of 422 patients, Kim and colleagues reported median times to bladder recurrence and muscle-invasive bladder cancer of 8 and 17 months, respectively.[34] The median reported time to bladder recurrence across all studies was 6 to 12 months. Bladder recurrences were noted as early as 1 month post-nephroureterectomy.

Following nephron-sparing procedures, bladder recurrences occurred in about 34% of patients.[70] In a retrospective series of 30 patients, the mean time to recurrence was 7 months and ranged from 6 to 72 months.[52]

Extravesical recurrences

Across all studies, post-nephroureterectomy recurrences of the retroperitoneum or pelvis occurred in a mean 4.6% (0-12%; 32.7 months). UTUC of the contralateral upper tract occurred in a mean 2.2% (0-4.6%; 46.7 months). Several studies report very low incidences of port-site recurrences, usually associated with inadvertent entry into the collecting system.[10,18,20,23,25] Among 72 patients with pT3 tumours and a median follow-up of 26.5 months, recurrences of the retroperitoneum/pelvis and contralateral upper tract were observed in 7% and 3%, respectively.[27]

Distant metastases occurred following nephroureterectomy in 16.4% of patients (8%-28%; 46.8 months). The reported sites of metastases included retroperitoneal lymph nodes in 5.2% (0-9.8%; 49.0 months), lung in 4.8% (0-8%; 50.2 months), bone in 4.1% (0-9%; 50.2 months) and liver in 3.7% (0-5%; 50.2 months). Less common sites included brain, adrenal gland and non-regional lymph nodes. The median time to metastases was 13 to 16 months. Metastases were reported as early as 1 month and as late as 50 months postoperatively.

Following nephron-sparing procedures, recurrences of the ipsilateral upper tract are common. In a retrospective series of 30 patients who underwent ureteroscopic or percutaneous management of UTUC, 90% developed upper tract recurrences necessitating a mean 3.3 endoscopic procedures per patient and nephroureterectomy in 33%.[52] In a systematic review by Cutress and colleagues, upper urinary tract recurrences occurred in 53% of patients.[70] Upper tract recurrence rates among patients with low- and high-grade tumours were 48% and 60%, respectively. Most recurrences were managed endoscopically, while 19% of patients underwent nephroureterectomy. Distant metastases occurred in 9% of patients.

Surveillance protocol

These guidelines for surveillance after surgical management of UTUC are based on a systematic review of primarily non-randomized retrospective series which report on patterns of postoperative recurrence (Level 3). None of these studies evaluated specific surveillance protocols. It remains unproven whether surveillance in asymptomatic individuals is superior to symptom-directed investigation. While direct evidence for a survival benefit is lacking, these recommendations are based on an assumption that early diagnosis of recurrence is optimal, and from extrapolations from level 3 evidence (Grade C).

The intensity of postoperative surveillance of UTUC varies according to the risk of disease recurrence. While multiple factors are independently associated with adverse oncologic outcomes, patterns of recurrence stratified by prognostic variables other than tumour stage, grade and lymph node status are undefined. This surveillance protocol is therefore based on pathologic tumour stage, grade and lymph node status.

The recommended protocol for postoperative surveillance of UTUC is shown in Table 1. Routine blood work should include renal function tests and a metabolic panel, including liver function tests, calcium and alkaline phosphatase. Although other published guidelines have recommended cystoscopy and urine cytology at 3 months then yearly after nephroureterectomy,[2] we advocate a more aggressive surveillance protocol given the high rates of urothelial recurrences in all patients and the reported median time to bladder recurrence of 6 to 12 months. Thus, the bladder should be assessed with cytology and cystoscopy in all patients at months 3, 6, 12, 18, 24 and annually thereafter up to 10 years of recurrence-free survival (Grade C).

Most patients following nephron-sparing procedures will develop ipsilateral upper tract recurrences. Computed tomography urography (CTU) lacks sensitivity to identify up to 75% of these recurrences.[56] Furthermore, the sensitivity of ureteroscopy with selective cytology or biopsy is superior to retrograde pyelography alone.[71] The ipsilateral upper tract should therefore be assessed by ureteroscopy and selective cytology or biopsy in all patients following nephron-sparing procedures at months 3, 6, 12, 18, 24 and annually thereafter up to 10 years of recurrence-free survival (Grade C).

To assess for local, contralateral and distant metastases in patients after nephroureterectomy or nephron-sparing procedures, imaging of the abdomen and pelvis with CTU is recommended (Grade C). Magnetic resonance imaging urography (MRI) or ultrasound (US) may be substituted for CTU in patients with contraindications to CTU (Grade D). Chest x-ray (CXR) is recommended to assess for lung metastases (Grade C). Bone scan is indicated in the presence of bone pain, elevated calcium or elevated alkaline phosphatase to

Table 1. Recommended protocol for follow-up after surgery for UTUC

Pathology	Investigations	No. months after surgery for UTUC								
		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	x
	CTU		x	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

UTUC: upper urinary tract urothelial carcinoma; LG: low grade; HG: high grade; Hx: history; PE: physical examination; CXR: chest x-ray; CTU: computed tomography urography; pT<2 includes pTis, pTa and pT1; *Ipsilateral ureteroscopy with selective cytology or biopsy should be performed following nephron-sparing procedures.

assess for bone metastases (grade C). In patients with low-grade, pT<2 (pTa/pTis/pT1) pNx/pN0 disease, imaging of the abdomen and chest is recommended annually (Grade C). Patients with pT2 pNx/pN0 of any grade or high-grade pT<2 should undergo imaging every 6 months for 2 years then annually thereafter (Grade C). Patients with pT>2 or pN+ of any grade should undergo imaging at 3 months, 6 months, then every 6 months for the first 3 years followed by annually thereafter (Grade C).

In the absence of evidence for an optimal duration of surveillance, we recommend lifelong annual surveillance with history, physical examination, blood work, urine cytology and abdominal/chest imaging in all patients with high-grade tumours or p≥2 or pN+ (Grade D). Annual cystoscopy and ipsilateral ureteroscopy (following nephron-sparing procedures) may be omitted after 10 years of recurrence-free survival (Grade D). Patients with low-grade pT<2 pN0/x may be discharged from annual surveillance after 10 years of recurrence-free survival (Grade D). A summary of these guidelines follows.

Surveillance for low grade pT<2 pNx/pN0 patients

History, physical examination, blood work, urine cytology and cystoscopy should be performed at months 3, 6, 12, 18, 24 and annually thereafter (Grade C). CXR and CTU should be performed annually (Grade C). Following nephron-sparing procedures, ipsilateral ureteroscopy with selective cytology or biopsy should be performed at months 3, 6, 12, 18, 24 and annually thereafter (Grade C). Patients may be discharged from surveillance after 10 years of recurrence-free survival (Grade D)

Surveillance for high grade pT<2 pNx/pN0 or any grade pT2 pNx/pN0 patients

History, physical examination, blood work, urine cytology and cystoscopy should be performed at months 3, 6, 12, 18, 24 and annually thereafter (Grade C). CXR and CTU should be performed every 6 months for 2 years then annually thereafter (Grade C). Following nephron-sparing procedures, ipsilateral ureteroscopy with selective cytology or biopsy

should be performed at months 3, 6, 12, 18, 24 and annually thereafter (Grade C). Cystoscopy and ureteroscopy may be omitted from the surveillance protocol after 10 years of recurrence-free survival (Grade D).

Surveillance for any grade pT>2 or pN+ patients

History, physical examination, blood work, urine cytology, and cystoscopy should be performed at months 3, 6, 12, 18, 24 and annually thereafter (Grade C). CXR and CTU should be performed at months 3, 6, 12, 18, 24, 30, 36 and annually thereafter (Grade C). Following nephron-sparing procedures, ipsilateral ureteroscopy with selective cytology or biopsy should be performed at months 3, 6, 12, 18, 24 and annually thereafter (Grade C). Cystoscopy and ureteroscopy may be omitted from the surveillance protocol after 10 years of recurrence-free survival (Grade D).

Competing interests: Dr. Kapoor is a member of the Speakers bureau for, and has received grants and honoraria from, Pfizer Oncology, GSK Oncology, Novartis Oncology and Amgen. He has also participated in clinical trials within the past 2 years with NCIC, Pfizer, GSK, Novartis and Amgen. **Dr. Allard** does not have an affiliation with a pharmaceutical, medical device or communications organization. **Dr. Black** is a member of the ad hoc Advisory Boards for Amgen, Janssen, Ferring and Astellas. He has received an industry-partnered grant (2012) from GenoneDx. **Dr. Kassouf** is an Advisory Board member and a speaker for Amgen and Astellas. He has also received grants and honoraria from these companies. He is currently participating in unpaid clinical trials within the past 2 years. **Dr. Morash** does not have an affiliation with a pharmaceutical, medical device or communications organization. **Dr. Rendon** is a member of the Advisory Board and the Speakers bureau for Amgen, Astellas, Ferring and Janssen.

This paper has been peer-reviewed.

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