

**Canadian Guidelines for Postoperative Surveillance of
Upper Urinary Tract Urothelial Carcinoma**

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INTRODUCTION

Upper urinary tract urothelial carcinoma (UUT-UC) is a rare malignancy, accounting for 5% of urothelial tumors.¹ The gold standard management for non-metastatic UUT-UC 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 Post-operative recurrences are common. The primary goal of postoperative surveillance for UUT-UC is to identify disease recurrence at an early stage when it may be amenable to treatment. Evidence pertaining to the optimal follow-up protocol for patients after radical nephroureterectomy is lacking. 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 UUT-UC. By performing a systematic literature review, we generated an approach to the surveillance of patients after surgery for UUT-UC based on the predictors, timing, and locations of recurrences reported in the literature. This evidence-based consensus protocol may serve as a guide to urologists in following patients after radical nephroureterectomy.

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, nephroureterectomy, ureterectomy, endoscopy, ureteroscopy, nephroscopy, percutaneous, follow-up, 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*. Studies which reported rates and/or patterns of recurrence after surgery (nephroureterectomy or nephron-sparing procedures) for UUT-UC were included. 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

Fifty-nine studies satisfied the inclusion criteria of which 33 pertained to nephroureterectomy⁴⁻³⁶ and 26 to nephron-sparing procedures.³⁷⁻⁶² The results of the search strategy are shown in **Figure 1**. One prospective study was included;²⁶ the rest are retrospective case-series, including several large multi-centre 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 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 post-operative 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 et al. 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 et al. 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 post-operative recurrence on multivariate analysis.¹⁹

Although routine 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 multi-centre 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) and previous or concomitant bladder tumours.^{4, 6, 7, 10-12, 14-19, 21-24, 26, 28-36, 65, 66} 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 correlates strongly; 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 In addition to tumour grade, 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 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 et al. 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 6-12 months. Bladder recurrences were noted as early as one month and as late as 146 months post-nephroureterectomy.

Following nephron-sparing procedures, bladder recurrences occur in approximately 34% of patients.⁶⁷ 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). UUT-UC of the contralateral upper urinary 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 urinary tract were observed in 7% and 3%, respectively.²⁷

Distant metastases occurred following nephroureterectomy in 16.4% of included studies (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 13-16 months. Metastases were diagnosed as early as 1 month and as late as 50 months post-operatively.

Following nephron-sparing procedures, recurrences of the ipsilateral upper urinary tract are common. In a retrospective series of 30 patients who underwent ureteroscopic or percutaneous management of UUT-UC, 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 et al., upper urinary tract recurrences occurred in 53% of patients.⁶⁷ Upper tract recurrence rates among patients with low and high grade tumours were 48% and 60% respectively. The majority of 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 UUT-UC are based on a systematic review of primarily non-randomized retrospective series (Level 3). While direct evidence for a survival benefit from any surveillance protocol 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 post-operative surveillance 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 unknown. This surveillance protocol is therefore based on pathologic tumour stage, grade, and lymph node status.

The recommended protocol for surveillance after surgery (nephroureterectomy or nephron-sparing procedures) for UUT-UC is shown in **Table 1**. Routine blood work should include renal function tests and a metabolic panel including liver function tests and an 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 6-12 months. Thus, the bladder should be assessed with cytology and cystoscopy in all patients at months 3, 6, 12, 18, 24, and annually thereafter. (Grade C).

The majority of patients following nephron-sparing procedures will develop ipsilateral upper urinary 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.⁶⁸ The ipsilateral upper urinary 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. (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 computed tomography urography (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). A routine bone scan is not necessary but is indicated in the presence of an elevated alkaline phosphatase or bone pain to 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, cystoscopy, cytology, and abdominal/chest imaging, (and ureteroscopy with selective cytology or biopsy in patients who underwent nephron-sparing procedures), in all patients with high grade tumours or pT>1 or pN+ (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 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). Lifelong annual surveillance is recommended (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). Lifelong annual surveillance is recommended (Grade D).

TABLES AND FIGURES

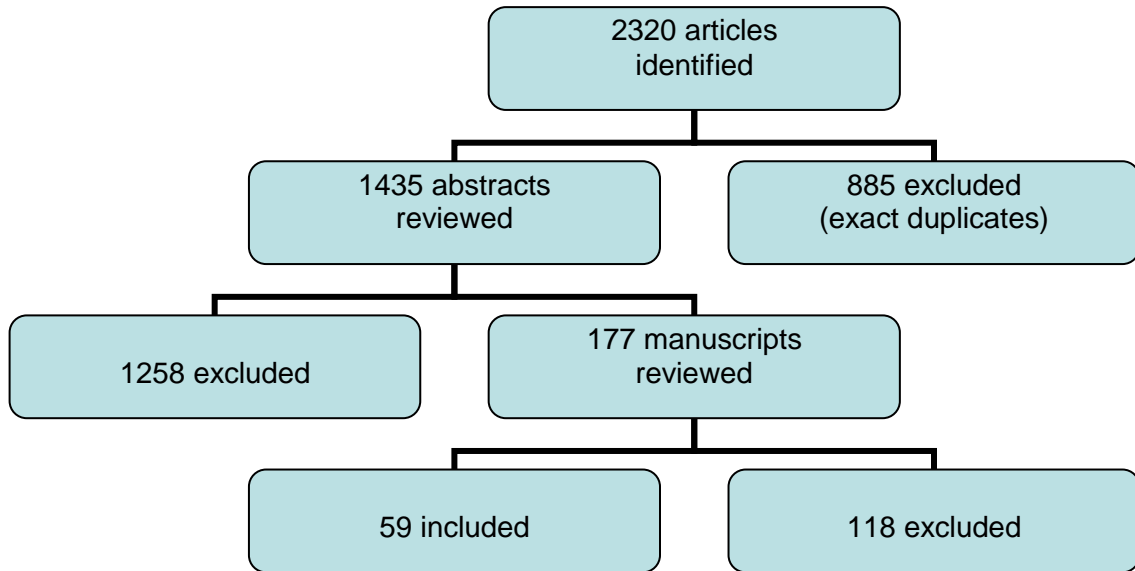


Figure 1: Results of systematic literature search

Table 1: Recommended protocol for follow-up after surgery for UUT-UC

Surgical Pathology	Investigations	Number of months after surgery for UTUC									
		3	6	9	12	18	24	30	36	48	60
LG pT<2 Nx/0	Hx and PE	x	x	x	x	x	x		x	x	x
	Blood work	x	x	x	x	x	x		x	x	x
	Urine cytology	x	x	x	x	x	x		x	x	x
	Cystoscopy	x	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 or LG/HG pT2 Nx/0	Hx and PE	x	x	x	x	x	x		x	x	x
	Blood work	x	x	x	x	x	x		x	x	x
	Urine cytology	x	x	x	x	x	x		x	x	x
	Cystoscopy	x	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	x	x
	Blood work	x	x	x	x	x	x	x	x	x	x
	Urine cytology	x	x	x	x	x	x	x	x	x	x
	Cystoscopy	x	x	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

LG: low grade; HG: high grade; Hx: History; PE: physical examination; CXR: chest x ray; CTU: computed tomography urograph; pT<2 includes pTis, pTa and pT1

*Ipsilateral ureteroscopy with selective cytology or biopsy should be performed following nephron-sparing procedures

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