

Nephron-sparing surgery for the management of upper tract urothelial carcinoma: an outline of surgical technique and review of outcomes

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Abstract: Upper tract urothelial carcinoma (UTUC) often occurs in elderly patients with multiple co-morbidities including renal impairment. As such, nephron sparing surgery (NSS) often needs to be considered. This article reviews the available NSS techniques for UTUC, including ureteroscopy, percutaneous approaches and segmental ureterectomy. PubMed and OvidMEDLINE reviews of available case series from the last 10 years demonstrated that recurrence was highly variable between studies and occurred in 19–90.5% of ureteroscopic cases, 29–98% of percutaneous resections and in 10.2–31.4% of patients who underwent segmental ureterectomy. The small number of included studies and variable follow up periods made comparison between techniques difficult. NSS is a necessary alternative for patients with significant comorbidities or renal impairment who cannot undergo radical nephro-ureterectomy. However, there is significant variation in oncological outcomes, with an increased risk of progression or death from cancer—salvage by radical surgery may sometimes be required.

Keywords: Upper tract urothelial carcinoma (UTUC); nephron sparing surgery (NSS); ureteroscopy; percutaneous nephroscopic surgery; segmental ureterectomy

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Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare malignancy, and accounts for around 5–10% of all urothelial carcinomas (UC). Radical nephroureterectomy (RNU) is the gold standard for the surgical management of UTUC, however nephron sparing surgery (NSS) is utilised in patients with a solitary kidney, significant renal impairment, multiple bilateral UTUC or comorbidities that will incur unacceptable risk with RNU (1). Additionally, NSS for low risk UTUC may be performed as a primary treatment option with no difference in oncological outcome compared with RNU (2).

The surgical techniques for NSS include endoscopic management (ureteroscopy and percutaneous access) and segmental ureterectomy. Endoscopic techniques allow for histopathological diagnosis and management of the tumour primarily by laser ablation. While ureteroscopy is more commonly used for the management of UTUC, percutaneous access may be useful for tumours that are

difficult to reach, while accepting a slightly higher rate of complications. Instillation of topical agents such as Bacillus Calmette-Guerin (BCG) and mitomycin C (MMC) are also possible in combination with ureteroscopy or percutaneous access.

The technique for segmental ureterectomy will depend on tumour location and extent. UTUC occurs more commonly in the renal pelvis than the ureter (3:1 ratio) (3). Of the ureteric tumours, 70% occur in the distal ureter, 25% in the mid ureter and 5% in the proximal ureter. As a result, techniques for resection of distal ureteric tumours are more commonly utilised including distal ureterectomy with reimplantation, or uretero-ureterostomy of iliac and lumbar segments of ureter.

The literature in the domain of NSS is sparse and raises questions about our current guidelines and management strategies. In this article we outline the surgical techniques for NSS for UTUC and review the literature from 2009 to 2019 using the MeSH terms 'upper tract urothelial carcinoma', 'UTUC', 'treatment', and 'nephron-sparing'. Outcome measures are variable between studies but include tumour recurrence, progression to RNU, cancer-specific survival (CSS) and overall survival (OS).

Endoscopic management—ureteroscopy and percutaneous access

Endoscopic management of urothelial tumours are most commonly performed via a retrograde approach, however percutaneous access can be considered for low risk UTUC in the renal pelvis. The goals of management are to diagnose the lesion, obtain samples for cytology or histology, and complete tumour ablation. Preoperative planning should include urine studies (culture and cytology), blood tests (full blood count, electrolytes and renal function), and radiographic upper tract imaging.

Ureteroscopy

Preoperatively the patient should be consented and informed of the likely need for an early second look, and more stringent surveillance compared to surgical management. Depending on prior management patients may already be preoperatively stented.

General anaesthesia is preferable however spinal

anaesthesia may be acceptable in high risk patients. Rigid cystoscopy is performed with a systematic assessment of the bladder for co-existing synchronous tumours. Transurethral resection of bladder tumour should always be prepared for in these patients, especially in those with prior bladder recurrence.

A good quality retrograde pyelogram is performed at the commencement of the procedure to assess the location of the tumour. A contralateral image should be obtained in the case of endoscopic surveillance. A guidewire is then passed into the renal pelvis under fluoroscopic guidance. Washings for cytological examination from the renal pelvis or ureter may be useful at this point, if a diagnosis has not yet been established.

Most ureteral tumours will require a rigid ureteroscope, short or long, however some tumours may be better suited to a flexible ureteroscope. A short ureteroscope can be used if more distal ureteral tumour is anticipated based on imaging. The tumour can be initially debulked and tissue obtained for histological analysis, using flexible cold cup biopsy forceps or wire basket to snare the tumour base. One of the pitfalls of biopsy in this setting is that the specimens obtained ureteroscopically are often sub-optimal, leading to under-staging in many cases (4).

Tumour ablation can be achieved to the tumour base after debulking, or in some instances may be appropriate for ablation of the whole tumour e.g., large or sessile tumours. This can be performed using bugbee diathermy or laser fulguration. A laser generator capable of holmium:yttrium-alluminium-garnet (Ho:YAG) and neodymium (Nd):yytrium-aluminium-garnet (Ng:YAG) is selected for use based on appropriate tissue penetration (5). Ho:YAG is suited for tumours in the ureter due to lesser depth of penetration and hence reduced stricture formation. Nd:YAG may be preferred for bulkier renal pelvis tumours due to greater depth of penetration. Care must be taken not to resect the tumour too deeply as the ureteric wall is much thinner than the bladder. Additionally, attempts should be made not to fulgurate circumferentially to minimise the risk of stricture formation. For more extensive tumours a second look within six weeks of the initial resection is recommended to ensure complete eradication of the tumour.

On completion of the most distal tumour, the proximal ureter and renal pelvis should be inspected using a flexible ureteroscope. Similarly, for tumours in the renal pelvis the flexible uretero-pyeloscope can be placed over the existing guidewire or a second safety wire. Alternatively, the existing wire can be used to pass an access sheath and flexible endoscope placed within this working channel.

A ureteric stent is commonly placed at the end of the procedure and removed in two weeks for more extensive tumours. For small superficial tumours or where instrumentation of the ureter was minimal, it may be reasonable to leave the stent on a string or a temporary ureteric catheter for removal within the first week. Furthermore, a ureteric catheter may be left at the end of the case for instillation of topical agents (see below). For patients at risk of stricture development such as ablation of circumferential tumours, or those with known ureteric strictures it may be sensible to leave the stent in for longer. Consideration should be given to leaving an in-dwelling catheter for best drainage of the upper tracts in patients who will remain in hospital.

The surveillance period is not well established for tumour ablation of low risk UTUC and given the risk of under-staging and under-grading, there should be a low threshold for progressing to radical surgical intervention in case of recurrence. For those who underwent tumour ablation as definitive NSS, initial endoscopic surveillance is often undertaken at 3-months. Where no tumour is found, the interval can be lengthened to 6-monthly with upper tract imaging performed yearly.

Table 1 summarises the outcomes of ureteroscopic management of UTUC in recent studies. The number of patients within each study was small ranging from 20 to 82. Rate of recurrence, the most commonly reported outcome measure, was highly variable and noted in between 19 and 90.5% of cases. Progression to RNU occurred at a median rate of 19% (range, 0–42.8%) over these studies. CSS was between 84–100% but with quite variable follow up periods (26 months to 5 years). Two studies reported OS at 5 years follow up of 75% and 45% respectively. The variable length of follow up makes comparison difficult between studies.

Percutaneous access

Percutaneous access may be best for tumours that are difficult to access endoscopically including lower pole tumours or for patients with more complex anatomy. However this technique is being utilised less frequently due to improvements in flexible ureteroscopes that permit better deflection and access (16).

Access is gained in a similar manner as for percutaneous stone removal. Given the risk of tumour seeding all attempts should be made to perform this procedure in one sitting. A nephrostomy tube may be left at the conclusion of the procedure and can provide access in the event of needing a second look. A nephrostogram may be obtained prior to removal, and in some instances the nephrostomy tube may be used for instillation of topical agents (see below).

The risk of complications associated with percutaneous access are generally greater than retrograde endoscopic alternatives. This includes the risk of bleeding and perinephric haematoma which may require blood transfusion or arterial embolisation. As previously mentioned, tumour seeding can occur along the perirenal space, cutaneous tract or systemically (17).

Table 2 summarises outcomes of percutaneous management of UTUC, including 3 available studies over the most recent ten years; one of these was a mixed cohort including both ureteroscopic and percutaneous resection of tumour. Motamedinia *et al.* reported the risk of recurrence as 37% in low grade and 63% in high grade tumours, with a median follow up of 66 months. Of the 114 patients included in this study, 13% progressed to RNU and the OS was 40%. Strijbos and van der Heij reported the outcomes of 44 patients with UTUC who experienced a 50% recurrence rate and 27.5% rate of progression to RNU.

Upper urinary tract instillation of topical agents

Topical agents can be instilled antegrade via a nephrostomy tube left *in situ* following percutaneous treatment or retrograde via a 5 F ureteric catheter left *in situ* after endoscopic management. Reflux via an in-dwelling double J pigtail stent of agents instilled intravesically has also been proposed. However, the adequacy of drug delivery to the renal pelvis is not always reliable. There are no standardised protocols on instillation techniques and the literature is scant in this domain, however BCG and MMC seem the most commonly investigated. Currently the OLYMPUS (Optimised Delivery of Mitomycin for primary UTUC study) trial is prospectively studying Mitogel for patients with low grade UTUC and is due for completion in 2020 (21). In addition to these agents, intravesical instillation of physiological saline or distilled water has been

Study	Ν	Treatment	Duration of follow-up	Outcomes
Scotland <i>et al.</i> 2018 (6)	80	Ureteroscopy with laser ablation	5 yrs	90.5% ipsilateral recurrence
				31.7% progressed in grade
				CSS: 84%
				OS: 75%
Musi <i>et al.</i> 2018 (7)	42	Ureteroscopic thulium laser	Median 26.3 mths	19% recurrence
			Range 2–54 mths	
Fajkovic <i>et al.</i> 2013 (8)	20	Endoscopic treatment	5 yrs	25% local recurrence
				15% bladder recurrence
				0% progression to RNU
				OS: 45%
Grasso <i>et al.</i> 2012 (9)	82	Ureteroscopy	Mean 38.2 mths	15.2% progressed from low to high grade
			Range 1–185 mths	19% progression to RNU
				CSS: 87%
				OS: 74%
Cutress <i>et al.</i> 2012 (10)	73	Ureteroscopy	Median 54 mths	68% upper tract recurrence
			Range 1–223 mths	19% progression to RNU
				CSS: (5 yr) 88.9%
				OS: 69.7%
Raymundo e <i>t al.</i> 2011 (11)	21	Percutaneous and/or	Mean 17.9 mths	48% ipsilateral recurrence
		ureteroscopic resection	Range 13.2–24.6 mths	5% mortality UTUC-related
				42.8% progressed to RNU
Gadzinski <i>et al.</i> 2010 (12)	34	Ureteroscopy	Median 77 mths	11% progression to RNU
				9.3% complication rate
				CSS: 100%
				OS: 75%
Cornu e <i>t al.</i> 2010 (13)	35	Ureteroscopy	Median 30 mths	60% recurrence
			Range 12–66 mths	11% progression to RNU
				CSS: 100%
				OS: 100%
Pak <i>et al.</i> 2009 (14)	57	Ureteroscopy	Mean 53 mths	80.7% renal preservation
			Range 24–146 mths	5.5 Mean recurrences/patient
				CSS: 94.7%
				OS: 93%
Hoffman <i>et al.</i> 2014 (15)	25	Ureteroscopic resection	Median 26 mths	44% recurrence
			Range 12–126 mths	

Table 1 Reported outcomes for urete	rosconic rese	ection of upper t	ract urothelial ca	reinoma in the n	ost recent 10 years
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N, no. of patients in sample population; CSS, cancer-specific survival; OS, overall survival; RNU, radical nephroureterectomy; yrs, years; mths, months.

Table 2 Reported outcomes for percutaneous rea	esection of upper tract urothelial carcinoma in the most re-	cent 10 years
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Study	Ν	Treatment	Duration of follow-up	Outcomes
Motamedinia et al.	141	Percutaneous ablation	Median 66 mths	Recurrence: 37% in LG, 63% in HG
2016 (18)				13% progression to RNU
				OS: 40%
Strijbos & van der Heij	44	Percutaneous resection	Median 53 mths	50% recurrence rate
2016 (19)				27.5% progression to RNU
				Complications seen in 35%
Adamis & Varkarakis	18–44	URS, PNRT	132 mths	Recurrence: URS: 29-98%, PNRT: 23-88%
2011 (20)				CSS at 5 yrs: URS: 86.5–100%, PNRT: 69.2–94.1%

N, no. of patients in sample population; mths, months; LG, low grade; HG, high grade; RNU, radical nephroureterectomy; URS, ureteroscopy; PNRT, percutaneous nephroscopic resection of tumour; CSS, cancer-specific survival; OS, overall survival.

utilised at the time of RNU and shown to reduce the rate of post-operative bladder recurrence (22).

Segmental ureteral resection

Segmental ureteral resection can be performed depending on tumour location. Care should be taken to obtain adequate margins of clearance. A significant advantage is that a full thickness histological specimen is obtained for adequate staging and grading. Concurrent lymph node dissection can also be carried out. Traditionally, segmental resection has been carried out by open surgery, but minimally invasive approaches have also been described including laparoscopic and robotic surgery.

For distal ureteric tumours complete distal ureterectomy can be performed with ureteric reimplantation. The type of reconstruction will vary depending on the length of ureter taken: for shorter segments uretero-neocystostomy can be performed. For higher lesions necessitating longer lengths of ureteric resection, a psoas hitch and/or Boari flap can provide up to 10cm of additional bladder mobility. Resection of iliac and lumbar portions of ureter with reconstruction by uretero-ureterostomy, are associated with higher risks in comparison to complete distal ureterectomy (2). The excised defect can be bridged with a spatulated anastomosis over a stent. Longer defects may require nephropexy, ileal replacement or auto-transplantation, however these approaches also carry greater risks and are consequently rarely undertaken. Historical procedures such as partial pyelectomy, partial nephrectomy and open resections of tumours in the renal pelvis are also very rarely performed, with RNU preferred.

The literature is again scarce in regard to segmental ureterectomy, we identified 7 reports over the last 10 years, outlined in *Table 3*. Tumour recurrence rates varied between 10.2% and 31.4%, with a median follow up duration between 26 and 51.5 months. CSS was between 77% and 89% in most studies. However, OS was more variable between 31 and 91%. Rate of death was reported in 2 studies at 5.7% over 48.3 months in one study, and 20.9% over 50 months in another.

Conclusions

A range of nephron sparing options are available for the surgical treatment of UTUC. These techniques are best suited to smaller tumours of lower grade and stage, and for each approach certain favourable anatomical and pathological features are ideal. NSS may be considered imperative in patients with solitary kidneys or pre-existing renal impairment unless the risks and morbidity of renal replacement therapy are to be taken on. The risks of recurrence are always a concern after NSS, although some published case series report favourable outcomes. Appropriate patient selection, careful surgical technique and close surveillance are crucial to the success of these approaches.

Study	Ν	Treatment	Duration of follow-up	Outcomes
Hung <i>et al.</i> 2014 (23)	35	Segmental ureterectomy	Mean 48.3 mths	Local and bladder recurrence was 14.3% and 31.4%
				Death in 5.7%
				CSS: 87.9%
				OS: 81.9%
Dalpiaz <i>et al.</i> 49 2014 (24)	49	Distal ureterectomy	Median 51.5 mths	10.2% recurrence
			Range 4–290 mths	CSS: 77%
				OS/RFS: 91%
Fukushima <i>et al.</i> 43 2014 (25)	43	Distal ureterectomy	Median 50 mths	20.9% recurrence
				20.9% deaths
				CSS: (5 yrs) 86%
				OS/RFS: 84%
Simhan <i>et al.</i> 320 2013 (26)	320	20 37.5% endoscopic ablation/observation62.5% segmental ureterectomy	Median 61 mths	Not provided
			Range 25–111 mths	
Colin <i>et al.</i> 5 2012 (27)	52	Segmental ureterectomy	Median 26 mths	CSS: (5 yrs) 87.9%
				OS/RFS: 37%
Silberstein <i>et al.</i> 33 2012 (28)	33	33 Parenchymal sparing ureteral resection	Median 4.2 yrs	CSS: (2 yrs) 89%
		(PSUR)		OS/RFS: 31%
Lughezzani <i>et al.</i>	222	Segmental ureterectomy	Median 39 mths	Not provided
2009 (29)			Range 0.1–203	

Table 3 Reported outcomes for segmental or distal ureterectomy of upper tract urothelial carcinoma in the most recent 10 years

N, no. of patients in sample population; mths, months; CSS, cancer-specific survival; OS, overall survival; RFS, recurrence free survival.

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