Review Article

Narrative review of nephron-sparing surgical management of upper tract urothelial carcinoma: is there a role for distal ureterectomy, segmental ureterectomy, and partial nephrectomy

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Background and Objective: Upper tract urothelial carcinoma (UTUC) is a relatively rare malignancy and radical nephroureterectomy (RNU) with bladder cuff excision (BCE) is considered as the standard of care for high-risk non-metastatic disease. Loss of the renal unit secondary to RNU, especially in elderly patients, causes significant decline in overall renal function which in turn negatively impacts the overall survival (OS). Such radical surgeries can be spared in a select group of the patients with segmental ureterectomy (SU) or distal ureterectomy to salvage the ipsilateral kidney. In this article, we will review the oncological and renal function outcomes following such procedures. This review excludes endourologic procedures.

Methods: This is a non-systematic review of the published literature focusing on the nephron-sparing surgical alternatives for the management of UTUCs. The following texts were used for literature search: "nephron-sparing surgery", "segmental ureterectomy", "total ureterectomy", "partial nephrectomy", and "ileal ureter". We included the articles indexed in PubMed, written in English language, and published within the last 15 years.

Key Content and Findings: The main argument against the utilization of these procedures is the lack of high quality, level I evidence, which is due to the rarity of this disease and the rates of ipsilateral recurrences. Despite that, the evidence in support of these nephron-sparing surgical alternatives is increasing over time. Published literature including single/multi-centric studies & systematic reviews, suggests comparable oncological outcomes and significantly improved renal function preservation. Lymph node dissection (LND) at the time of nephron-sparing surgical alternatives is largely underutilized. Similarly, the role of neoadjuvant or adjuvant systemic chemotherapy following such procedures is also not established currently.

Conclusions: With comparable oncological outcomes while preserving renal function, the nephron-sparing surgical alternatives to RNU are gaining momentum. These options can be offered to patients with low volume, localized UTUC with imperative indication for renal preservation such as solitary kidney, compromised baseline, and expected significant decline in post-RNU renal function without compromising oncological principles during surgery.

Keywords: Upper tract urothelial carcinoma (UTUC); distal ureterectomy with or without bladder cuff excision (distal ureterectomy with or without BCE); ureteroneocystostomy; segmental ureterectomy (SU); ureteroureterostomy

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Introduction

Radical nephroureterectomy (RNU), bladder cuff excision (BCE) with regional/retroperitoneal and/or pelvic lymph node dissection (LND) is considered as the standard of care for all high-risk non-metastatic upper tract urothelial carcinomas (UTUCs) which is based on the data-driven understanding of multifocality of this disease and the rates of ipsilateral recurrences (1-4). Since this disease is often diagnosed in geriatric age group in whom the renal function is already compromised secondary to advancing age and medical comorbidities, the radical resection negatively impacts the overall renal function. The expected decline in estimated glomerular filtration rate (eGFR) following the loss of a renal unit, which in turn influence the overall survival (OS) by adversely impacting the cardiovascular & cerebrovascular health (5,6), is one of the main arguments favoring nephron-sparing surgery/partial nephrectomy over radical nephrectomy for the management of localized renal masses (7). Surgical alternatives to RNU include segmental ureterectomy (SU)/distal ureterectomy, total ureterectomy (TU), and partial nephrectomy. We present this article in accordance with the Narrative Review reporting checklist to provide a comprehensive review and the status of these evolving alternative techniques, with oncological and functional outcomes (available at https://tau.amegroups.com/article/view/10.21037/tau-23-123/rc).

Methods

This is a non-systematic review of the literature published on outcomes of nephron-sparing alternatives to RNU. We limited our search to include articles published within the last 15 years. Although nephron-sparing management also include endoscopy-guided procedures through antegrade or retrograde approach, we are primarily including nephron-sparing alternatives with surgical resection of UTUC in this review. The electronic search for literature on PubMed (*Table 1*) was performed using UTUC with "nephron-sparing surgery", "segmental ureterectomy", "total ureterectomy", "partial nephrectomy", and "ileal ureter" as free text.

Patient selection

As per the recent European Association of Urology (EAU) guidelines, the nephron-sparing alternatives could be offered to patients with localized low-risk tumors (strong recommendation) (3). The main issue with this risk stratification is the significant dependance on the histopathological findings obtained on initial ureteroscopic biopsy. Previous studies have highlighted the challenges with ureteroscopy-guided biopsies which not just includes lack of adequate tissue sampling but is also associated with substantial discordance rates (clinical under-staging/under-grading) between the pathological findings at biopsy and final histopathology after extirpative surgery (8).

Appropriate patient selection is very crucial in achieving acceptable oncological & functional outcomes. Therefore, retrograde pyelogram, ureteroscopic biopsy along with cross-sectional imaging must be considered for diagnostic evaluation before offering these alternative techniques to salvage ipsilateral kidney. Low volume localized urothelial cancer should be the prime consideration besides other factors such as patient's age, solitary functioning kidney or compromised pre-operative overall renal function, associated comorbidities, patient's preference, and surgeon/institutional experience with these procedures.

Alternatives to RNU

SU/TU

These alternative options are based on the location of the primary tumor in the ureter. More distally located tumors can be managed with distal ureterectomy with BCE and ureteroneocystostomy with or without psoas hitch. If the defect is too large to bridge, ureteral re-implantations on Boari flap reconstruction could be utilized (9,10). For more proximally located tumors, segmental ureteral resection with end-to-end uretero-ureterostomy after adequate proximal & distal ureteral mobilization, to allow for tension free anastomosis, can be performed (9,10). TU with ileal segment replacement have also been reported in more widespread/multifocal ureteral involvement (11). These procedures can be performed with open, laparoscopic or robotic-assisted approaches based on surgeon's discretion/experience.

With the obvious advantages of minimally invasive approach robotic-assisted management of UTUC is gradually emerging for these technically demanding surgical procedures (12,13). We have previously published our initial experience with robotic-assisted nephron-sparing management of ureteral tumors (14,15) and recently highlighted (in our most updated series), various reconstructive options including an anecdotal case report of utilizing a wedge of ileum to patch a significant defect following SU (16). Other single and multi-institutional

Table 1 Search strategy summary

Items	Specification
Date of search	02-15-2023
Databases and other sources searched	PubMed
Search terms used	"Upper tract urothelial carcinoma", "transitional cell carcinoma", "segmental ureterectomy", "total ureterectomy", "partial nephrectomy", "uretero-ureterostomy", "ileal ureter", "nephron-sparing surgery", and "kidney sparing surgery"
Timeframe	2008–2023
Inclusion criteria	Only articles published in English language were included
Selection process	All authors performed independent search and collected articles relevant to the objective of the manuscript

Table 2 Summary of studies safety, feasibility and effectiveness of robotic-assisted nephron-sparing management of ureteral tumors

Author, year	No. of patients	HG UTUC with ≥ T2 (%)	Complications (%)	Follow-up (months)	Recurrences (%)
Saini *et al*., 2023, (16)	17	29.4	23.5	41	23.5
Palagonia *et al*., 2021, (17)	11	27.3	36.4	25.5	36.4
Campi *et al*.[†], 2019, (18)	15	NR	53.3	21	46.7
Pugh *et al*., 2015, (19)	4	50	25.0	21	NR
Fifer *et al*., 2014, (20)	10	NR	NR	6	NR
Elsamra *et al*., 2014, (21)	6	NR	NR	16	NR
McClain *et al*., 2012, (15)	6	16.7	0.0	33	16.7
Singh *et al*., 2009, (14)	2	0.0	0.0	2.5	NR

[†], multicenter study. HG, high grade; UTUC, upper tract urothelial carcinoma; NR, not reported.

studies have also reported the safety, feasibility and effectiveness of robotic-assisted nephron-sparing management of ureteral tumors (17-21) (*Table 2*).

Partial nephrectomy

For urothelial tumors located within the kidneys, options that have been tried previously include an *ex-vivo* open partial resection of the renal pelvis with complete ipsilateral ureterectomy with auto-transplantation and pyelovesicostomy, open partial resection of renal pelvis with free peritoneal flap reconstruction, combined open resection with calicoscopic laser coagulation, and open partial/hemi nephrectomy (22-24). Only a few case reports/series could be found in the published literature and these procedures were done for the imperative indication of solitary kidney or pre-existing or anticipated significantly compromised post-operative renal function to prevent end-stage renal disease.

Oncological outcomes

Earliest reported results on SU dates to early 1970s which suggested similar incidence of local recurrence between RNU and distal ureterectomy with re-implantation (25). The first evidence based on a large SEER database, advocating comparable cancer control between SU and RNU was reported in 2009 (26). Their study included 569 *vs.* 1,222 *vs.* 253 patients of SU *vs.* RNU with BCE *vs.* RNU without BCE and found 86.6% *vs.* 82.2% *vs.* 80.5% 5-year cancer-specific mortality free rates. Another population-based analysis of 2,299 patients, published around the same time, reported durable cancer control with SU or RNU in patients with organ-confined (pT1–T2) UTUC (27). Over the years, these findings were reiterated by both multi-institutional and single-center studies with longer follow-up. A multi-institutional study reported from France found 5-year cancer-specific survival (CSS) probability

Table 3 Summary of the contemporary studies (multi & single center) demonstrating oncological outcomes following SU/DU *vs*. RNU

Author, year	No. of patients (SU or RNU)	HG UTUC with ≥ T2 (SU *vs*. RNU)	Complications	Follow-up (months)	Outcomes
Abrate *et al*., 2022, (28)	SU: 27; RNU: 150	SU: 44.4%; RNU: 57.3%	SU: 7.4%; RNU: 34%	36	3-year OS: SU: 86.6%; RNU: 65.6% (P=0.129)
Kim *et al*.[†], 2021, (29)	SU: 40; RNU: 40	SU: 60%; RNU: 47.5%	NR	23.2 [10.8–33]	3-year OS: SU: 71.5; RNU: 87.5% (P=0.032)
					3-year CSS: SU: 82.6%; RNU: 93% (P=0.30)
					3-year PFS: SU: 73.2%; RNU: 68.2% (P=0.93)
					3-year IV-RFS: SU: 36.9%; RNU: 42.3% (P=0.82)
Kato *et al*.[‡], 2018, (30)	SU: 12; RNU: 14	NR	NR	48.5 [7–148]	5-year OS: SU: 77.8; RNU: 60.1%
					5-year CSS: SU: 87.5%; RNU: 71.9%
					5-year RFS: SU: 34.4%; RNU: 50%
					5-year MFS: SU: 80.8%; RNU: 73.5%
Fukushima *et al*., 2014, (10)	DU: 43; RNU: 86	DU: 32.6%; RNU: 55.9%	NR	50	5-year CSS (T2–T4 subgroup): DU: 60%; RNU: 65% (P=0.64)
					5-year RFS (T2–T4 subgroup): DU: 60%; RNU: 57% (P=0.93)
Dalpiaz *et al*.[‡], 2014, (31)	DU: 49; RNU: 42	DU: 30%; RNU: 45%	DU: 6.2%; RNU: 4.8%	7.6 [2–123]	5-year CSS: DU: 77%; RNU: 78%
					5-year RFS: DU: 91%; RNU: 96%
Bagrodia *et al*., 2013, (32)	PU: 81; RNU: 754	PU: 30.9%; RNU: 53.8%	NR	34 [1–246]	5-year CSS: PU: 65.7%; RNU: 72.1% (P=0.60)
					5-year RFS: PU: 69.4%; RNU: 75.9% (P=0.60)
Colin *et al*., 2012, (9)	SU: 52; RNU: 416	SU: 34.6%; RNU: 46.2%	NR	26 [10–48]	5-year CSS: SU: 87.9% *vs*. RNU: 86.3% (P=0.99)
					RFS: SU: 37% *vs*. RNU: 47.9% (P=0.48)
					MFS: SU: 81.9% *vs*. RNU: 85.4% (P=0.51)
Lughezzani *et al*., 2009, (27)	SU: 222; RNU: 653	Overall: 63%	NR	39	5-year CSM-free survival: 77.6%
		SU *vs*. RNU: NR			SU *vs*. RNU: NR

[†], RNU *vs*. SU (open: 52.5% *vs*. 85%; laparoscopic: 47.5% *vs*. 2.5%; robotic: 0.0% *vs*. 12.5%); [‡], single-center study. SU, segmental ureterectomy; RNU, radical nephroureterectomy; HG, high grade; UTUC, upper tract urothelial carcinoma; OS, overall survival; NR, not reported; CSS, cancer-specific survival; PFS, progression-free survival; IV-RFS, intra-vesical recurrence-free survival; MFS, metastasis-free survival; DU, distal ureterectomy; CSM, cancer specific mortality.

of 87.9% *vs*. 86.3% for SU *vs*. RNU for organ-confined UTUC. They also reported recurrence-free survival (RFS) of 37% *vs*. 47.9% for SU *vs*. RNU (P=0.48) (9). These reported outcomes objectively highlight comparable cancer control with nephron-sparing surgical alternatives and these procedures could be considered to salvage the ipsilateral kidney. *Table 3* summarizes the oncological outcomes of various contemporary studies (multi & single center) on nephron-sparing surgical procedures (SU/distal ureterectomy) *vs*. RNU.

TU with ileal ureter substitution for patients with multifocal/long segment involvement of ureter

A study comprising 141 patients which included 10, 35, and 96 patients, who underwent TU with ileal ureter substitution, SU and RNU respectively, reported no significant difference in RFS, CSS, and OS, when RNU was compared to SU or TU (11). Despite the small cohort of patients in this study, oncological outcomes are encouraging, and TU can be considered for multifocal/long segment ureteral UTUC.

Distal ureterectomy

Distal ureterectomy with BCE

In a single-center analysis from Austria, comparing 49 and 42 patients treated with DU and RNU, respectively, found no significant difference in 5-year CSS (77% *vs.* 78% for DU *vs.* RNU) and RFS (91% *vs.* 96% for DU *vs.* RNU). Also, on univariable and multivariable analysis, they found no influence of the type of surgery on CSS and RFS, for the management of distal ureteral UTUC (31). In another multi-institutional study from Japan, no significant difference in 5-year CSS (P=0.70) and RFS (P=0.22) between distal ureterectomy and RNU was noted (10). Our group has previously highlighted the consequences of inadequate excision of the distal ureter (without complete ureterovesical junction & BCE) at the time of RNU, leads to inferior oncological outcomes (33). Although the oncological outcomes comparing distal ureterectomy and RNU seem promising, irrespective of the procedure considered for the management of distal ureteral UTUC, complete circumferential BCE is of utmost importance.

Distal ureterectomy without BCE

A multicentric study compared the oncological outcomes of 84 patients with distal ureteral UTUC, 65 and 19 patients underwent distal Ureterectomy with BCE and re-implantation and SU with termino-terminal ureteric anastomosis, respectively (34). At median follow-up of 22.7 months, no significant difference in 5-year OS, CSS, and RFS was noted between the two nephron-sparing options for distal ureteral UTUC. Interestingly, they also concluded that BCE is not imperative for the management of distal ureteral UTUC. Though, as highlighted in the "Distal ureterectomy with BCE" section, inadequate excision of the distal ureter & bladder cuff, yields inferior oncological outcomes and one may not want to compromise on this step (33). These varied findings require further investigation and thus, consideration for SU over distal ureterectomy with BCE for distal ureteral UTUC, must be at surgeon's discretion & based on patient-related factors with a shared decision-making process with the patient and family.

Partial nephrectomy

Only a few case reports/series have reported the feasibility of partial nephrectomy for UTUC. A series published in 2014 comprising of eight patients, reported recurrences in 71.4% of patients with four patients who eventually died on follow-up (23). Another series from Germany reported RFS of 24 months with *ex-vivo* partial nephrectomy, auto-transplantation & pyelovesicostomy through open approach with/without combined calicoscopic approach (24). Feasibility of laparoscopic approach for nephrectomy with *ex-vivo* excision of high-grade UTUC in calyceal diverticulum and auto-transplantation have also been reported previously in two patients (35). Due to the small sample size of these studies with limited follow-up, no significant conclusions can be drawn.

Renal function outcomes

The published literature on the impact of SU *vs.* RNU suggests better preservation of eGFR with SU and this preservation of renal function may favorably impact non-cancer-related mortality. The renal function preservation may also allow the administration of adjuvant chemotherapy, which might not be feasible secondary to significant drop in eGFR following RNU. A recent single-center propensity-matched analysis comparing SU *vs.* RNU, found significantly improved preservation of eGFR with SU (P<0.001) with comparable CSS, progression-free survival (PFS), and intra-vesical RFS (IV-RFS) (29).

Similarly, a previous analysis of a relatively smaller sample size (SU *vs.* RNU: 12 *vs.* 14 patients) with comparable pre-operative eGFR (P=0.19), reported significant decline in eGFR in patients who underwent RNU, at 6 (P<0.01) and 12 months (P=0.02), while eGFR following SU was largely preserved (30).

A prior meta-analysis (SU *vs.* RNU: 983 *vs.* 2,980 patients) also reported significantly decreased risk of impairment of renal function following SU in comparison to RNU, with similar oncological outcomes (36). On the contrary, a relatively recent multicentric study comparing RNU *vs.* SU reported non-significant eGFR decline irrespective of the procedure received (37). For their analysis they included patients with pre-operatively reduced eGFR (<90 mL/min/1.73 m^2), with 67 and 26 patients in the RNU and SU groups, respectively. Interestingly, both pre- & post-operative eGFR was significantly higher in patients who received SU and despite significant postoperative increase of creatinine levels in the RNU group (P=0.028), non-significant worsening of eGFR was found in both RNU (P=0.219) and SU patients (P=0.239), postoperatively. The data/literary findings are continuously evolving and in future, probably would provide better understanding of the impact of nephron-sparing surgical procedures on the renal function outcomes.

Role of LND

The utility of LND in patients undergoing RNU continues to evolve. The most important point to consider is the rarity of the disease condition itself which limits high quality, level I evidence. Although staging and prognostic benefit is demonstrated, the evidence in support for survival has not yet been clearly established. A recent National Cancer Database (NCDB)-based analysis including 423 patients with cN positive UTUC, noted no significant improvement in survival with the performance of LND (38). Whereas a systematic review found improved CSS with template based and complete LND in patients with high stage (≥ pT2) tumors of the renal pelvis at the time of RNU. Although, similar benefit was not found in ureteral tumors (39).

The templates for LND at the time of RNU have been reported but, no such templates exist for SU. A relevant point to consider is the underutilization of the LND at the time of surgical management of UTUC. Interestingly, as per the published literature, performance of LND was primarily based on surgeon's discretion and patient/disease-related factors. In a NCDB-based analysis, rate of the performance of lymphadenectomy with SU and RNU was noted to be 30.1% and 19.9%, respectively (40). Although the performance of LND with SU favored improved survival, it did not reach statistical significance [hazard ratio (HR): 0.87; 95% confidence interval (CI): 0.57–1.32]. Thus, no conclusions can be drawn on the utility and outcomes following LND with nephron-sparing surgical alternatives to RNU.

Extrapolating from above, following templates can be utilized based on primary tumor location at the time of nephron-sparing surgeries (41).

For proximal ureteral tumors:

- Right-side: hilar, paracaval, precaval and retrocaval ± interaortocaval;
- Left-side: hilar, para-aortic and preaortic ± interaortocaval.

For mid ureteral tumors:

- Right-side: paracaval + interaortocaval + right common iliac;
- Left-side: para-aortic + interaortocaval + left common iliac.

For distal ureteral tumors (extended pelvic lymphadenectomy):

- Right-side: right pelvic nodes (obturator, internal & external iliac, and common iliac lymph nodes) ± paracaval;
- Left-side: left pelvic nodes (obturator, internal & external iliac, and common iliac lymph nodes) ± para-aortic.

Role of systemic chemotherapy

The role of systemic chemotherapy (neoadjuvant or adjuvant) with RNU is still evolving, although, more recent data does imply benefit with gemcitabine-cisplatin/carboplatin-based adjuvant chemotherapy in high-risk invasive disease (42). It is still largely underutilized even in patients receiving RNU, with up to 85.3% of patients [1,673/1,962] of a large NCDB-based analysis, not receiving any form of systemic chemotherapy (40). In the same analysis, they found 1.3% and 29.6% utilization of neo-adjuvant and adjuvant chemotherapy, respectively, in patients receiving SU but the benefit of its utilization was not found (40). Thus, the role of systemic chemotherapy with nephron-sparing surgical management of UTUC could not be established at this time.

Conclusions

With comparable oncological outcomes and favorable preservation of renal function, nephron-sparing surgical alternatives to RNU can be offered to carefully selected patients. While the evidence is open to selection bias, these options are best suited for patients with low volume, localized UTUC with imperative indication for renal preservation such as solitary kidney, compromised baseline renal function and expected significant decline in post-RNU eGFR. The role of LND could not be clearly established due to the paucity of data but can be performed along with nephron-sparing surgical resection, based on patient/disease-related factors. With established feasibility and effectiveness, robotic-assisted approach can be offered based on surgeon's discretion/experience as an alternative to open approach in such cases. The role of systemic chemotherapy following nephron-sparing surgical alternatives needs further dedicated studies and may evolve in future especially in setting of high-grade urothelial cancer. The promising results of adjuvant chemotherapy trials (POUT) following RNU could be interpreted and extrapolated to select patients (high-risk invasive disease) for systemic chemotherapy after nephron-sparing management of UTUC. With better renal function preservation, these procedures, can allow the administration of such systemic therapies. Close surveillance following these procedures is also of utmost importance as

the risk of recurrence is always a concern.

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