



Oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma: a literature review

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Background and Objective: Radical nephroureterectomy (RNU) represents the gold standard treatment for non-metastatic upper tract urothelial cancer. We sought to provide a comprehensive review of reported oncologic outcomes of the RNU procedure and of factors that might impact these outcomes.

Methods: A non-systematic review of the literature was conducted by performing an electronic literature search using PubMed with “radical nephroureterectomy” and “oncologic outcomes” as free text search terms. Both original articles and systematic reviews were considered. Search was limited to articles in English that were published in the last 20 years.

Key Content and Findings: Open and laparoscopic RNU offer comparable oncologic outcomes. In more recent years, the discussion has *de facto* shifted towards the “oncological safety” of robotic RNU, which also seems to offer comparable oncologic outcomes. Several studies have looked at the impact of different treatment-, patient- and tumor-related factors. Among treatment-related factors, attention has been given to diagnostic ureteroscopy and the risk of intravesical recurrence. Surgical wait time and perioperative blood transfusion have also been studied. Perioperative chemotherapy, specifically adjuvant therapy, was shown to improve survival. Among patient-related factors, baseline chronic kidney disease, diabetes mellitus, body mass index, and systemic inflammation have gained recent attention. Some tumor related factors, such as stage, grade, location, and multifocality may negatively impact survival outcomes. Lymphovascular invasion and histologic variants are clinically significant pathological findings.

Conclusions: RNU is a procedure with measured long-term oncologic outcomes. Minimally invasive techniques have gained an established role as they seem to offer comparable oncologic “safety”, although special attention is needed in relation to the method of bladder cuff excision. Robotic RNU is gaining popularity, and while evidence remains limited, the current literature supports the oncologic safety of this procedure. Several factors, which can be categorized as treatment-related, patient-related, and tumor-related, might impact the oncologic outcomes of UTUC patients undergoing RNU. These factors can provide crucial information to stratify patients based on their relative risk of disease recurrence and mortality which may guide clinical decision-making.

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Introduction

Radical nephroureterectomy (RNU) still represents the gold standard treatment for non-metastatic upper tract urothelial cancer (UTUC) (1), despite an increasing role of kidney-sparing procedures (2). While the RNU procedure was traditionally performed with open surgery, there has been a major shift towards minimally invasive techniques over the past two decades, first with laparoscopy and more recently with robotic assisted surgery (3). This shift has translated into lower surgical morbidity and faster postoperative recovery (4). In general, the assessment and treatment of UTUC patients has evolved over the years, and multi-disciplinary management is required to optimize the oncologic outcomes for what remains a potentially deadly disease (5).

The aim of the present non-systematic review is to provide a comprehensive analysis of reported oncologic outcomes of the RNU procedure, as well as an overview of factors that might impact these oncologic outcomes. We present this article in accordance with the Narrative Review reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-882/rc>).

Methods

This is a non-systematic review of the literature focusing on the studies reporting on oncologic outcomes of RNU. An electronic literature search was performed using PubMed using “*radical nephroureterectomy*” and “*oncologic outcomes*” as free text search terms (Table 1). Both original articles and systematic reviews were considered. Search was limited to articles published in the last 20 years, and only articles in English were considered. Articles cited in review articles from the original literature search were also considered.

The impact of surgical technique

From open to laparoscopic RNU and the role of bladder cuff excision

Since the early 2000s, there has been a significant amount

of literature dedicated to comparing outcomes for open and laparoscopic RNU. The overwhelming majority of retrospective studies (6-29), as well as the only reported randomized prospective trial (30), concluded that these two techniques have comparable oncologic outcomes for organ-confined disease (Table 2).

This is also confirmed in a recent large meta-analysis involving over 20,000 patients by Liu *et al.*, who found no difference in 2-5-year recurrence-free survival, cancer-specific survival, or overall survival between patients undergoing open or laparoscopic RNU (32).

However, when looking at patients with advanced stage disease, a recent systematic review by the European Association of Urology Guidelines panel suggested that laparoscopic bladder cuff excision might translate into worse oncologic outcomes, including increased rate of intravesical recurrence (33). In two recent multicenter propensity score matched analyses from Japan, Shigeta *et al.* found more atypical recurrence sites and an increased risk of subsequent intravesical recurrence in the “pure” laparoscopic group (34), as well worse oncologic outcomes when only considering T3N0M0 UTUC populations (35). On the other hand, in a smaller study by Lee *et al.*, the oncologic outcomes of laparoscopic RNU in patients with high stage disease were comparable to those of open surgery (24). In one of the largest studies with the longest follow-up to date, Veeratterapillay *et al.* performed a retrospective analysis of RNU at a UK tertiary referral center. Median follow-up was 9.2 years. The 5- and 10-year CSS rates were 70.5% and 67.1%, respectively (31).

The advent of robotic RNU

In more recent years, the discussion has *de facto* shifted towards the “oncological safety” of robotic RNU, which seems to offer less surgical morbidity when compared to open RNU (4). A small number of retrospective studies have shown robotic RNUs to produce comparable oncologic outcomes to laparoscopic and open RNUs (36-40) (Table 3). In a large meta-analysis involving over 80,000 patients, no correlation was found between surgical technique—

Table 1 Literature search methodology

Items	Specification
Date of search	11/14/22–4/2/23
Databases and other sources searched	PubMed
Search terms used	Free text search terms: radical nephroureterectomy, upper tract urothelial carcinoma, oncologic outcomes
Timeframe	2000–2023
Inclusion criteria	Inclusion criteria: Original articles and systematic reviews, written in English
Selection process	The selection process was performed by two of the authors (GG, DR) and consensus was obtained when needed with the assistance of the senior author (RA)

including open, laparoscopic, and robotic—and recurrence-free and cancer-specific survival outcomes (4).

In a recent NCDB (2010–16) analysis including 2,631 patients, the robotic RNU group showed increased rates of lymph node dissection (41). Soria *et al.* recently proposed a “tetrafecta” composite outcome—including lymph node dissection, bladder cuff excision, lack of complications, negative surgical margins—which they found to be associated with higher 5-year overall survival rates (42). In another recent propensity score matched analysis, Veccia *et al.* found robotic RNU to be associated with higher rates of “tetrafecta” achievement when compared to laparoscopic RNU (43).

Factors associated with oncologic outcomes

Several studies have looked at the potential impact of different treatment-, patient- and tumor-related factors on the oncologic outcomes of RNU (*Figure 1*).

Treatment related factors

Diagnostic ureteroscopy

Multiple meta-analyses have found diagnostic ureteroscopy prior to RNU to be associated with increased risk of intravesical recurrence (IVR) (44,45). Marchioni *et al.* analyzed 6 studies including 2,382 patients, 765 of which underwent diagnostic URS prior to RNU. All examined studies were retrospective, and the majority examined Asian populations. The IVR rate ranged from 39.2% to 60.7% and from 16.7% to 46% in patients with and without prior URS, respectively. In the pooled analysis, a significant association was found between performance of URS prior to

RNU and IVR (HR 1.56; $P < 0.001$) (44). Despite higher risk of IVR, no association between ureteroscopy and long-term survival outcomes seems to be proven in the metaanalysis by Guo *et al.*, which included 8 eligible studies containing 3,975 patients (45).

In a more recent UK study (not included in the above meta-analyses), prior URS, T2 stage, proximal ureter tumor and bladder cancer history were predictors of metachronous intravesical recurrence (31). Also, in a recent analysis of 485 cases of minimally invasive RNU from the ROBUUST collaborative group, a diagnostic ureteroscopic biopsy was found to be associated to a 50% higher chance of developing IVR (46).

It has been suggested that future studies examine if immediate administration of intravesical chemotherapy following ureteroscopy might reduce the rates of intravesical recurrence (45).

Surgical wait time

A systematic review by Nowak *et al.* investigated surgical wait time following UTUC diagnosis and found inconsistent results, suggesting that a safe delay in RNU may be different for different subsets of UTUC patients (47). A review of 138 patients by Lee *et al.* also found no significant impact of surgical wait time after UTUC diagnosis on cancer-specific survival and recurrence-free survival (48). Interestingly, in a subgroup of 80 of these patients who had urothelial carcinoma of the ureter, cancer-specific survival and recurrence-free survival were significantly higher for those who underwent RNU within a month of their diagnosis than those that waited longer than one month for surgery (48). This suggests that surgical wait time should be minimized for those with ureteral tumors.

Table 2 Key studies reporting oncologic outcomes of open and laparoscopic nephroureterectomy

Author	Study period	No of cases (technique)	Median FU, mo	5-yr RFS, %	5-yr CSS, %	Comment
Bariol (9)	1992–1999	42 (open)	96	82.1*	nr	–
		26 (lap)	101	72*	nr	
Muntener (11)	1993–2001	39 (lap)	74	59	68	–
Rouprêt (14)	1994–2004	26 (open)	78	51.2	61.5	–
		20 (lap)	68.5	71.6	90	
Capitanio (15)	1987–2007	979 (open)	73	76.2	73.1	Lap group: more favorable path stage and lower rate of LVI
		270 (lap)	31	86.8	85.8	
Greco (16)	1999–2003	70 (open)	60	73	–	RFS decreased as path stage increased
		70 (open)		75		
Waldert (17)	1999–2006	59 (open)	41	76	80	T stage and grade independent factors for progression and cancer specific mortality
		43 (lap)		79	85	
Simone (18)	2003–06	40 (open)	44	–	89.9	Prospective randomized trial—for pT3 and high-grade, CSS and MFS in favor of open
		40 (lap)			79.8	
Walton (20)	1987–2008	703 (open)	36	73.7	75.4	–
		70 (lap)	17	63.4	75.2	
Stewart (21)	1992–2000	39 (open)	163	79^	–	–
		23 (lap)		76^		
Ariane (22)	1995–2010	459 (open)	27	50.7	–	Oncologic outcomes for locally advanced disease similar between open and lap
		150 (lap)		52.2		
Fairey (23)	1994–2009	403 (open)	26.4	43	73	–
		446 (lap)		33	76	
Zou (25)	1999–2013	101 (open)	53	–	87.1	pT stage, tumor grade and LVI independent predictors of cancer specific mortality
		21 (lap)			85.7	
Liu (26)	2000–2013	213 (open)	60	47	63	–
		52 (lap)		59	70	
Moschini (28)	2006–2018	3,227 (open)	62	–	–	Lap not inferior to open
		757 (lap)				
Veeratterapillay (31)	2004–2018	422 (any)	110.4	–	70.5	–

*, Metastasis free survival; ^, 10-yr progression free survival. FU, follow-up; RFS, recurrence-free survival; CSS, progression free survival; LVI, lymphovascular invasion; MFS, metastasis free survival.

Perioperative blood transfusion (PBT)

A few studies have reported an association between PBTs during or after RNU and oncologic outcomes. A study by Rink *et al.* involving 285 UTUC patients found PBT associated with advanced tumor stage and higher tumor grade, and worse overall survival on multivariate

analysis (49). Rieken *et al.* found PBT to be associated with disease recurrence, cancer-specific survival, and overall survival in univariate analysis, but no association was found in a multivariate Cox regression (50). A study by Bagrodia *et al.* retrospectively separated patients into groups based on if they received an intraoperative blood transfusion,

Table 3 Robotic assisted laparoscopic nephroureterectomy: reported oncologic outcomes

Author	Study period	No of cases	Median FU, mo	5-yr RFS, %	5-yr CSS, %	Comment
Lim (36)	2007–10	32	45.5	68.1	75.8	Female gender and stage \geq pT2 associated with shorter RFS
Aboumohamed (37)	2008–14	65	25	57.1	69.5	LVI associated with worse CSS
Lee (38)	2004–17	161 (open) 137 (lap) 124 (robotic)	41.71 38.1 23.7	–	–	Surgery type not significantly associated with survival outcomes
De Groote (39)	2008–17	78	15	53*	–	–
Zeuschner (40)	2009–19	65 (open) 66 (robotic)	30.9	55.3^ 66.7^	68.4# 76.2#	Lymph node metastases and patient age with strongest impact on PFS

*, 4-yr; ^, 2-yr progression free survival; #, 2-yr overall survival. FU, follow-up; RFS, recurrence-free survival; CSS, progression free survival; LVI, lymphovascular invasion.

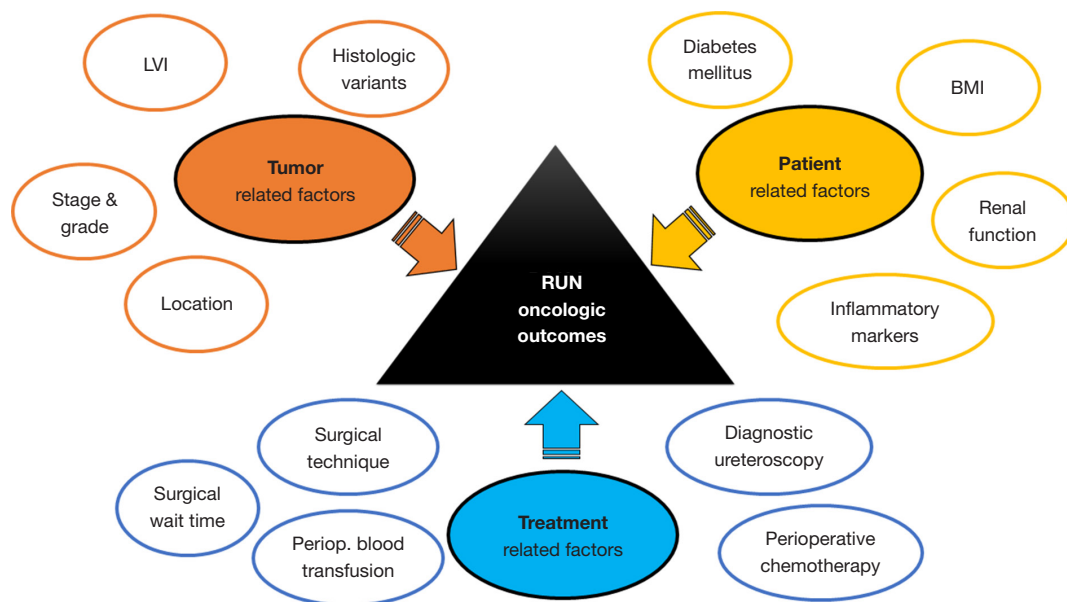


Figure 1 Factors with a potential impact on the oncologic outcomes of RNU. RUN, radical nephroureterectomy; LVI, lymphovascular invasion; BMI, body mass index.

postoperative blood transfusion, or no blood transfusion, and found no association with survival outcomes on multivariate analysis (51). The varied results suggest that the relationship between PBT and survival in UTUC patients requires further investigation.

Perioperative chemotherapy

There is growing evidence that platinum-based perioperative

chemotherapy improves survival for UTUC patients. The only randomized controlled trial to date that has investigated this is the POUT trial (Peri-Operative chemotherapy versus sUrveillance in upper Tract urothelial cancer), which found in a study of 261 participants that adjuvant chemotherapy significantly improved disease-free survival (52). Birtle *et al.* argued that adjuvant chemotherapy should be the standard of care for patients with pT2-T4

pN0–N3 M0 or pTany N1–3 M0 disease (52). Multiple retrospective studies found that perioperative chemotherapy offers a survival benefit specifically for UTUC patients with pathologic vascular invasion (53) and positive lymph nodes (54,55), but not for patients without these disease features.

Compared to adjuvant chemotherapy, there is less evidence to support neoadjuvant chemotherapy for UTUC patients, especially considering the challenge of accurately staging UTUC prior to RNU (56,57). Pinar *et al.* argued that there is a strong rationale for neoadjuvant chemotherapy because of the impact of RNU on renal function, however there is insufficient evidence to fully recommend it over adjuvant chemotherapy at this time (58).

Patient-related factors

Baseline renal function

In a meta-analysis of over 4,000 patients by Kim *et al.*, there was a significant negative association between preoperative renal function and survival (59). Another large meta-analysis noted similar findings after dividing patients into two groups: those with chronic kidney disease (CKD; eGFR <60 mL/min/1.73 m²) and those with normal kidney function. The CKD group had worse five-year overall (67.5% vs. 79.4%), cancer-specific (73.6% vs. 83.5%), and progression-free survival (61.5% vs. 74.6%) than the normal kidney function group (60). A linear relationship between eGFR and prognostic survival was suggested also in the study by Li *et al.* (61). These findings stress the importance of identifying UTUC patients with renal insufficiency prior to RNU.

Diabetes mellitus (DM)

A retrospective multi-institutional study by Rieken *et al.* evaluated the impact of DM and metformin use among UTUC patients. Their analysis found that diabetic patients who did not use metformin had a significantly higher risk of disease recurrence and worse cancer-specific mortality than diabetic patients who used metformin as well as non-diabetic patients (62). Another study by Gao *et al.* evaluated DM among UTUC patients, and while no correlation with survival outcomes was identified, they did find higher rates of IVR among patients with DM (63).

Body mass index (BMI)

A single-institutional study of 237 patients found that obesity (measured as BMI ≥ 30 kg/m²) was independently associated with higher risk of disease recurrence and cancer-specific mortality in patients treated with RNU for

UTUC (64). In a study by Murakami *et al.*, obesity was also associated with worse cancer-specific survival, although it was not found to be a prognostic factor on multivariate analysis (65). Interestingly, a study by Inamoto *et al.* in a Japanese population actually found obesity to be associated with improved cancer specific survival (66), suggesting that the impact of BMI may be controversial. On the other end of the spectrum, multiple studies have found being underweighted (67,68) or having a smaller BMI (69) to be associated with worse cancer-specific survival among UTUC patients.

Markers of systemic inflammation

The neutrophil/lymphocyte ratio (NLR), which is a marker of stress and systemic inflammation, has gained attention in recent years due to its prognostic value for various cancers, including urothelial cancer (70). In UTUC patients, a “high” or “altered” preoperative NLR has been associated with poorer oncologic outcomes as well as worse pathologic features including more advanced tumor stage, lymph node metastasis and lymphovascular invasion (71–75). The NLR may even be able to subclassify patients within a clinical stage and identify a “poor prognostic group”, which may help guide future clinical decision-making (76).

Another marker of systemic inflammation, C-reactive protein (CRP), has been evaluated among UTUC patients. Obata *et al.* found that patients with an elevated preoperative CRP, >0.5 mg/dL, had significantly lower 5-year recurrence-free and cancer-specific survival rates than those without elevated CRP (77). Similarly, Aziz *et al.* found that serum CRP above 0.9 mg/dL was associated with more aggressive tumor biology and poorer survival (78). Interestingly, postoperative normalization of CRP level has been associated with improved survival (79).

The Glasgow Prognostic Score (GPS) and modified GPS, which are based on CRP and albumin levels, have also been associated with clinicopathologic features and survival outcomes in UTUC patients (80,81).

Tumor related factors

Tumor stage and grade

A meta-analysis by Cha *et al.* across 23 institutions found T classification independently associated with disease recurrence and cancer-specific mortality on univariate and multivariate analysis (82). They found high tumor grade associated with these outcomes only on univariate analysis. An analysis across 12 institutions by Margulis *et al.*

found high tumor grade and advancing pathologic T stage associated with disease recurrence and cancer-specific survival (83). Multiple other studies have also reported the significance of tumor stage and grade (84).

One thing to keep in mind is that UTUC might be often underestimated on initial biopsy. A study by Koll *et al.* found that 61% of patients with < pT1 disease on endoscopic biopsy were upstaged to \geq pT1 in final pathology, and 30% of patients with low-grade disease were upgraded to high-grade (56). A larger analysis of over 1,200 patients found clinical under-staging to occur in 59.5% of patients and under-grading to occur in 42.4% of patients (57). These findings suggest that one should not solely rely on ureteroscopic biopsy results when stratifying patients based on risk, especially if considering more conservative treatment options.

Tumor location

A difference in risk based on primary tumor location was found in a meta-analysis by Krajewski *et al.* of over 16,000 patients (85). Patients with ureteral tumors were found to have significantly worse cancer-specific survival, overall survival, and disease-free survival than patients with renal pelvic tumors (85). Another meta-analysis by Wu *et al.* reported similar findings, except for patients with pT3/4 and pN+ tumors (86). Conversely, a study by Tai *et al.* found ureteral tumor location to negatively impact survival outcomes only for patients with pT3 disease (87). A related finding by Inamoto *et al.* is that patients with lower ureteral tumors have a higher rate of urothelial recurrence than those with upper ureteral and pelvic tumors, after adjusting for many prognostic factors (88). This may play a role in the association between ureteral tumor location and poorer survival outcomes.

Tumor multifocality has also been shown to negatively impact survival outcomes. A study by Chromecki *et al.* involving almost 2,500 patients identified 23.7% to have tumor multifocality at the time of RNU and found this to be an independent predictor of disease progression and cancer specific mortality in patients with organ-confined disease (89). The large meta-analysis by Wu *et al.* (86) and a single institution study by Milojevic *et al.* (90) also found multifocal tumors to be negatively associated with survival outcomes.

Lymphovascular invasion (LVI)

After patients undergo RNU, one of the most significant pathological findings is LVI. In a large meta-analysis of almost 30,000 patients by Stangl-Kremser *et al.*, patients

with LVI were found to be 43% more likely to have IVR and have 53% lower cancer-specific survival (91). Other smaller retrospective studies also found that LVI predicted or was associated with adverse progression free survival and decreased cancer-specific survival (92,93). This suggests that adjuvant therapies should be strongly considered for patients with a diagnosis of LVI following RNU.

Histologic variants

Another noteworthy pathologic finding following RNU is the presence of a histologic variant, such as a micropapillary, squamous, or sarcomatoid tumor. Rates of histologic variants have been reported between 7.9% and 11.8% (94,95). In a propensity score matched analysis of 1,173 patients by Chung *et al.*, variant histology was independently associated with worse recurrence-free survival, cancer-specific survival, and overall survival (94). In this same study, when they only analyzed patients with variant histology who underwent adjuvant chemotherapy, no significant differences in survival were found, which suggests adjuvant therapy may mitigate the dangers of variant histology.

Conclusions

RNU is a procedure with measured long-term oncologic outcomes. Minimally invasive techniques have gained an established role as they seem to offer comparable “oncologic safety”, although special attention is needed in relation to the method of bladder cuff excision. Robotic RNU is gaining popularity, and while evidence remains limited, the current literature suggests this to be a valid surgical option. Several factors might impact the oncologic outcomes of UTUC patients undergoing RNU. Because of the non-systematic nature of the present review, not all of them are discussed herein. These can be broadly categorized in treatment-related, patient-related, and tumor-related factors. These factors can provide crucial information to help stratify patients based on their relative risk of disease recurrence and overall mortality, which may guide clinical decision-making.

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