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A Case for Nephron Sparing Surgery in the Management of Upper Tract Urothelial Carcinoma

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Abstract

Upper tract urothelial carcinoma (UTUC) is rare and its management presents many challenges. Outside of distal ureterectomy for select cases, management has been primarily radical nephroureterectomy. Endoscopic nephron sparing management (NSM) is recognized to have some role in UTUC treatment; however, it is yet to gain firm footing in the treatment algorithm. In this review, we discuss the benefits of NSM with regards to oncologic outcomes, renal function preservation, and cost savings. Finally, we propose recognition of endoscopic NSM as a first-line treatment in selected patients with low risk disease.

Introduction

The management of upper tract urothelial carcinoma (UTUC) presents many challenges. Contrary to conventional bladder urothelial cancer in which only one-fifth of patients have evidence of invasion at initial diagnosis, 60% of patients with UTUC present with advanced disease.[1] Identification of low risk patients is difficult due to significant under-staging through endoscopic biopsy.[2,3] Rather, surrogates such as tumor grade and unifocality are relied upon for risk stratification.[4,5] Given the propensity to under-stage patients with UTUC, current European guidelines advocate for radical nephroureterectomy (RNU) as the gold standard treatment for UTUC rather than risk undertreatment. These guidelines thus propose quite a limited subset of patients who should be considered for nephron sparing management (NSM), namely those with low grade, small, and unifocal tumors.[1] Accounting for only 5% of all urothelial cancers, UTUC is relatively rare and high-quality prospective trials to explore the more conservative treatment options for UTUC are not available.

Several issues arise with a broad advocacy toward RNU, a challenging operation in a comorbid patient population. The average age of patients with UTUC ranges between 70 and 90 years and comprises a population with moderate comorbidities compounding surgical risk. RNU can also significantly impact renal function, the consequences of which will be discussed below.

In this review, we present what is currently known about the NSM of UTUC, specifically renal preservation rates and oncologic outcomes of endoscopic management compared with RNU. We will explore the consequences of RNU on renal function and the overarching impact renal insufficiency has on these patients' well-being. Finally, we touch on the cost savings of renal preservation in patients with UTUC.

The intent of this review is to highlight the benefits of renal preservation in appropriately selected patients with UTUC. Hopefully, with a shift in culture, radical surgery will only be considered in selected patients *after* excluding NSM options first.

Renal Preservation Rates

Several groups have described their experiences with the endoscopic management of UTUC and mostly have published their renal preservation rates; that is, patients who did not progress to RNU (Table 1).[6–17] When the data are combined, the weighted average renal preservation rate is 80%. Mean follow-up averaged just less than 5 years, although the actual duration may be longer as some only reported median times. Four of the earlier studies presented ureteral stricture rates ranging 10%–15%; however, they did not elaborate on supposed risk factors.[7,8,10,11] The patients presented in these retrospective studies underwent either an endoscopic (retrograde ureteroscopy) ablation or percutaneous tumor resection, and in some cases a combination of both. Segmental ureterectomy for select patients with anatomically agreeable tumors has also been described for renal preservation when managing UTUC.

The application of elective endoscopic management for those with low-grade locally resectable tumors is certainly appealing given the high likelihood of renal preservation. Imperative indications such as medical comorbidities, bilateral disease, or a solitary kidney precluding radical surgery, even in the face of disease progression, may have artificially inflated the expected preservation rates for all comers.

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Table 1. Follow-Up Time, and Imperative and Renal Preservation Rates of Studies Using NSM for Upper Tract Urothelial Carcinoma

Study	*Year*	N	*Mean follow-up (months)*	*Imperative NSM*	*Renal preservation (%)*
Deligne et al.[6]	2002	61	39.9	25 (41%)	81
Iborra et al.[7]	2003	54	84	0 (0%)	78
Milner et al.[8]	2006	10	33	10 (100%)	80
Roupret et al.[9]	2006	43	54	—	74
Sowter et al.[11]	2007	40	41.4	14 (35%)	71
Krambeck et al.[10]	2007	37	32.4[a]	37 (100%)	75
Thompson et al.[13]	2008	83	55.2[a]	0 (0%)	67
Lucas et al.[12]	2008	39	53.5[a]	0 (0%)	87
Gadzinski et al.[14]	2010	34	77[a]	16 (47%)	68
Fajkovic et al.[16]	2012	20	20.4	12 (60%)	100
Grasso et al.[20]	2012	66	38.2	26 (39.4%)	83
Cutress et al.[15]	2013	59	58	21 (35.6%)	83
Motamedinia et al.[17]	2015	141	66	68 (48.2%)	87
Weighted average		687	54.5	194 (37.4%)	80

[a]Follow-up time reported as a median and excluded from the overall weighted average.
NSM = nephron sparing management.

Preservation rates relative to the proportion of patients undergoing NSM for imperative indications do not reveal an obvious correlation (Table 1); however, the retrospective nature of theses studies precludes controlling for selection biases. Certain factors have been shown to increase the rates of progression in patients undergoing endoscopic management. The most widely accepted of these include high-grade tumors and findings on imaging suggestive of invasive disease such as infiltration and hydronephrosis independent of obvious obstruction.[18] Nonetheless, the advantages of avoiding RNU in the majority of patients and delaying it in a small minority are readily apparent.

Oncologic Outcomes

In the early days of oncologic surgery, William Halsted and his contemporaries advocated for gross removal of whole organs and their surrounding structures, coining the term ''radical'' surgery to excise out the roots of the offending cancer. However, through improved imaging, stratified staging, and surgical technique, partial organ resection or ablation has permeated the surgical management of nearly all solid malignancies. The concern for compromising oncologic outcomes through conservative procedures is addressed in multiple published reports comparing outcomes in patients who underwent endoscopic resection *vs* RNU.[9,12,14–16,19,20] A meta-analysis combining these eight studies found no differences in the cancer-specific (CSS) or overall survivals (OSs) between these groups.[21] Examining the study that suggested poorer OS for the endoscopic groups revealed that the endoscopic group also had older patients with greater comorbidities, which would ultimately increase all-cause mortality rate.[16] A subset analysis of the remaining studies showed that, among patients with high-grade disease, CSS was favorable for those undergoing RNU, but management approach conferred no survival advantage for patients with low-grade disease.[14,21–23] A similar article utilizing the SEER database in patients with non-high-grade (e.g., low grade, G1, and G2) cT1 tumors found no difference in CSS for patients who underwent NSM *vs* RNU.[24] Yakoubi and others[21] plainly state that the retrospective nature of these studies, differences in follow-up, and site-specific variability in endoscopic expertise all impose biases, which limit rapidly accepting shifts in treatment guidelines toward conservative management. Alternatively, the heterogeneity of these groups without any overt differences in outcomes shows that, in current practice, there appears to be no measurable advantage for RNU when comparing equivalent stages and grades of UTUC.

The risk of local recurrence following NSM is moderate, but the low probability of disease progression spares most patients the need for radical surgery. Reported rates differ, but generally lie in the range of 15%–19%.[20,25] A tenet of effective NSM is contingent on regimented surveillance, quite possibly lifelong, to identify and manage disease recurrence and progression as early as feasible. In fact, the ability and willingness of a patient to commit to regular surveillance should be considered integral to, and advocated for before, the decision to embark on NSM.

Endoscopic surveillance remains paramount; however, cross-sectional imaging at regular intervals plays an important role in identifying infiltration or extrarenal disease. Weizer and colleagues describe their experience in which three patients developed renal parenchymal or extrarenal recurrences following complete endoscopic resection, despite frequent endoscopic evaluation.[26] Only one patient had high-grade disease during follow-up. Two patients had evidence of progression on imaging prompted by gross hematuria. Computed tomography (CT) with contrast, or magnetic resonance imaging in patients with renal insufficiency or allergies precluding contrast use, should be integrated into all follow-up regimens in patients with UTUC. The optimal frequency is unknown, but most favor imaging at least annually, with more frequent scans for higher risk disease.

Another valid consideration before accepting a paradigm shift away from RNU is whether disease progression following NSM is associated with worse outcomes. Does delayed RNU following a trial of endoscopic resection fare worse than immediate RNU at the time of diagnosis? Gadzinski and coworkers[27] proposed this question and compared their endoscopic cohort who subsequently progressed to RNU *vs* those who underwent immediate radical surgery. Of

great interest, they found no difference in CSS or OS during the study period.[27] In addition, there were no differences in perioperative outcomes with regards to surgical difficulty or postoperative complications between the two groups. While this study was small (with only 11 patients in the delayed RNU cohort), there have been no conflicting studies demonstrating a disadvantage to delayed nephroureterectomy following disease progression.

Renal Function Preservation

In 2006, Huang and associates showed a clear relationship between radical nephrectomy and new-onset chronic kidney disease (CKD) in patients with renal-cell carcinoma.[28] Three years after surgery, 80% and 95% of those who had partial nephrectomy maintained an estimated glomerular filtration rate (eGFR) above 60 and 45 mL/minute/1.73 m^2, respectively, *vs* only 35% and 64% after radical surgery. With equivalent oncologic outcomes, appreciation of the benefits of renal preservation prompted acceptance of nephron sparing surgery through partial nephrectomy.

Unsurprisingly, RNU has also been demonstrated to significantly reduce renal function, particularly when considering the patient demographic most at risk for this disease. A large multi-institutional study looked at 414 patients undergoing RNU for UTUC and found a significant decline in renal function across the board (59–51 mL/minute/1.73 m^2).[29] Strikingly, 25% of patients experienced new-onset eGFR below 60 mL/minute/1.73 m^2 and 15% fell below 45 mL/minute/1.73 m^2. Xylinas and colleagues corroborated these findings in their study, which demonstrated RNU resulting in a median decline in eGFR by 18.2%.[30]

One obvious consequence of surgically-induced renal insufficiency in patients with UTUC is eligibility for platinum-based adjuvant chemotherapy. Raman and coworkers found that lower eGFR following RNU was associated with receiving second-line adjuvant therapy due to avoidance of cisplatin.[29] In addition, 72% of those patients who did not receive cisplatin-based adjuvant chemotherapy had an eGFR over 60 mL/minute/1.73 m^2 *before* RNU, meaning that radical surgery precluded first-line therapy for advanced urothelial disease in many patients who would have otherwise been eligible. Kaag et al. reported similar findings, but went further by showing that older patients (≥70 years) were even more likely to progress to significant renal insufficiency following RNU.[31]

To be certain, renal preservation should not come at the expense of oncologic outcomes, and first-line therapy for most patients with advanced or high-grade UTUC remains RNU. However, surgeons must also appreciate that patients with localized and low-grade UTUC are at risk for metachronous, advanced contralateral UTUC or bladder cancer in the future and preserving renal function would best preserve systemic treatment options.

Renal function has far-reaching consequences beyond platinum chemotherapy eligibility. Decline in renal function has been shown to incrementally and proportionately increase the risk of death for individuals with an eGFR <60.[32] The risk of cardiac events rises in parallel, and these effects are independent of age. Specifically to those with UTUC, CKD has been shown to correlate with higher grade disease and poorer overall prognosis.[33] In addition, the development of CKD following RNU has been linked to a higher rate of bladder recurrence.[34]

While the risk of progression to hemodialysis comes into play when considering whether to proceed to RNU, these data suggest that the consequences of even moderate renal insufficiency are critical to consider at an earlier point of intervention in UTUC.

NSM should also be considered in patients with an increased risk of metachronous bilateral disease. Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is a recognized hereditary cancer syndrome with an increased risk for UTUC, and NSM should be considered in the affected patient.

HNPCC is an autosomal dominant syndrome that increases the risk of colorectal and endometrial cancer and urothelial carcinomas of the renal pelvis and ureter. There are several mutations associated with the syndrome and individuals with *MSH2*, and to a lesser extent *MLH1*, are specifically at a higher risk for UTUC. HNPCC is associated with 6% lifetime risk of UTUC; however, there is no increased risk of bladder cancer outside of potential drop-metastases from an upper tract primary.[35] Individuals with HNPCC present with UTUC in their early 60's and are more likely to have carcinoma of the ureter rather than the renal pelvis compared with sporadic cases.[36] Men and women are equally at risk, as well as nonsmokers. There is a greater proportion of high-grade disease at presentation; however, tumors are less likely to be invasive.[37,38]

What has not been well reported in the literature is the risk of bilateral UTUC, but given a germ line mutations etiology, there is a presumed increase in the risk of metachronous tumors. The increased risk of contralateral disease favors an up-front preference toward NSM when feasible. In addition, young patients with UTUC and a personal history of colorectal or endometrial cancer, or a strong family history of HNPCC-type malignancies, should be counseled toward genetic testing.[38]

Cost Analysis

Pak and colleagues examined the potential 5-year costs associated with various UTUC management algorithms.[39] Endoscopic management was dichotomized into a best-case scenario of initial ureteroscopy with tumor ablation followed by surveillance without recurrence costing $41,474 *vs* $134,320 for a worst-case scenario of recurrence with ablation at each follow-up. Laparoscopic RNU ranged from $125,684 for patients with only chronic kidney disease *vs* $385,146 for those requiring subsequent venous access fistula and hemodialysis.

Of course, there are several more complicated paths that may result in higher costs, including an initial period of endoscopic management with progression requiring RNU, subsequent renal failure, and hemodialysis. However, progression rates to RNU appear to be low. Pak and colleagues also included a pathway for a patient who might obtain a renal transplant for resulting renal insufficiency, amounting to $155,591 over 5 years. Most patients with a history of cancer and in need of renal transplant are required to demonstrate a period free from recurrence before being able to proceed; it is unclear if Pak and colleagues accounted for renal replacement therapy costs during this period.

One important point that the authors do make is that the quality of life for patients on dialysis has been repeatedly shown to be poor. They specifically cite a study showing that patients on dialysis would give up 25%–50% of their remaining life expectancy in exchange for a shorter life of ''full health,'' illustrating how taxing hemodialysis can be.[37]

The cost savings of nephron sparing surgery have been shown in several studies, including patients with non-urothelial cancers. Klinghoffer and colleagues examined the costs, over a 10-year period, associated with open and laparoscopic partial nephrectomy *vs* laparoscopic radical nephrectomy for a small renal mass in a 65-year-old man with normal renal function.[40] All potential charges were considered, including operating room, hospitalization, surveillance imaging, complication management, and treatment of chronic kidney disease. They found that partial nephrectomy (either open—$25,941 or laparoscopic—$26,829) was more cost effective and yielded more quality-adjusted life years than radical nephrectomy ($66,935). The greatest contributor of long-term costs was related to CKD management. In the long run, patients may consider the specific procedure or approach to managing a small renal mass irrelevant, especially with equivocal oncologic outcomes; however, the incurred consequences of CKD would significantly impact quality of life for the remaining part of their lives.

In a similar vein, future quality of life considerations, which result from our surgical management in UTUC patients, must be used to inform our selection of optimal treatment.

Conclusions

NSM of UTUC is enticing. One great limitation of nearly all studies focusing on conservative UTUC management is that they are invariably retrospective and include a highly selected group of patients who undergo NSM. While many make efforts to control for potential biases, it is in fact these biases (favorable tumor characteristics and patient comorbidities) that drive the outcomes being studied. Unfortunately, the relative infrequency of UTUC and the paucity of large prospective trials have limited a data-driven stratified treatment protocol, which can guide physicians as to when conservative endoscopic nephron sparing management or RNU is most appropriate.

It should again be noted that the European guidelines narrowly define eligibility for endoscopic management of those with small (<1 cm), unifocal, and low-grade tumors.[1] However, the treatment paradigm is slowly broadening to include NSM in a wider selection of patients. More nuanced treatment algorithms have been proposed that take multiple other factors into consideration such as evidence of infiltration of hydronephrosis on CT scan along with tumor size, grade, and location to help identify low-risk patients suitable for NSM.[18,41] In addition, there is a greater appreciation for the consequences of renal insufficiency following RNU, including increased all-cause mortality rate and, more specifically for patients with UTUC, the need for intact renal function to receive first-line platinum-based chemotherapy.

Encouragingly, through the demonstration of equivalent oncologic outcomes for appropriately selected patients, improved quality of life and lower cardiac risks associated with preservation of function, and broader experience with endoscopic interventions, endoscopic NSM appears to have a recognizable and desirable place as first-line therapy in selected patients with UTUC.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

CKD = chronic kidney disease
CSS = cancer-specific survival
CT = computed tomography
eGFR = estimated glomerular filtration rate
HNPCC = hereditary nonpolyposis colorectal cancer
NSM = nephron sparing management
OS = overall survival
RNU = radical nephroureterectomy
UTUC = upper tract urothelial carcinoma