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Upper tract urothelial carcinoma: Paradigm shift towards nephron sparing management

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Abstract

Upper tract urothelial carcinoma (UTUC) is relatively rare compared to urothelial carcinoma of the lower tract, comprising only 5%-10% of all urothelial cancers. Although both entities share histologic properties, UTUC tends to be more invasive at diagnosis and portend a worse prognosis, with a 5 year overall mortality of 23%. To date, the gold standard management of UTUC has been radical nephroureterectomy (RNU), with nephron sparing techniques reserved for solitary kidneys or cases where the patient could not tolerate radical surgery. Limited data from these series, as well as select series where nephron-sparing endoscopic management has been offered to a broader patient base, suggest that minimally invasive, nephron sparing techniques can offer comparable oncologic and survival outcomes to RNU in appropriately selected patients. We review the current literature on the topic and discuss long term outcomes and sequelae of the gold standard treatment, RNU. We also discuss the oncologic outcomes of minimally invasive, endoscopic management of UTUC. Our goal is to provide the reader a comprehensive overview of the current state of the field in order to inform and guide their treatment decisions.

Key words: Urothelial carcinoma; Ureteroscopy; Upper tract; Endoscopy; Minimally invasive

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Core tip: In the appropriate patient population, minimally invasive endoscopic treatment of upper tract urothelial carcinoma provides comparable oncologic and survival outcomes to the gold standard radical nephroureterectomy.

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INTRODUCTION

Urothelial cell carcinoma (UCC), a common malignancy encountered by urologists, is the 4th most common

overall neoplasm and the 8th most common cause of cancer death in men. Upper tract urothelial carcinoma (UTUC), however, is a relatively rare neoplasm, comprising only 5%-10% of all UCCs and 5%-7% of all renal neoplasms[1-3]. Despite their histologic similarities, UTUC and lower tract UCC may represent two distinct oncologic entities. The natural history of both disease states differs, in that 60% of UTUCs are invasive at diagnosis compared to 15%-25% of lower tract UCCs. UTUC portends a worse prognosis, with an overall 28% 5-year extra vesicle recurrence rate and a 23% 5-year mortality[4]. The prognosis for muscle invasive UTUC is particularly grim, with a 5 year cancer specific survival (CSS) less than 50% for pT2 /T3 lesions and less than 10% for pT4 lesions[5,6].

Given the wide body of lower tract UCC literature and the well documented bladder tumor recurrence rate following UTUC, management and surveillance of lower tract disease is standardized and well adhered to. In contrast, most of the recommendations for management of UTUC and subsequent surveillance have been extrapolated from current guidelines for lower tract UCC. Only one specific guideline from the European Association of Urology (EUA) currently exists for the surgical management of UTUC, as well as no randomized controlled trials (RCT) compared to 238 RCTs for bladder cancer[7,8]. UTUC is, at best, included as a subset in guidelines for bladder cancer amongst other professional societies such as the American Urological Association (AUA) and International Consultation on Urological Diseases (IDUC)[9-11].

The gold standard treatment for UTUC is radical nephroureterectomy (RNU) with ipsilateral bladder cuff excision[4]. As our instrumentation technology improves, endoscopic management of UTUC has become feasible. Early experience with endoscopic management of UTUC has been limited to patients with solitary kidneys, bilateral disease, or those who are not surgical candidates to undergo RNU. Data from these cases, though limited to retrospective, unmatched comparative studies, demonstrates no short and mid-term difference in overall survival and CSS between endoscopic management and RNU[12].

The lack of concrete management guidelines for UTUC, as well as the feasibility of nephron sparing treatment techniques, raises questions of the appropriateness of our current management strategies. In this article we review existing treatment options for UTUC, their effectiveness from an oncologic standpoint, as well as the morbidity incurred long term due to impaired renal function. Though we encourage the reader to come to their own conclusion, we propose that in appropriately selected patients, endoscopic treatment of UTUC is as effective as RNU with lower long term renal complications.

We performed a review of the literature from January 1980 to January 2015, including all English language articles using the search terms "endoscopic management", "ureteroscopic management", "percutaneous management" and "UTUC". A total of 236 articles were reviewed, yielding 66 articles pertinent to the topic. Outcome measures of upper tract recurrence, overall survival, and CSS were extracted from retrospective and prospective studies.

EPIDEMIOLOGY

As previously discussed, UTUC represents a relatively rare subset of urothelial carcinoma. Bladder tumors represent 90%-95% of all UCs, while UTUCs account for only 5%-10% of all UCs, with an annual incidence in western countries of 2 new cases per 100000 people[3]. Among UTUCs, pyelocaliceal tumors are twice as common as ureteral tumors. Concurrent bladder tumors are diagnosed with UTUC in 17% of UCC patients. Bladder recurrence after UTUC is common, occurring in 22%-47% of patients, while contralateral upper tract recurrence occurs in only 2%-6%[13]. Upper tract recurrence after a primary bladder tumor is reported as rare, with an incidence of 1.7%-3.1%[14,15]. UTUCs have a peak incidence in the elderly population, between age 70 and 80, and are three times more prevalent in men than in women[16]. Hereditary UTUC exists as a component of hereditary nonpolyposis colorectal carcinoma (HNPCC) or Lynch syndrome[17].

DIAGNOSIS AND STAGING

The most common presenting symptom of UTUC, occurring in 70%-80% of cases, is either gross or microscopic hematuria[18]. Flank pain is less common, occurring in 20%-40% of cases, while presentation with a lumbar mass is even more rare, occurring 10%-20% of the time. Both of these entities likely represent advanced disease with worsened prognosis[19,20].

CT imaging with and without IV contrast has replaced IV excretory urography and ultrasound as the gold standard imaging modality with the highest accuracy for diagnosing UTUC. Its sensitivity ranges from 67%-100% and specificity from 93%-99%, depending on the technique used[18]. CT imaging cannot accurately stage UTUC, as staging relies on depth of invasion, which is difficult to determine on imaging alone. However, the presence of hydronephrosis in conjunction with known or suspected UTUC portends a worse prognosis, as it is associated with advanced stage disease[21,22]. Other imaging modalities, such as contrast enhanced MRI, are still in their infancy for diagnosis of UTUC, with a limited sensitivity of 75% for tumors < 2 cm[23].

Cytology alone is of limited utility as it is less sensitive for UTUC than for bladder tumors. If utilized, it should be performed in situ, with samples being taken directly from the collecting system or ureter *via* the ureteroscope[24]. Flexible ureteroscopy is a highly effective means of diagnosis, either through direct visualization of tumor in the ureter, renal pelvis and collecting system, or *via* ureteroscopic biopsies, which approach 90% accuracy regardless of the total volume of tissue sample

obtained[25]. As with CT imaging, accurate staging is difficult with ureteroscopy and biopsies, as the nature of the biopsy forceps makes obtaining muscle in the specimen difficult. Tumor grade is often used as a proxy for stage given that most high grade tumors are also high stage[5]. Though there are some who advocate for use of imaging findings alone for diagnosis of UTUC, this makes determining the prognosis difficult, as one is not able to determine tumor grade (and thus, by proxy, estimate stage) without tissue specimens. Our recommendation is thus to perform ureteroscopic biopsies on all patients with suspected UTUC.

TREATMENT OPTIONS

RNU

The gold standard treatment for UTUC is RNU with concomitant management of the ipsilateral intramural ureter[4]. Traditionally this was performed as an open procedure, adherent to standard oncologic principles, namely avoiding entry into the urinary tract to prevent gross spillage of tumor. With the evolution of laparoscopic and robotic surgery, minimally invasive variants of RNU have been developed. Thus far, short to mid term oncologic outcomes seem to be equivalent between laparoscopic and open techniques; however, we currently lack the follow up to prove long term oncologic equivalence between these modalities[26]. Management of the ipsilateral intramural ureter is critical for adequate recurrence free survival (RFS), as this is the area of highest recurrence. Various methods exist for excising the intramural ureter - extravesical, transvesical, and endoscopic (the "pluck" technique). All three have shown no difference in CSS and OS; endoscopic management techniques have, however, shown higher local bladder recurrence rates[27]. It is not currently standard practice to perform a retroperitoneal lymph node dissection (LND) along with RNU; a growing body of data suggest it increases median time until recurrence and improves CSS[28].

LONG TERM IMPACT OF RNU

Aside from the immediate perioperative complications of RNU, which do not differ greatly from any large oncologic resection, patients undergoing this procedure must contend with the long term impact of losing an entire renal unit. Initial studies on creatinine clearance and GFR, performed on the donor nephrectomy population, did not show a long term decrease in renal function[29-31]. However, one could argue that these donor nephrectomy patients represent a carefully selected cohort of patients that lack the risk factors for renal deterioration after major surgery. A study of patients undergoing nephrectomy for renal cell carcinoma, arguably a patient cohort more closely matched to that of the UTUC population, showed that 10% of patients had significant deterioration of their creatinine post nephrectomy[32]. A study of 131 patients undergoing nephroureterectomy showed an 18% decrease in GFR at a median of 5 year follow up[33]. Another retrospective study of 374 patients undergoing RNU showed an even higher decrease in GFR, at 32%, with no significant trend towards GFR recovery over time[34]. It would seem apparent from the data that nephroureterectomy does indeed lead to significant impairment of renal function.

Renal impairment, end stage renal disease (ESRD) in particular, accounts for a large percentage of health care spending in the elderly[35]. Cost analysis data from UTUC patients undergoing either RNU or renal sparing treatment for UTUC demonstrates a 3-fold to 10-fold cost savings of nephron sparing treatment over RNU over a 10 year period with similar oncologic outcomes[36]. Perhaps more importantly, overall survival and quality of life of patients whose renal insufficiency necessitates dialysis has been proven to be greatly diminished compared to the non dialysis dependent population[37]. Urologists have globally accepted the aforementioned arguments as strong reasons for renal preservation in the management of small renal masses - could these principles be selectively applied to UTUC?

NEPHRON SPARING TREATMENTS FOR UTUC

The rationale for conservative surgery for UTUC stems from the fact that most UTUC is superficial and low grade[38]. Thus, coupled with the aforementioned drawbacks of renal loss and decreased GFR, as well as improvements in endoscopic technology, allow for pursuit of renal sparing techniques. Currently available nephron-sparing treatments for UTUC include ureteroscopic retrograde tumor ablation, percutaneous antegrade tumor ablation, or segmental ureterectomy. As the focus of this review is endoscopic management of UTUC, segmental will not be discussed further here.

Patient selection is critical, as currently endoscopic management techniques are only advisable for low grade, small volume tumors or for patients who would otherwise not be fit to undergo RNU[7] (Figure 1). The decision between retrograde ureteroscopic tumor management and antegrade percutaneous ablation depends primarily on tumor size and location. Large tumors in the renal pelvis are best approached in a percutaneous fashion, while ureteral tumors lend themselves to a ureteroscopic approach. Small tumors in the collecting system may be approached by either fashion[12,38].

Currently no randomized controlled trials exist comparing endoscopic management techniques to the gold standard radical nephroureterectomy. Most of the published data come from small, retrospective and unmatched comparative studies. A 2014 meta-analysis of eight retrospective series, totaling 1002 patients, demonstrated no statistically significant difference in overall survival and CSS between the two modalities. The authors hesitated to conclude oncologic equivalence given the low level of the evidence[12] Additionally, patients tended to be selected for favorable tumor characteristics, such as low grade features and small tumor size. Analysis

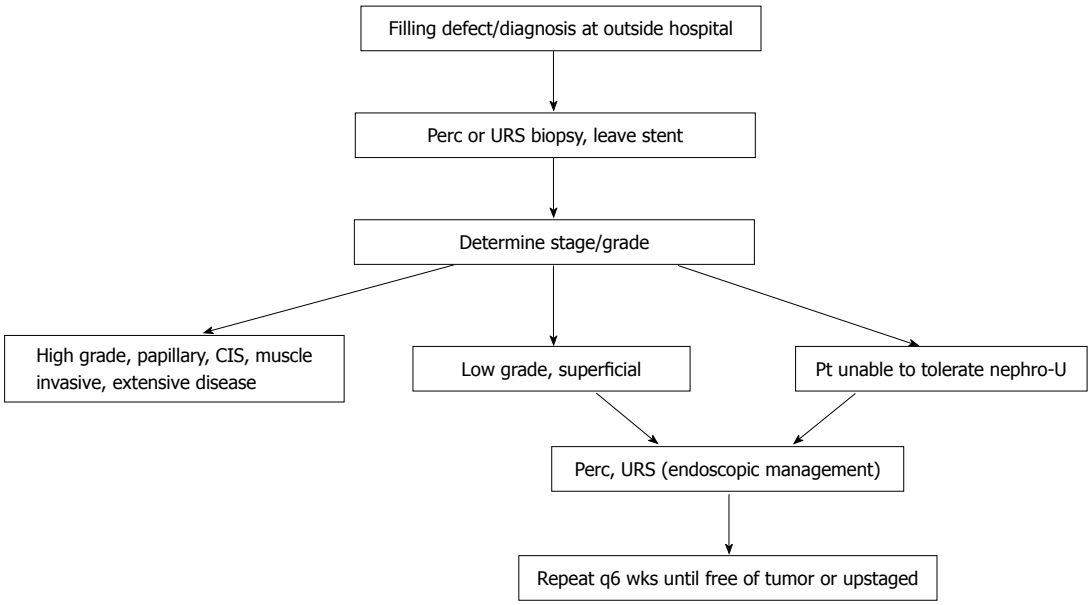

Figure 1 Sample treatment algorithm for patients with upper tract urothelial carcinoma.

of all the existing literature reveals that ureteroscopic ablation of the tumor is associated with high rates of upper urinary tract recurrence (15%-90%) and intravesical recurrence (12%-70%). Tumor grade, size and multi-focality predict upper tract recurrence while previous history of bladder cancer predicts intravesical recurrence (Table 1)[39-57]. The large variations in population size, initial tumor characteristics and length of follow up likely explain the broad range of observed outcomes.

Similarly, the only data on outcomes of percutaneous management of UTUC come from retrospective series (Table 2)[58-66]. Overall, patients managed percutaneously had similar clinical features to those managed ureterscopically - namely low grade, small focal tumors. Those undergoing percutaneous ablation had lower rates of upper tract recurrence (10%-65%) and intravesical recurrence (10%-42%) than those treated with the ureteroscopic approach. Given the high rate of comorbidities, much like in the uretoscopic population, the overall survival was poor (68%-96%) while the CSS was high (75%-100%).

DISCUSSION - BROADENED INDICATIONS FOR NEPHRON SPARING TREATMENTS?

Currently, the only "imperative" indications for systematically offering nephron sparing treatment of UTUC include anatomically or functionally solitary kidneys, substantial renal insufficiency with the impending threat of hemodyalisis or bilateral UTUC[7]. We believe that, though limited in its retrospective nature, the exisiting data indicate that the patient population to whom nephron sparing treatment is routinely offered as a first line option should be expanded.

UTUC continues to challenge urologists as a potentially devastating disease that tends to affect older, sicker patients. As this review of the literature demonstrates, patients treated with ureteroscopic or percutaneous means have a much higher CSS than OS, meaning that they eventually succumb to their comorbidities, and not their cancer. Thus, we believe that patients with significant comorbidities make excellent candidates for first line nephron sparing options. Ureteroscopic and percutaneous approaches offer similar CSS, at least according to medium term data, while avoiding the morbidity and potential of a RNU for an already unhealthy patient population.

Amongst otherwise healthy UTUC patients, we believe nephron sparing treatments should still be offered to those patients with low grade, low stage disease. Although UTUC is more often invasive at diagnosis, truly low grad and low stage disease seems to follow a similarly indolent course, with frequent recurrence but rare progression, as low grade bladder cancer[2,3,7]. Thus, as endoscopic technology and techniques improve, allowing for better ureteroscopic evaluation and biopsy, we should be better able to separate low grade from high grade disease. Patients with low grade disease have shown excellent CSS in the existing endoscopic management literature; using these treatments would allow us to spare them the morbidity of losing a renal unit.

Post-treatment surveillance is critical for achieving excellent CSS outcomes. Thus, patients considered for endoscopic management of their UTUC must be compliant. At our institution we repeat ureteroscopic or percutaneous surveillance ever 3-6 mo for 2 years and then annually; similar variations on this surveillance protocol exist throughout the literature. Additionally, CT imaging allows for detection of progression to metastatic disease and should be performed at regular time intervals.

Table 1 Outcomes of ureteroscopic management of upper tract urothelial carcinoma

Ref.	*n*	Grade on biopsy (G1/G2/G3 *vs* LG/HG)	F/U (mo)	Outcomes (%)
Schmeller *et al*[39] (1989)	16	6/10/0	14	19 UTR, 100 OS, 100 CSS
Andersen *et al*[40] (1989)	10	NA	35	NA
Gaboardi *et al*[41] (1994)	18	12/6/0	15	50 UTR, 100 OS, 100 CSS
Engelmeyer *et al*[42] (1996)	10	9/1/0	10	70 UTR, 90 OS, 100 CSS
Chen *et al*[57] (2000)	23	22LG/21HG	23	64 UTR, 12 IVR
Daneshmand *et al*[43] (2003)	30	7/6/14	31	90 UTR, 23 IVR, 77 OS, 97 CSS
Matsuoka *et al*[44] (2003)	27	10/2/0	33	26 UTR, 15 IVR
Iborra *et al*[45] (2003)	23	NA	NA	35 UTR, 96 CSS
Johnson *et al*[46] (2005)	35	35/0/0	32	68 UTR, 100 CSS
Rouprêt *et al*[47] (2006)	27	19LG/8HG	52	15 UTR, 22 IVR, 77 OS, 81 CSS
Reisinger *et al*[48] (2007)	10	10/0/0	73	50 UTR, 70 IVR, 100 OS, 100 CSS
Krambeck *et al*[49] (2007)	37	2/13/7	32	62 UTR, 37 IVR, 35 OS, 70 CSS
Painter *et al*[50] (2008)	45	NA	NA	89 CSS
Lucas *et al*[51] (2008)	39	27LG/12HG	33	46 UTR, 62 OS, 82 CSS
Pak *et al*[36] (2009)	57	NA	53	90 UTR, 93 OS, 95 CSS
Cornu *et al*[52] (2010)	35	16LG/6HG	24	60 UTR, 40 IVR, 100 OS, 100 CSS
Gadzinski *et al*[53] (2010)	34	NA	58	84 UTR, 75 OS, 100 CSS
Cutress *et al*[54] (2012)	73	34/19/6	54	69 UTR, 43 IVR, 60 OS, 90 CSS
Grasso *et al*[55] (2012)	80	66LG/14HG	38	81 UTR, 59 IVR, 74 OS, 87 CSS
Fajkovic *et al*[56] (2013)	20	14LG/3HG	20	25 UTR, 15 IVR, 45 OS, 95 CSS

G1: Grade 1; G2: Grade 2; G3: Grade 3; LG: Low grade; HG: High grade; F/U: Follow up; UTR: Upper tract recurrence; IVR: Intra-vesical recurrence; OS: Overall survival; CSS: Cancer specific survival; NA: Not available.

Table 2 Outcomes of percutaneous management of upper tract urothelial carcinoma

Ref.	*n*	Grade on biopsy (G1/G2/G3 *vs* LG/HG)	F/U (mo)	Outcomes (%)
Tasca *et al*[58] (1992)	10	1/5/0	19	50 UTR, 90 OS, 100 CSS
Fuglsig *et al*[59] (1995)	26	NA	21	31 UTR, 96 OS, 100 CSS
Plancke *et al*[60] (1995)	10	6/3/11	28	10 UTR, 10 IVR, 90 OS, 100 CSS
Patel *et al*[61] (1996)	26	11/11/1	45	35 UTR, 42 IVR, 75 OS, 91 CSS
Clark *et al*[62] (1999)	17	6/7/4	24	33 UTR, 75 OS, 82 CSS
Goel *et al*[63] (2003)	20	15LG/5HG	64	65 UTR, 15 IVR, 75 CSS
Palou *et al*[66] (2004)	34	7/21/5	51	44 UTR, 74 OS, 94 CSS
Rouprêt *et al*[64] (2007)	24	17LG/7HG	62	13 UTR, 17 IVR, 79 OS, 83 CSS
Rastinehead *et al*[65] (2009)	89	50LG/39HG	61	33 UTR, 68 OS
Fiuk (current study)	65	34LG/33HG	28	55 OS, 87 CSS

G1: Grade 1; G2: Grade 2; G3: Grade 3; LG: Low grade; HG: High grade; F/U: Follow up; UTR: Upper tract recurrence; IVR: Intra-vesical recurrence; OS: Overall survival; CSS: Cancer specific survival; NA: Not available.

Urinary cytology is not as useful in UTUC and thus is left to the surgeon's discretion.

We thus propose that nephron sparing treatment of UTUC, either ureteroscopic or percutaneous, be offered as a first line therapy to the following patient populations: (1) any patient with an anatomically or functionally solitary kidney; (2) any patient with renal insufficiency great enough to impose the threat of hemodyalisis with any further renal insult; (3) any patient with multiple bilateral UTUC tumors; (4) any patient with comorbidities great enough to be life limiting or to incur additional risk with nephroureterectomy; and (5) any patient with low grade, low stage disease who can be trusted to commit to 3-6 mo surveillance.

By using a risk-adapted strategy for expanding current indications for first line endoscopic treatment of UTUC, we hope to minimize renal unit loss without compromising oncologic safety. Development of improved biopsy techniques, urothelial cancer biomarkers, and improved prediction nomograms may help further delineate these indications in the future.

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