



# Future strategies to enhance kidney preservation in upper urinary tract urothelial carcinoma

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**Abstract:** Though radical nephroureterectomy remains the gold standard treatment for high grade or invasive disease in upper tract urothelial cancer (UTUC), kidney-sparing surgery has become preferred for low risk disease, in order to minimize morbidity and preserve renal function. Many methods exist for endoscopic management, whether via an antegrade percutaneous or retrograde ureteroscopic approach, including electroresection, laser ablation, and fulguration. There has been an increase in use of adjuvant intracavitary therapy, predominantly using mitomycin and bacillus Calmette-Guerin (BCG), to reduce recurrence after primary endoscopic management for noninvasive tumors, although efficacy remains questionable. Intraluminal BCG has additionally been used for primary treatment of CIS in the upper tract, with around 50% success. Newer investigations include use of narrow band imaging or photodynamic diagnosis with ureteroscopy to improve visualization during diagnosis and treatment. Genomic characterization may improve selection for kidney-sparing surgery as well as identify actionable mutations for systemic therapy. The evolution in adjuvant management has seen strategies to increase the dwell time and the urothelial contact of intraluminal agents. Lastly, chemoablation using a hydrogel for sustained effect of mitomycin is under investigation with promising early results. Continued expansion of the armamentarium available and better identification and characterization of tumors ideal for organ-sparing treatment will further improve kidney preservation in UTUC.

**Keywords:** Upper tract urothelial carcinoma (UTUC); kidney-sparing; organ preservation

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Upper tract urothelial cancer (UTUC) accounts for 5% to 10% of all urothelial carcinoma (1,2). First described in 1934 (3), radical nephroureterectomy has long been the gold standard treatment for any upper urinary tract tumor (4). The original utilization of kidney-sparing approaches, in lieu of nephroureterectomy, was targeted to highly selected patients with imperative indications such as sparse renal reserve (solitary kidney or severe baseline renal impairment), bilateral disease, or coexistent morbidity precluding radical extirpative surgery. Over time, particularly with improvement of endoscopic techniques

for both diagnosis and management, organ-sparing has been applied more broadly. Kidney-sparing is now the recommended approach in low risk cancers and in those with isolated distal ureteral tumors, as well as in patients with severe renal insufficiency or a solitary kidney on a case-by-case basis (5).

## Current approach to kidney preservation

The goal of organ-sparing treatment is to avoid the morbidity of a radical operation while maintaining

equivalent oncologic outcomes. The need for development of therapies for organ-preservation for UTUC has been recognized for 30 years (6). The rates of minor and major complications after nephroureterectomy may be as high as 40% and 29%, respectively (7,8), and are similar among open, laparoscopic, and robotic approaches (9). A population-based sample found the 90-day mortality to be 4.4% (10). Kidney preservation in upper tract cancer is also desirable due to unique concerns of nephroureterectomy, such as the risk for severe renal insufficiency and subsequent cardiovascular events (11). A retrospective review by Kaag *et al.* showed a mean decline in estimated glomerular filtration rate (eGFR) of 24% after nephroureterectomy, with over half of patients with a baseline eGFR above 60 mL/min falling below 60 mL/min postoperatively (12). Similarly, Raman *et al.* found that around one quarter of all patients experienced a decline in eGFR below 60 mL/min, with around 15% falling below 45 mL/min after nephroureterectomy. As expected, renal functional outcomes have been shown to be superior with kidney-sparing approaches (13). This complication of renal functional decline is compounded by the morbidity related to CKD, with an overall mortality almost three times that of the population without CKD and over 50% rate of hospitalization per patient-year (14).

Several reports have now shown that in addition to avoiding the complications of nephroureterectomy, initial endoscopic management has comparable oncologic outcomes to nephroureterectomy in carefully selected patients, particularly for low grade disease (15). Endoscopic management of UTUC was initially utilized for imperative indications, such as solitary kidney, bilateral disease, or coexistent morbidity prohibiting nephroureterectomy (16). Over time, coupled with improved diagnostic techniques that more reliably distinguish low grade disease, endoscopic management has been applied more broadly (17,18). Current recommendations for first line treatment of low risk disease, defined as unifocal tumors <1 cm in size with low grade cytology and biopsy and no invasive aspect on CT, are for organ-sparing approaches such as endoscopic ablation, which can be performed retrograde ureteroscopically or antegrade percutaneously (5). However, series of patients managed endoscopically showed high recurrence rates (19-21) and rates of salvage nephroureterectomy ranging from 16.7% in low grade disease to 28.6% in high grade (22).

Due to high recurrence rates, endoscopic management evolved to include adjuvant treatment, as intraluminal therapies for non-muscle invasive bladder cancer were

extrapolated to the upper urinary tract. Most reports are from small case series, with the majority using bacillus Calmette-Guerin (BCG) and mitomycin, although epirubicin (23,24), adriamycin (25), thiotepa (26-28), and BCG with interferon (29,30) have also been reported. Instillation has been attempted retrograde via vesicoureteral reflux (31), via double-J stents with the patient in Trendelenburg (32), and via an open-ended ureteral catheter (27), as well as antegrade via a nephrostomy tube (23). Intracavitary therapy has been utilized as adjuvant therapy after endoscopic resection or ablation of papillary disease (*Table 1*) as well as for primary treatment of carcinoma in situ (CIS) in the upper urinary tract (*Table 2*).

Mitomycin has been used as adjuvant therapy postoperatively after endoscopic management. Over the years, endoscopic techniques have included ureteroscopic laser ablation or fulguration and percutaneous resection (with or without fulguration or laser ablation). For example, a retrospective review of 19 patients (20 renal units) treated with adjuvant postoperative mitomycin after laser ablation of ureteral or renal pelvic tumors found a cancer-free survival of 65% (recurrence rate 35%), and 85% remained disease-free without nephroureterectomy at last follow up with stable renal function in all patients (42). Regimens vary slightly for upper tract instillation of mitomycin, with doses of 40 mg being dissolved in 30, 40, or 1,000 mL of saline or 5 mg in 20 mL saline. Ureteral integrity may be verified by a retrograde pyelogram or antegrade nephrostogram prior to instillation; other authors have waited until gross hematuria resolves, usually 1-3 days postoperatively. The solution is infused slowly, with reported rates of 1 mL/min. For instillation via a ureteral catheter, the catheter can be clamped after administration for around 30 minutes prior to gravity drainage.

Additionally, adjuvant therapy with mitomycin has been evaluated utilizing an induction and maintenance course, the largest series to date of adjuvant mitomycin and the only one with more than 20 patients (21). In this series, 28 renal units were treated (75% of which had low grade UTUC), using 40 mg in 20 mL saline instilled either via ureteral catheter or via nephrostomy tube over two hours. Six weekly instillations were performed for induction, with maintenance done either once monthly for at least three months or three weekly instillations following the Southwest Oncology Group BCG protocol (52), with 61% completing the first maintenance course, 36% completing the second, 18% completing up to the fifth, and 7% completing a sixth maintenance course. The recurrence

**Table 1** Adjuvant therapy

Author, year	Agent	Approach	# pts	No. of renal units	Mean follow up (months)	Recurrence or progression (%)
De Kock and Breytenbach 1986 (27)	Thiotepa <sup>†</sup>	Retrograde ureteral catheter	1	1	78	0
Orihuela 1988 (23)	BCG/MMC	Antegrade nephrostomy	6/1	6/1	20/22	17/100
Schoenberg 1991 (32)	BCG, BCG+MMC	Antegrade Nephrostomy or Retrograde Ureteral Catheter, JJ stent, or VUR	9	9	24	22
Eastham 1993 (33)	MMC	Antegrade nephrostomy or retrograde ureteral catheter	7	7	7.4 <sup>††</sup>	29
Vasavada 1995 (34)	BCG	Antegrade nephrostomy	8	8	21	13
Martinez- Pineiro 1996 (28)	MMC/BCG/thiotepa/IFN	Ret ureteral catheter or JJ stent or antegrade nephrostomy; retrograde ureteral catheter or antegrade nephrostomy/antegrade nephrostomy or retrograde ureteral catheter or reflux	29/14/8/5/1	29/14/8/5/1	31	14/13/60/0
Keeley 1997 (35)	MMC <sup>‡</sup>	Retrograde ureteral catheter	19	21	30	62
Patel And Fuchs 1998 (36)	BCG/MMC	Retrograde JJ or single J stent externalized via suprapubic cystostomy	12/1	16/1	15/3	13/0
Clark 1999 (37)	BCG	Antegrade nephrostomy	17	18	21	33
Thalmann 2002 (38)	BCG	Antegrade nephrostomy	15	16	42 <sup>§</sup>	75
Palou 2004 (39)	BCG/MMC	Antegrade Nephrostomy or Retrograde Ureteral Catheter or JJ stent	14/5	NR/NR	51	58
Katz 2007 (29)	BCG+IFN <sup>†</sup>	Retrograde ureteral catheter	7	8	35	13
Rastinehad 2009 (40)	BCG	Antegrade nephrostomy	NR	50	61	36
Giannarini 2011 (41)	BCG	Antegrade nephrostomy	NR	22	41 <sup>§</sup>	59
Aboumarzouk 2013 (42)	MMC	Retrograde ureteral catheter	19	20	24	35
Metcalfe 2017 (21)	MMC <sup>†</sup>	Retrograde Ureteral Catheter or Antegrade Nephrostomy	27	28	19 <sup>§</sup>	39

Recurrence or progression rate includes those with recurrent upper urinary tract disease after treatment, including recurrence of a tumor of higher grade and/or stage when this information was available; it does not include those with bladder recurrence or progression to metastatic disease. Follow up and recurrence or progression rate are per renal unit. <sup>†</sup>, included maintenance; <sup>††</sup>, in those with no evidence of disease; <sup>‡</sup>, 13 had gross residual disease and were thus treated with primary intent; <sup>§</sup>, median. BCG, bacillus Calmette-Guerin; MMC, mitomycin C; IFN, interferon-alpha2B.

**Table 2** BCG as primary therapy for cis

Reference	Approach	Duration (weeks)	# pt	# renal units	Mean F/U (months)	Failure rate (%)
Studer 1989 (6)	Antegrade nephrostomy	6	8	10	18–28	20
Sharpe 1993 (43)	Retrograde ureteral catheter	6	11	17	37	12
Yokogi 1996 (44)	Retrograde ureteral catheter or antegrade nephrostomy	6	5	8	24 <sup>††</sup>	38
Martinez-Pineiro 1996 (28)	Antegrade nephrostomy or retrograde ureteral catheter or reflux	6	1	2	31	0
Nishino 2000 (45)	Retrograde JJ stent or ureteral catheter	8	6	8	22	0
Nonomura 2000 (46)	Retrograde JJ stent	6	11	11	20 <sup>††</sup>	36
Okubo 2001 (47)	Retrograde ureteral catheter or antegrade nephrostomy	6	11	14	50	57
Irie 2002 (48)	Retrograde JJ stent	6	9	13	36 <sup>§</sup>	8
Miyake 2002 (49)	Antegrade nephrostomy or retrograde JJ or single J stent	6	16	16	30	19
Thalmann 2002 (38)	Antegrade nephrostomy	6	22	25	50 <sup>§</sup>	52
Hayashida 2004 (50)	Antegrade nephrostomy or retrograde ureteral catheter or J stent	6	10	11	51	27
Kojima 2006 (51)	Retrograde JJ stent	8	11	13	51	38
Katz <sup>¶</sup> 2007 (29)	Retrograde ureteral catheter	6 <sup>†</sup>	3	3	24	33
Giannarini 2011 (41)	Antegrade nephrostomy	6	NR	42	41 <sup>§</sup>	40
Shapiro <sup>¶</sup> 2012 (30)	Retrograde ureteral catheter	6 <sup>†</sup>	11	11	14 <sup>§</sup>	18

Failure rate includes those with persistent disease and those with upper urinary tract recurrence or progression after treatment. Follow up and failure rate are per renal unit. <sup>†</sup>, included maintenance; <sup>††</sup>, in those with no evidence of disease; <sup>§</sup>, median; <sup>¶</sup>, bacillus Calmette-Guérin (BCG) + interferon-alpha2B (IFN).

rate was 39% at a median follow up of 19 months. The 3-year progression-free survival rate was 80%, with 18% of patients ultimately undergoing nephroureterectomy.

The first use of upper tract instillation of BCG for the cure of upper tract CIS was by Studer *et al.* in 1989 (6), after a report by Herr of intravesical BCG in a patient after resection and reconstruction of a pelvic kidney with pyelovesical anastomosis for persistent CIS of the renal pelvis in 1985 (53). Six patients with a history of urothelial cancer and unfit or unwilling to undergo major surgery who had positive cytology with negative bladder and prostatic urethral biopsies were treated with BCG perfusions as a course of 6 weekly instillations via nephrostomy tube, where the BCG was dripped in by gravity at approximately 1 mL/min. In four patients, cytology converted to negative and remained as such for 18–28 months; in one patient with bilateral disease, cytology converted to negative after several courses of BCG and remained so at 18 months;

in one a papillary tumor persisted but CIS disappeared. Since that time, several series have reported outcomes with antegrade or retrograde instillation of BCG for cure of CIS (*Table 2*). As with mitomycin, various protocols have been described. Generally, the solution is administered slowly, usually no more than 1 mL/min, and all but two series used six weekly instillations, similar to its use for bladder cancer. Various doses, in volumes ranging from 40 to 250 mL, have been used. The initial positive response rates ranged from 63–100% with upper tract recurrence in up to half.

Adjuvant BCG has also been utilized after endoscopic treatment of papillary disease. Several small series have reported recurrence rates from 13% up to 75% (*Table 1*). In a review of patients treated with BCG for either cure of CIS or as adjuvant therapy after endoscopic treatment of Ta/T1 tumors, there was a 59% recurrence rate and 41% progression rate in patients with Ta/T1 tumors, with 23% going on to nephroureterectomy, which was worse than

those treated with curative intent for CIS (41). While about half of renal units with CIS may be cured by BCG, there is no definitive evidence for the efficacy of adjuvant topical chemotherapy or immunotherapy after endoscopic ablation of T1/Ta tumors (40,41,54,55).

Several challenges remain in attempts to translate the success of intravesical immunotherapy and chemotherapy in NMIBC to UTUC. Endoscopic resection or ablation may be incomplete, resulting in adjuvant therapies treating more residual disease. Accurate identification and staging remain elusive. Lastly, achieving adequate dwell time in the upper urinary tract is a problem for intraluminal therapy. Additional techniques continue to be developed to address challenges in nephron-sparing for upper tract urothelial carcinoma.

### Future strategies

There are several diagnostic difficulties with upper tract neoplasms. Endoscopic localization of the tumor may be difficult, and there may be no readily visible lesion with CIS. The varying diagnostic criteria for CIS used in the literature reflects this diagnostic difficulty (56). Narrow band imaging (NBI) may improve patient selection for nephron-sparing approaches by enhancing imaging at diagnosis. It may also benefit endoscopic treatment by defining the borders of lesions or helping identify additional tumors. In a review of 27 patients who underwent standard white light as well as NBI flexible ureteroscopy, NBI provided additional information in 38.4% of patients by allowing detection of additional tumors or recognition of the lesion's borders (57).

Photodynamic diagnosis (PDD) has also been used to improve visualization of lesions in the upper urinary tract with oral administration of 5-Aminolevulinic Acid prior to ureteroscopy (58). In one review of 26 biopsies performed for suspicious upper tract lesions, 38.5% of biopsies were taken from lesions seen only under blue light, and 70% of these were malignant (59). A similar review of ureteroscopy of 106 renal units found that PDD detected significantly more CIS and dysplasia than white light and also had higher sensitivity (60).

When tumors are visualized, grade is commonly used as a surrogate for stage to determine which patients should get nephroureterectomy due to difficulty with determining stage via biopsy.

However, the biologic basis for upper tract CIS and papillary tumors as well as their distinction from bladder cancer continue to be investigated and may provide more

guidance than biopsy or cytology alone on which tumors are most appropriate for kidney-sparing approaches. Complete genomic characterization of UTUC has begun (61-63). Some biologic distinctions from bladder cancer have been detailed, such as more common microsatellite instability in UTUC (61,64) and more common and more extensive promoter hypermethylation (65). Although a similar array of genes was mutated in one analysis of 59 high grade upper tract tumors and 102 bladder tumors, the prevalence of mutations was different (61). This finding was corroborated in a separate analysis of 195 upper tract and 454 bladder cancer samples. Specifically, there was a higher rate of FGFR3- and HRAS-altered high grade tumors in the upper tract compared to bladder, possibly consistent with a model in which low grade tumors more frequently progress to high grade invasive disease when they arise in the upper tract (61). It may also be that UTUC fits predominantly within the "luminal" subtype identified in bladder cancer (66), which shows a similar FGFR3 mutation frequency (67).

Further work has been done using whole exome sequencing and gene expression profiling to characterize and group UTUC into expression-based subtypes, similar to work that has been done in bladder cancer (62). In this analysis based on 31 tumors there was an even higher rate of FGFR3 mutations (74% compared to 36% in the prior study), which also was present in 60% of high grade tumors. Genes related to DNA damage repair and chromatin-modification appear to play a critical role for UTUC based on whole exome sequencing. Also in this analysis, samples segregated into four subtypes that were correlated with clinical variables such as grade, stage, and recurrence, with some clusters having no bladder recurrence.

In the largest genomic study of UTUC to date, over half of the tumors in the cohort of 195 patients had potentially actionable genomic alterations (63). By comparing UTUC specimens to subsequent bladder tumors in the same patient in a subgroup of 29 patients, it was determined that bladder recurrences were clonally related to upper tract disease. Additionally, alterations in FGFR3, KDM6A, CCND1, and TP53 increased the risk of recurrence in the bladder.

As the above-mentioned studies indicate, there has been a great deal of recent genomics and genetics work for UTUC. However, genomic analyses in these cases were from samples from radical nephroureterectomy. To translate this developing knowledge into potential organ-sparing therapy, testing would need to be performed on specimens prior to extirpative surgery. In an effort to determine the feasibility of next-generation sequencing on ureteroscopic

specimens, Bagrodia *et al.* obtained biopsies of upper tract tumors via ureteroscopic techniques then extracted and sequenced tumor DNA (68). In their evaluation, 92% had adequate material for sequencing. The molecular landscape was similar to a cohort previously analyzed by the authors as well as to other reports. The biopsies were then compared to nephroureterectomy specimens from the same patient in twelve cases. For the patients not receiving neoadjuvant chemotherapy, 71% of all mutations and 92% of likely pathogenic mutations were present in both specimens, with 100% concordance in 40%. The concordance was lower for patients receiving neoadjuvant chemotherapy (53% of all and 62% of likely pathogenic). However, 82% of the likely oncogenic mutations in the nephroureterectomy specimens were found in the prior biopsies. In the future, urinary cell-free DNA may also be able to provide similar information. While these findings are not yet diagnostic or actionable, the field is evolving perhaps to be able to use these findings to promote kidney-sparing approaches to UTUC.

Another evolving facet in the management of UTUC is in the approach taken towards intraluminal therapy. The adequacy of simple instillation of mitomycin has been in question since early feasibility studies in the upper tract (33,35), because exposure time to urothelium is critically important for efficacy with mitomycin (69,70). Urine production and ureteral peristalsis may both contribute to diminished efficacy in the upper urinary tract by reducing dwell time. One approach to prolong drug retention in the upper tract is sustained release of chemotherapy using drug-eluting stents. Barros *et al* combined hydrogel technology with ureteral stents in the development of a biodegradable drug-eluting stent (71). Biodegradable ureteral stents were prepared and then impregnated with chemotherapeutics (paclitaxel, epirubicin, doxorubicin, and gemcitabine). In an *in vitro* artificial acidic urine solution with sink conditions, almost 50% of the drug was released by four hours; there was then sustained release of the remaining drug until around 72 hours, and the stent degraded after 9 days. The impregnated stent also showed *in vitro* potency in urothelial cancer lines, with the amount of drug released higher than the half maximal inhibitory concentration (IC<sub>50</sub>, a measure of the concentration needed to inhibit cell survival) of the cancer cells but lower than that of control cells. The viability of cancer cells decreased around 50% after 72 hours in contact with drug-loaded stents, and killing efficacy of the impregnated stent was confirmed with microscopy.

Bilayer swellable drug-eluting stents have also been

developed to try to take advantage of sustained delivery as well as improve apposition with the urothelium (72). In this design, a drug-impregnated hydrogel swells with contact with urine to augment contact with the urothelium, minimizing wash out from urine flow; this also increases transfer through the impermeable urothelium. The stents were loaded with mitomycin for evaluation of *in vitro*, *ex vivo*, and *in vivo* drug release and transfer using a porcine model, with increased drug release over seven days and increased drug transfer to the explanted porcine ureter with use of the hydrogel. The release of mitomycin was also found to be modifiable based on parameters of the saturated amount of drug and thickness of the polymer coating of the stent. A decrease in human bladder stroma fibroblast cell growth in the presence of hydrogel eluted mitomycin culture medium was also shown. Lastly, the prototype was evaluated *in vivo* in a porcine model that showed good apposition of the hydrogel to the ureter and mitomycin in the targeted portion of the ureter.

UGN101 (MITOGEL™) likewise seeks to overcome the obstacles of upper tract instillation as well as the difficulty of complete endoscopic ablation. This investigational hydrogel formulation of mitomycin is liquid when injected in retrograde fashion into the upper urinary tract, becomes a gel, and slowly dissolves with urine, resulting in sustained release of the drug to the urothelium. It is being investigated, however, as primary chemoablation for tumors *in situ*, rather than adjuvant therapy once the tumor has been resected. The first use of mitomycin for the chemoablation of UTUC was reported by Smith *et al.* in 1987 in the treatment of upper tract recurrence in two patients with a history of low grade bladder cancer was (73). Both had low grade noninvasive bladder cancer overlying a ureteral orifice, with recurrence in the ipsilateral ureter. Vesicoureteral reflux was confirmed with a cystogram, and intravesical mitomycin was used to treat the ureteral tumors, with complete resolution of the tumors confirmed with biopsy and no upper tract recurrence at two years. Now a clinical trial evaluating the effectiveness of 6 weekly instillations of UGN101 for patients with biopsy proven unilateral low grade UTUC has completed enrollment (NCT02793128). In the initial interim analysis (74), 57% of patients in the intention to treat cohort had a complete response, defined as negative ureteroscopic evaluation and negative wash cytology at approximately 5 weeks after the instillation. For patients with a complete response, treatment is continued with once monthly maintenance instillations for up to eleven months. Subsequent topline

data showed all evaluated patients with a complete response remained disease-free at six months. While long-term durability has yet to be reported, the short-term results are promising as a potentially new therapeutic option for low grade UTUC.

## Conclusions

As more insight has been gained into risk classification for UTUC, applicability of kidney-sparing treatment has expanded. Moving forward, continued expansion of the armamentarium available and better identification and characterization of tumors ideal for organ-sparing treatment will further improve kidney preservation in UTUC.

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