

# Surgical management of upper tract urothelial carcinoma

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## ABSTRACT

Upper tract urothelial cell carcinoma accounts for 5% of all urothelial tumors. Compared to lower urinary tract tumors, upper tract urothelial carcinoma is diagnosed more frequently at advanced stages. Open radical nephroureterectomy remains the gold standard treatment option for upper tract tumors. However, with the advancement of minimally invasive techniques and the benefits of these procedures regarding perioperative morbidity, cosmesis, and earlier convalescence, these options have shown promise in managing the patients with upper tract urothelial carcinoma. Despite the perioperative advantages, concerns exist on the oncological safety after minimally invasive surgery. In this article, we provide a comprehensive overview of the surgical management of upper tract urothelial carcinoma.

**Key words:** Upper tract urothelial cell carcinoma, ureteroscopy, endoscopic surgery, ureteropyeloscopy

## INTRODUCTION

In contrast with lower tract urothelial carcinoma, upper tract urothelial cell carcinoma (UTUCC) presents a different set of challenges for the genitourinary surgeon. Critical issues relating to the upper urinary tract include assessment of grade and stage of disease, which at times even after imaging and endoscopy, may be less than certain. Although a number of studies demonstrate that grade of upper tract urothelial tumor can often be assessed, proper or complete staging generally remains a challenge.<sup>[1-4]</sup> This uncertainty is largely based on the nature of resection of upper urinary tract tumor, which is most often performed in a retrograde fashion through the use of small-caliber endoscopes and even smaller caliber devices for resection. The procedure must also be performed with the consideration of risk of perforation through the relatively thin wall of the ureter and the risk of hemorrhage that may

result from resection of tumor associated with underlying renal parenchyma. When indicated imaging should also be performed for the evaluation of potential metastatic tumor. As such, radical nephroureterectomy, performed in both laparoscopic and open fashion, is considered the best approach in cases where high-grade tumor or large tumor volume precluding endoscopic resection are suspected or known to be present.<sup>[5-7]</sup> Nonetheless, though nephroureterectomy is often the best option for the patient in such circumstances, the impact of this procedure on renal function and overall patient health must carefully be considered.<sup>[8]</sup>

Another challenge relating to upper urinary tract tumor relates to the often multifocal nature of urothelial carcinoma and the overall impact on renal function associated with nephroureterectomy. In select cases involving isolated distal ureteral tumor, distal ureterectomy with ureterovesical anastomosis may be performed.<sup>[9]</sup> However, careful patient selection is imperative. Cases of solitary kidney, chronic renal insufficiency, or bilateral tumors are generally indications for segmental resection of the ureter. Additionally, patients with a normal contralateral kidney, with unifocal tumor <2 cm with no evidence of invasion, have also been subjected to segmental resection.<sup>[8]</sup> The presence of a solitary kidney or otherwise limited renal function may also give impetus for the selection of a variety of nephron-sparing options such as retrograde endoscopic resection, percutaneous antegrade resection, aforementioned distal ureterectomy, and other forms of segmental upper urinary tract resection with more complex upper urinary tract reconstruction such as ileal interposition.

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Herein is a review of potential surgical approaches for patients with UTUCC. Indications for these procedures for any specific patient vary and often depend on the overall health status of the patient, overall renal function, number of renal units present, individual patient anatomy, previous surgical procedures (possibly for urothelial tumor), presence of lymphadenopathy/metastases, and specific location of tumor. All patients need to be thoroughly counseled regarding the risks and benefits of all these procedures. Patients with limited renal function or severe medical comorbidity must also be informed that nephron-sparing procedures performed for control of tumor are limited by their nature of focal resection and may not always result in adequate local control of tumor.

### RETROGRADE URETEROPYELOSCOPY

Retrograde ureteropyeloscopy is commonly performed whenever UTUCC is suspected. This procedure may also possibly serve as a treatment modality<sup>[10,11]</sup> but has certain limitations. This is due to the small caliber of the ureter, intrarenal anatomy, the limited manoeuvrability of the ureteropyeloscope, and the equipment available for biopsy and resection.

Upper tract endoscopy for evaluation of urothelial tumor is generally initiated with a thorough inspection of the urethra and bladder for evaluation of any concomitant lower urinary tract tumor. Washings for cytological analysis may also be taken at this time. The portion of the upper urinary tract in question is cannulated with a ureteral catheter (preferably with a side-hole catheter), at which point ureteropelvic washings and ureteropyelography is performed. In patients with suspected UTUCC, the sensitivity and accuracy of urine cytology as a whole has been reported to be 29% and 59%, respectively.<sup>[12]</sup> Lodde *et al.* compared the clinical performance of urine cytology and immunocytochemical tests in patients with suspected UTUCC. They reported that urine cytology had low sensitivity in detecting low-grade UTUCC. Sensitivity increases in the detection of high-grade tumors. Urine cytology combined with immunocytochemical tests demonstrated higher sensitivity in the diagnosis of both low- and high-grade UTUCC.<sup>[13]</sup> Additionally, staining for uroplakin, the Fibrin Degradation Product Test (AuraTek FDP, PerImmune Inc., Rockville, MD, UDS) and the Bladder Tumor Antigen test (BTA, Bard UK, Ltd., UK), when combined with urine cytology, have shown to have a better diagnostic yield in patients with suspected UTUCC.<sup>[13]</sup> Currently, there is a continually growing availability of a variety of noninvasive tests for the detection of urothelial carcinoma.

Tumor grade is of considerable importance as it may influence ultimate treatment options. Although visualization of tumor often establishes the diagnosis, biopsy is often of value in determining whether high- or low-grade tumor

is present. Although sampling error is a possibility, tumor grade can generally be determined in the majority of cases where adequate tissue is available for histopathological examination.<sup>[11]</sup> Low-grade tumor, if feasible, may be resected in entirety, with preservation of the renal unit. If tumor is limited to the distal ureter, a rigid ureteroscope may be used, possibly in combination with a ureteral resectoscope, if such equipment is available. Biopsy is most commonly performed with the use of small-caliber biopsy forceps or baskets of flatwire design. Acquisition of adequate tissue volume for histopathological diagnosis may require multiple passes of the ureteropyeloscope, which may be relatively more cumbersome in cases of more proximal tumor where flexible ureteropyeloscopes are generally necessary. Ureteral access sheaths have been employed to ameliorate this problem.<sup>[16]</sup> Ureteral access sheaths can be deployed after the entire upper tract has been assessed and locations of all tumors are known. Ureteral access sheaths may also prove to be advantageous with the introduction of larger ureteroscopic biopsy forceps that are assembled distally after the proximal portion of the apparatus has been introduced through the ureteropyeloscope. The entire assemblage is then passed through the ureteral access sheath for biopsy.<sup>[10]</sup> Tumor ablation and hemostasis are commonly performed by means of electrocautery, neodymium, or holmium:YAG laser.<sup>[11,17]</sup> Neodymium:YAG laser penetrates tissues to a depth of 5–6 mm, and has been used in the treatment of both upper tract and bladder tumors. However, the holmium:YAG laser penetrates to a depth of 0.5 mm, and as such is predominantly used to treat ureteral tumors.<sup>[18]</sup> Use of electrocautery in the ureter, due to its small caliber, should generally be avoided or used with caution and at low power setting, in order to avoid development of ureteral stricture. A ureteral stent is commonly placed upon completion of procedures involving biopsy, resection, and ablation.

Ureterorenoscopy is also performed for surveillance of patients treated for UTUCC with preserved renal units. With the availability of small-caliber ureteropyeloscopes, this procedure can be performed with relatively low impact on the patient in an outpatient or even an office setting.<sup>[19]</sup> Washings can be obtained, ureteropyelography can be performed, if imaging is available, and if no tumor is seen, there is generally no need for the placement of a ureteral stent after the procedure. Table 1 summarizes reported results of ureteroscopic management of UTUCC.

As is the case for lower urinary tract tumor, endoscopy with preoperative administration of agents that may enhance abnormal urothelial tissue may also be employed. Studies have commonly used administration of 5-aminolevulinic acid as a reliable tool to assess tumor presence and surgical margins during laparoscopic nephron-sparing surgery.<sup>[20]</sup> Additionally, Herr *et al.* reported that narrow-band light cystoscopy improved the detection of recurrent non-muscle-invasive bladder tumors over standard white-light

**Table 1: Ureteroscopic management of upper tract urothelial cell carcinoma**

Author	N	Follow-up (months)	Patient characteristics	Disease-free survival	Recurrence rate (%)
Gadzinski <i>et al.</i> <sup>[15]</sup>	34	57.7	Low-grade TCC	100% 5-year survival	71
Sowter <i>et al.</i> <sup>[14]</sup>	40	41.6	23 low grade, 12 high grade*	80% 5-year survival	74.30
Cornu <i>et al.</i> <sup>[10]</sup>	35	30	16 low grade, 6 high grade*	100% 3-year survival	60
Painter <i>et al.</i> <sup>[15]</sup>	45	24	19 low grade, 26 high grade	65% 2-year survival	62

\*Tumor grade was unavailable for remaining patients.

**Table 2: Percutaneous management of upper tract urothelial carcinoma**

Author	N	Patient characteristics	Mean follow-up (months)	Disease free survival
Goel <i>et al.</i> <sup>[22]</sup>	24	22 Malignant, 2 benign. Grade 3: 5, Grade 1-2: 15. SCC-2	64	Grade 1-2: 60% Grade 3: 20%
Palou <i>et al.</i> <sup>[23]</sup>	34	Grade 1: 7, grade 2: 21, grade 3: 5	51	73.50%
Rouper <i>et al.</i> <sup>[24]</sup>	24	Low grade: 17, high grade: 7	62	75%

cystoscopy.<sup>[21]</sup> To date, there is limited experience and data relating to the use of these techniques for the upper urinary tract; nonetheless, initial results with lower urinary tract suggest that these techniques may hold promise for future use.

## PERCUTANEOUS ANTEGRADE ENDOSCOPY

Although performed less commonly, this endoscopic approach may be employed in cases where a retrograde approach is not feasible due to previous surgery or reconstruction, tumor location, or tumor volume. The percutaneous antegrade approach allows for larger endoscopes to be placed within the upper urinary tract with concomitant use of larger ancillary equipment for tumor resection. In addition to biopsy forceps and baskets, resectoscopes used for the resection of bladder tumor have been used.<sup>[18]</sup> In such cases, resection of tumor must be performed with great caution due to the presence of underlying renal parenchyma. Deep resection may result in significant hemorrhage. Both the Holmium:YAG laser and electrocautery have been used for further tumor ablation and hemostasis.<sup>[18]</sup> A nephrostomy tube is generally placed upon conclusion of the procedure.

Reviews of series of patients treated with antegrade percutaneous resection reveal that this procedure can be performed with reasonable safety and good long-term outcomes for low-grade UTUCC<sup>[22-24]</sup> [Table 2], but nonetheless is also associated with certain risks, namely recurrence, hemorrhage, and seeding of the percutaneous tract. The issue of tumor seeding associated with this procedure is well recognized; however, its overall risk appears to not be very high, and this phenomenon appears to occur in cases of high-grade tumors.<sup>[25]</sup> Use of sheaths may aid in decreasing intrarenal pressure and may mitigate against tumor seeding. Additionally, immediate irrigation of the collecting system and percutaneous tract with 5-fluorouracil or inserting radioactive iridium wires into the percutaneous

tract to deliver prophylactic radiation (4500 cGy) has shown promise in preventing tumor seeding.<sup>[25]</sup> However, only limited data exist as to the efficacy of these measures.

## DISTAL URETERECTOMY

Although performed relatively infrequently, this nephron-sparing surgical option may suit select patients well. This procedure has typically been performed in open fashion and requires that the surgeons have certainty regarding the anatomic location of the tumor(s). Preprocedural ureteroscopy and retrograde pyelogram may be of benefit in the identification of the exact location of the upper tract tumor(s) in question.<sup>[26]</sup> Various techniques have been described for excision of the distal ureter: open and laparoscopic (including robot-assisted).<sup>[26]</sup> A variety of incisions have also been described to provide adequate exposure to the perivesical space: lower mid-line, Pfannenstiel, or Gibson.<sup>[26]</sup> Although this procedure has benefits, namely that it is nephron-sparing in nature, one cannot dismiss the recurrent and multifocal nature of urothelial carcinoma. Recurrence and survival rates for low-grade/stage distal tumors do not differ regardless of the therapeutic approach.<sup>[26]</sup> Long-term follow-up data on these patients are scarce. Open or laparoscopic distal ureterectomy is feasible in select patients, and, to date, results show no short-term recurrence.<sup>[26]</sup> Continued surveillance for these patients is certainly necessary.

After the initial portion of the procedure, the ureterectomy, various procedures have been performed to maintain continuity of the urinary tract. In patients with adequate ureteral length, ureteroneocystostomy is performed in either extravesical or transvesical fashion. In patients where a longer segment of ureter requires removal, and who are not candidates for ureteral reimplant, autotransplantation of the kidney into the iliac fossa or ileal interposition can be performed.<sup>[27]</sup> Although rarely performed for anatomic

reasons relating to ureteral blood supply, ureteroureterostomy can also be performed in select patients.<sup>[27]</sup>

## RADICAL NEPHROURETERECTOMY

Nephroureterectomy remains the gold standard treatment for UTUCC due to the multicentric nature (15–44%), low incidence of bilateral tumors (2–5%), and high tumor recurrence in the remaining distal ureter (16–58%).<sup>[28-30]</sup> This procedure involves *en bloc* excision of the kidney, ureter, and cuff of urinary bladder. Such extirpation is performed to minimize risk of tumor recurrence in the upper urinary tract. As is the case for lower tract urothelial tumor, concomitant lymphadenectomy has been advocated for some as part of both staging and possible therapeutic treatment of UTUCC.<sup>[31]</sup> Studies report that 30–40% of patients undergoing surgery for UTUCC have positive lymph nodes.<sup>[32]</sup> However, various portions of the upper urinary tract, which range from the kidney to the distal ureter, have unique lymphatic drainage patterns, making it difficult to determine what type of lymphadenectomy is required and whether the added potential morbidity of this procedure will positively impact overall assessment of extent of disease and ultimate outcome of the patient.<sup>[31]</sup> Kondo *et al.* reported that the extent of lymphadenectomy improves survival in advanced stage UTUCC.<sup>[33]</sup> Brausi *et al.* reported that lymphadenectomy improves disease-free survival (DFS) and cancer-specific survival (CSS) in patients with muscle invasive UTUCC.<sup>[34]</sup> Roscigno *et al.* demonstrated that the extent of lymphadenectomy has a statistically significant effect on the DFS and CSS.<sup>[35]</sup> Furthermore, a large multicenter study revealed that an extended lymphadenectomy results in lower recurrence rates and decreased cancer-specific mortality in UTUCC patients treated with RNU.<sup>[31]</sup>

### Open radical nephroureterectomy

Due to the anatomy and extent of the kidney and its entire associated ureter, a key consideration in open RNU is where to make incision(s) for safe extirpation of the renal unit in question. A number of different approaches have been employed and may to some degree rely on individual surgeon experience and preference. Factors to consider are body habitus, location of tumor, tumor extent, previous surgical procedures, presence of suspicious lymphadenopathy, consideration of performing concomitant extensive lymphadenectomy, and impact of the incision(s) on the patient during the postoperative period.

Open nephroureterectomy is commonly performed via a two-incision approach, with a flank incision for dissection of the kidney and a Gibson-type incision for excision of the distal ureter/bladder cuff. This approach allows for the procedure to be completed entirely in an extraperitoneal fashion. Another option includes an infraumbilical midline

abdominal incision for the distal ureter and bladder cuff. This approach also allows for transvesical excision of the distal ureter and bladder cuff should this be desired.

Although a midline abdominal incision can be used for the performance of a single-incision open approach, this may be associated with suboptimal access to the kidney, more so in patients of large body habitus. Alternatively, in cases where the primary tumor, usually within the kidney, is large, or there is substantial lymphadenopathy, or possible need for vascular surgery, a subcostal of hemi-Chevron type of incision can be made for renal/renovascular dissection. Although these larger anterior abdominal incisions may be associated with more postoperative morbidity, they are in select cases quite optimal for renal dissection and vascular control, and may serve the patient well. Cerwinka *et al.* reported on implementing liver transplantation technique to surgically manage large, advanced UTUCC with or without vena cava thrombus.<sup>[36]</sup> The outcome of four patients was reported, of which two had vena cava thrombus. Mean tumor size was 11.6 cm. The authors concluded that the use of liver transplantation techniques was successful in surgically treating this select patient population.

### Laparoscopic radical nephroureterectomy

Shortly after the inception of transperitoneal laparoscopic nephrectomy, laparoscopic techniques evolved and were modified for the performance of virtually all types of renal procedures, which include radical nephroureterectomy. LRNU was first performed by Kerbl *et al.* in 1993.<sup>[37]</sup> Although RNU can be performed completely by conventional laparoscopy, a surprisingly large number of hybrid laparoscopic alternative surgical techniques have been put forth for this procedure. Desai *et al.* reported their experience of performing laparoendoscopic single-site (LESS) nephroureterectomy in two patients with UTUCC. In both patients, there was no need for open conversion, extra ports, and no complications were reported.<sup>[38]</sup> Similarly, White *et al.* reported the outcome of seven patients who underwent LESS nephroureterectomy. Mean operative time was 198 minutes, estimated blood loss was 396 ml, and duration of hospital stay was 3.9 days. One patient required open conversion; however, no complications were reported.<sup>[39]</sup> Eandi *et al.* reported on 11 patients treated with robot-assisted laparoscopic nephroureterectomy.<sup>[40]</sup> Jeon *et al.* reported on three patients treated with robotic LESS nephroureterectomy.<sup>[41]</sup> Although multiple hybrid laparoscopic procedures have been reported to surgically manage UTUCC, long-term oncological and morbidity data to date are scarce. A variety of techniques exist for performing both the renal portion of the procedure as well as the distal ureterectomy/excision of bladder cuff. Factors driving this diversity of surgical approaches are numerous, and include individual surgeon's experience with conventional laparoscopy, access to different surgical technologies, patient's prior history of



surgery, and approach to the distal ureter and bladder cuff. Due in part to the large number of approaches that exist for the performance of LRNU, considerable controversy has arisen as to which is/are the best in terms of oncologic efficacy, perioperative results in terms of pain, time of discharge/resumption of regular activity, and operative efficacy in terms of need for repositioning and additional trocars. This controversy, however, is mostly focused on how the distal ureter is manipulated, such that risk for tumor spillage is minimized.

The “pluck” technique,<sup>[42]</sup> originally described as transurethral resection of the ureteral orifice at inception of the procedure, has been criticized frequently as this technique leaves the distal ureter open while operative manipulation takes place for most of the remainder of the procedure, thus leaving considerable risk for tumor spillage. Other techniques involving transurethral resection/excision of the distal ureter/bladder cuff have often been confused with the “pluck” technique; however, the specifics of these procedures vary in important aspects. LRNU is commonly performed with dissection of the kidney and proximal ureter first. Using such a technique, the ureter below the level of the pathology can be dissected and identified early in the procedure and clipped, thus precluding risk of tumor spillage. Further aspects of the procedure, whether they involve conventional or hand-assisted ureteral dissection, with or without a transurethral portion, are of less critical importance in terms of tumor spillage as the tumor is already contained inside the surgical specimen. Tumor located more distally in the ureter may require initial distal dissection or clipping. Alternatively, in cases where tumor is located most distal, possibly involving the intramural ureter/orifice, open surgical control is generally best. In the laparoscopic approach, when a transurethral portion is employed as part of the procedure, one can be relatively certain that the bladder cuff/distal ureter are completely excised, as this is done under direct vision. If no transurethral portion of the procedure is used, the surgeon must make certain that the distal ureter is completely dissected through the bladder wall to the level of the epithelium of the bladder, thus ensuring that the entire ureter is excised. If meticulous dissection is not performed, premature clipping or stapling of the distal ureter may leave a remnant of the distal ureter in place, which is then a site at risk for recurrence.

LRNU can be performed via transperitoneal or retroperitoneal access. Transperitoneal approach provides better exposure and a larger operating field, but the risk of bowel injury is high and recovery of bowel function is prolonged. Retroperitoneal access limits the risk of bowel injury and ileus postoperatively, but the risk of vascular injury is high. However, data from published literature state that both the approaches are equally efficient in terms of technical feasibility.<sup>[7]</sup> Centers with long-term experience prefer the exclusive laparoscopic approach over hand-

assisted as the latter represents a compromise between open and laparoscopic techniques. Hand-assisted approach allows to overcome some of the disadvantages associated with conventional laparoscopy, such as three-dimensional orientation, tactile sensation, and loss of proprioception.<sup>[43]</sup> Additionally, hand assistance permits manual blunt dissection and *en bloc* specimen retrieval thus reducing tumor spillage and adhering to the oncological principles utilized in open surgery. Furthermore, the learning curve and operative time are shorter for hand-assisted surgery. Management of the distal ureter remains to be controversial. The open extravesical or the transvesical approach is accepted as the most oncologically safe procedure to perform.<sup>[44]</sup> However, patient factors and history of prior radiation and surgery can make ureteral excision more difficult. Laparoscopic stapling of the distal ureter and bladder cuff has been reported to be associated with decreased overall survival and higher positive surgical margin rate.<sup>[44]</sup> Kurzer *et al.* reported on 49 patients with a mean follow-up of 10.6 months who underwent cystoscopic circumferential excision of the distal ureter without primary closure of the bladder cuff. No cases of local pelvic or peritoneal recurrences were reported.<sup>[45]</sup> Vardi *et al.* described *en bloc* excision of the bladder cuff using a flexible cystoscope and 5F electrode.<sup>[46]</sup> Nanigan *et al.* described using robotic assistance for excision of the distal ureter in 11 patients.<sup>[47]</sup> Despite the various techniques described for handling the distal ureter, most studies have not shown any significant differences. The best option is to follow individual surgeon’s preference adapting to the fundamental oncological concepts.

It is likely that a number of the reported techniques and their permutations will yield good results if meticulous surgical technique is used and that specific steps are taken to prevent tumor spillage during the procedure. A number of series involving many of these techniques have been reported and have shown good short-term and intermediate-term results. Table 3 lists select series (some are comparative) of patients undergoing various types of minimally invasive RNU. This table reflects experience with a variety of approaches and their results and is not a comprehensive list of all series of minimally invasive RNU. Kamihira *et al.* reported the largest multicenter analysis of laparoscopic nephroureterectomy to date. They reported on 1003 patients treated in 51 centers. This multicenter analysis included LRNU performed by a variety of different techniques. Overall survival rate was 70% at 5 years. The authors reported that male gender and the use of hand-assisted approach to be the risk factors for decreased recurrence-free survival and intravesical recurrence.<sup>[48]</sup> However the reasons for these findings, in a study from many different centers, are not clear. Berger *et al.* reported the longest follow-up post-LRNU. One hundred patients were followed up over a period of 7 years. At 2, 5, and 7 years follow-up, overall survival rate was 81%, 59%, and 50% respectively. Cancer specific survival was 91%, 77%, and 72% at 2, 5, and 7 years, respectively. They

**Table 3: Selected studies of various open and laparoscopic nephroureterectomy for UTUCC**

Author	Surgical technique	N	Results
Kamihira <i>et al.</i> <sup>[48]</sup>	Laparoscopic RNU (various techniques)	1003	Overall 5-year survival rate 70%. Intravesical recurrence (43%) was more common in males, patients with multifocal tumors, previous or concomitant bladder tumors, and in patients who underwent HAL approach.
Simone <i>et al.</i> <sup>[49]</sup>	Laparoscopic vs. open RNU	80	40 patients in each arm. Mean time of discharge was low in laparoscopic RNU ( $P<0.001$ ). At 44 months follow-up, CSS and MFS were equal in both groups. High-grade tumors had better CSS and MFS ( $P<0.004$ ) in open radical nephroureterectomy arm.
Tai <i>et al.</i> <sup>[50]</sup>	Open RNU vs. HAL RNU	49	33 patients underwent HAL RNU, 16 underwent open RNU. HAL RNU was associated with earlier bowel recovery, earlier convalescence, shorter hospital stay. None of the HAL RNU patients required open conversion. Median follow-up was 35 and 46 months for HAL RNU and open RNU patients, respectively. Recurrence was similar in both groups. CSS was similar in both groups.
White <i>et al.</i> <sup>[39]</sup>	LESS RNU	7	Mean operative time 198 minutes. Mean estimated blood loss 396 ml. Length of hospital stay 3.9 days. 1 patient required open conversion, no other complications were encountered and none of the cases required extra ports.
Eandi <i>et al.</i> <sup>[40]</sup>	Robot-assisted laparoscopic RNU	11	Mean follow-up was 15.2 months. Mean operative time 326 minutes. Length of hospital stay 4.7 days. 4 patients developed recurrence and 2 patients died due to metastatic disease.
Jeon <i>et al.</i> <sup>[41]</sup>	Robot-assisted-LESS RNU	3	The authors used a homemade single-port device. Mean length of hospital stay was 3 days. None of the patients required open conversion and placement of extra ports. Mean operative time 150 minutes. Mean estimated blood loss 105 ml. Mean length of hospital stay 4.2 days. No complications were reported.

RNU, Radical nephroureterectomy; HAL, Hand-assisted laparoscopy; CSS, Cancer-specific survival; MFS, Metastasis-free survival; LESS, Laparoendoscopic single site, UTUCC - Upper tract urothelial cell carcinoma.

concluded that long-term outcome after LRNU was similar to that of open surgery.<sup>[49]</sup>

## POSTCYSTECTOMY UPPER TRACT TUMORS

Patients treated with radical cystectomy (RC) can subsequently develop transitional cell carcinoma of the upper urinary tract. Reports suggest that approximately 3% of patients undergoing RC develop metachronous tumors in the upper tracts and these tumors can be multiple and multifocal in occurrence. Upper tract recurrence can be early (<3 years from RC) or late (>3 years from RC).<sup>[50]</sup> With increased surveillance, early tumor relapse accounts for >80% of all tumor recurrences. Despite detecting these tumors early, survival in this cohort remains to be poor even with surgical intervention and adjuvant chemotherapy. On the contrary, though late recurrences are diagnosed based on tumor-related symptoms (i.e., loin pain, hematuria, weight loss) survival in this cohort is significantly better than for early recurrences.<sup>[51]</sup> Sanderson *et al.* studied the prognostic factors and outcomes of 1069 patients who underwent RC for transitional cell carcinoma of the bladder.<sup>[52]</sup> They reported that patients with evidence of tumor involvement within the urethra are at increased risk for upper tract recurrence. Although, RNU can provide prolonged survival, early detection of asymptomatic upper tract recurrence through surveillance does not predict a lower nephroureterectomy tumor stage, absence of lymph node metastasis, or improved survival.<sup>[53]</sup> Urine cytology may have a valuable role in detecting upper tract recurrence after RC. Most patients with positive urine

cytology after RC eventually have radiological evidence of urothelial recurrence.<sup>[54]</sup>

## CONCLUSION

RNU remains the reference standard for treating UTUCC. The role of concomitant lymphadenectomy as an adjunct to nephroureterectomy has not been well defined. However, recent studies have demonstrated that the extent of lymphadenectomy has a statistically significant effect on DFS and CSS. Further investigation is required to determine whether extended lymphadenectomy results in lower recurrence rates and decreased cancer-specific mortality in UTUCC patients treated with radical nephroureterectomy. The accuracy of determining tumor stage and aggressiveness via non- or minimally invasive tools remains controversial. Hence, there exists a significant risk of understaging and undertreatment in conservatively managed tumors. Laparoscopic nephroureterectomy has yielded comparable results to open surgery with regard to cancer outcomes and also offers advantages in terms of morbidity and earlier convalescence. However, since LRNU may be selectively performed in low-risk patients (less tumor extent), it cannot be said with certainty that open nephroureterectomy and LRNU have the same oncologic efficacy in poor-risk patients. Long-term oncological and morbidity data in patients treated with LRNU are required prior to accepting the procedure as standard of care for patients with high-grade and muscle-invasive UTUCC. Patients undergoing radical cystectomy for muscle-invasive bladder cancer are at lifelong risk to develop metachronous tumors of the upper urinary tract.

Adequate counseling and surveillance are mandatory prior to and postoperatively. Further strategies and surveillance methods must be developed and validated to improve the outcomes in high-risk patients.

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