Review Article

Robotic nephroureterectomy supplanting open and laparoscopic approach for upper tract urothelial carcinoma management: a narrative review

Laura Zuluaga^, Jordan M. Rich, Shirin Razdan^, Burak Ucpinar, Kennedy E. Okhawere^, Indu Saini, Ketan K. Badani

Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Contributions: (I) Conception and design: L Zuluaga, KK Badani; (II) Administrative support: KK Badani, I Saini; (III) Provision of study materials or patients: S Razdan, JM Rich, KE Okhawere; (IV) Collection and assembly of data: L Zuluaga, JM Rich, B Ucpinar; (V) Data analysis and interpretation: L Zuluaga, KE Okhawere; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Laura Zuluaga, MD, MSc. Department of Urology, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, 6th Floor New York, NY 10029, USA. Email: laura.zuluaga@mountsinai.org.

Background and Objective: The use of robotic surgery for managing upper tract urothelial carcinoma (UTUC) has increased significantly over the years. Minimally invasive techniques (MIS) are now used for approximately half of all robot-assisted laparoscopic nephroureterectomy (RAL-NU) performed in the USA. However, there are currently no specific management guidelines that recommend the use of a robotic approach, and the available literature on this topic is limited. For this reason, we reviewed the history and current literature regarding this technique.

Methods: We searched Web of Science and PubMed for articles between 1934 to 2023 using 20 different search terms and combinations. We restricted our selection to only publications in English language.

Key Content and Findings: Comparative retrospective studies between techniques [open nephroureterectomy (ONU), laparoscopic nephroureterectomy (LNU), and RAL-NU] and case series of surgical groups, mostly at short- and mid-term follow-up, were included.

Conclusions: Robotic surgery for UTUC is on the rise and is predicted to become the preferred method for nephroureterectomy. A comparison of RAL-NU to LNU and ONU shows several advantages, including less blood loss, pain, and hospital stay, as well as a quicker recovery time. The safety and effectiveness of robotic surgery for lymphadenectomy also supports its use in RAL-NU. As more medical facilities adopt the technique and further studies support its benefits, it is likely that robotic surgery will become the preferred method for NU.

Keywords: Robotic surgery; nephroureterectomy; bladder cuff excision (BCE); upper tract urothelial carcinoma (UTUC)

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^ ORCID: Laura Zuluaga, 0000-0002-2612-6950; Shirin Razdan, 0000-0002-9098-3447; Kennedy E. Okhawere, 0000-0002-7165-0823.

Introduction

Urothelial carcinoma (UC) can occur anywhere in the lower (bladder and urethra) or upper (kidneys and ureter) urothelial lining of the urinary tract. It is the fourth most common cancer in the United States, with an estimated 164,000 cases in 2022 (1). Upper tract urothelial carcinoma (UTUC) is less common, accounting for only 5–10% of all UC (1). The incidence of UTUC has slowly risen over the past four decades, likely due to improved survival rates and diagnostics methods, and the average age of diagnosis has also risen from age 68 to 73 years (2,3). At the time of diagnosis, UTUC tends to be more invasive compared to urothelial carcinoma of the bladder (UCB), with over 60% of cases with muscle invasion as opposed to 15–25% in UCB (4,5). The diagnostic approach for UTUC involves a combination of clinical, laboratory, imaging, and endoscopic methods like cystoscopy and imaging of the upper tract and collecting system (4,6). Computed tomography (CT) urogram is the most accurate imaging technique for diagnosis. In cases where imaging and cytology are not sufficient, more invasive diagnostic techniques like urethrocystoscopy and flexible diagnostic procedures may be employed to assess tumor architecture and location (4,6). These tools together allow for risk stratification of UTUC. Additionally, the NCCN recommends that providers thoroughly assess the patient's family history, as recent evidence suggests a high prevalence of Lynch syndrome (approximately 8.7%) among individuals with UTUC (6-8).

Both the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines recommend kidney sparing surgery (KSS) for patients with low-risk disease and select patients with solitary kidney or chronic kidney disease (CKD) (4,9). Low risk UTUC is characterized by unifocal disease, tumor size <2 cm, low grade cytology and ureteroscopic biopsy, and the absence of invasive disease on CT urography (4). However, the majority of patients with UTUC will have high risk features, such as hydronephrosis on imaging, tumor size >2 cm, high grade cytology or ureteroscopic biopsy, multifocal disease, or a history of previous bladder cancer (6). For these patients, the preferred treatment is surgery with radical nephroureterectomy, which involves resecting the entire ipsilateral urinary tract, including the bladder cuff (4,6,10), as studies have shown a high rate of tumor formation in the remaining ureteral stump when only nephrectomy is performed (11).

Traditionally, this procedure was performed using the open approach. However, concerns about perioperative morbidity and postoperative recovery associated with long incisions prompted the exploration and adoption of minimally invasive methods (12,13). Laparoscopic nephroureterectomy (LNU) was first reported in the literature in 1991 with multiple articles replicating its feasibility shortly thereafter (14,15). Many surgeons found pure LNU technically challenging for the management of the distal ureter and bladder cuff, so these aspects of the procedure were often performed with an open approach (16). Initially, there were questions surrounding its oncologic efficacy, which limited its widespread adoption, but those have been alleviated by numerous retrospective and prospective studies, as well as meta-analyses demonstrating equivalent oncologic outcomes with reduced perioperative morbidity and complication rates compared to the open approach (17-20). The favorable oncologic and functional outcomes spurred increased adoption of this technique (21). The da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA, USA) offered improved visualization and mobility, and in 2006, a combined laparoscopic nephrectomy with robotic management of the bladder cuff was performed (22). In 2007, a complete robot-assisted laparoscopic nephroureterectomy (RAL-NU) was performed for the first time (23). Subsequent studies have shown comparable perioperative and short-term outcomes of RAL-NU *vs.* LNU (24-26). In recent years, there has been a growing adoption of minimally invasive options for nephroureterectomy, with no clear advantages for either the laparoscopic or robotic technique (27). In this narrative review article, our aim is to review the relevant literature regarding the history and current state of nephroureterectomy for treatment of UTUC, and explore whether RAL-NU has supplanted the open approach. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-73/rc).

Methods

We conducted a comprehensive literature review using the PubMed and Web of Science databases in order to identify the most relevant articles related to the specified topics. Our inclusion criteria included full-text English articles published in peer-reviewed journals from 1934 to 2023. The search terms we utilized were as follows: "robotic nephroureterectomy", "nephroureterectomy", "urothelial carcinoma", "upper tract urothelial cancer",

Table 1 Search strategy summary

Items	Specification
Date of search	5th January 2023
Databases and other sources searched	Web of Science, PubMed
Search terms	"Robotic nephroureterectomy", "nephroureterectomy", "urothelial carcinoma", "upper tract urothelial cancer", "upper tract urothelial carcinoma", "bladder cancer", "upper tract urothelial carcinoma treatment", "robotic lymphadenectomy", "robotic lymphadenectomy versus open lymphadenectomy in nephroureterectomy", "robotic surgery", "bladder cuff excision", "lymph node dissection AND nephroureterectomy", "Intravesical administration of chemotherapeutic agent", "robotic surgery AND nephroureterectomy", "open approach AND nephroureterectomy", "laparoscopic approach AND nephroureterectomy", "robotic approach AND nephroureterectomy", "nephroureterectomy AND oncological outcome", "nephroureterectomy AND perioperative", "nephroureterectomy AND clinical trial"
Time frame	1934–2023
Inclusion criteria	English
Selection process	Selection was decided collectively
Any additional considerations, if applicable	In some cases, highest number of citations was used as a filter

"upper tract urothelial carcinoma", "bladder cancer", "upper tract urothelial carcinoma treatment", "robotic lymphadenectomy", "robotic lymphadenectomy versus open lymphadenectomy in nephroureterectomy", "robotic surgery", "bladder cuff excision", "lymph node dissection AND nephroureterectomy", "Intravesical administration of chemotherapeutic agent", "robotic surgery AND nephroureterectomy", "open approach AND nephroureterectomy", "laparoscopic approach AND nephroureterectomy", "robotic approach AND nephroureterectomy", "nephroureterectomy AND oncological outcome", "nephroureterectomy AND perioperative", "nephroureterectomy AND clinical trial". Additionally, we manually examined the reference lists of the identified articles to identify other pertinent papers (*Table 1*).

Open radical-nephroureterectomy

The evolution of the surgical management of upper urinary tract UTUC has been partly influenced by its tumor behavior *vis-a-vis* its multifocal nature and high recurrence rate (*Figure 1*). The first technique for open nephroureterectomy (ONU)—which included the removal of the kidney and a portion of the ureter—was described in 2015 by Abbott *et al.* (28). Subsequently, in 1934, Kimball and Ferris established the need for a primary complete nephroureterectomy following the findings of high tumor recurrences in the remaining distal portion of the ureter or ureter stump after initial resection (29). The ONU is typically performed with a flank or sub-coastal resection, followed by a distal ureter resection using a Gibson, low midline, or modified Pfannenstiel incision. Alternatively, a single incision can be used in conjunction with an endoscopic resection of the distal ureter. In 1952, McDonald *et al.* (30) described the first endoscopic attempt at nephroureterectomy through a transurethral resection of the ureteral orifice (pluck approach), which lead to a shorter operation time. Since then, several novel endoscopic methods for performing nephroureterectomy have been described in literature, e.g., modified pluck technique, intussusception technique or ureteric stripping (31). The open approach can be used for the management of the distal ureter after a previous minimally invasive procedure or open procedure for the excision of the kidney and ureters. The complete distal ureter down to the intramural ureter and bladder cuff can be excised *en bloc* using an extravesical or transvesical approach. The extravesical approach involves mobilization of the distal ureter towards the bladder, whereas the transvesical approach is performed with an anterior cystotomy providing direct visualization of the ureter from within the bladder. Currently, there is no established evidence of significant oncological difference between the two approaches (32,33). Although there are

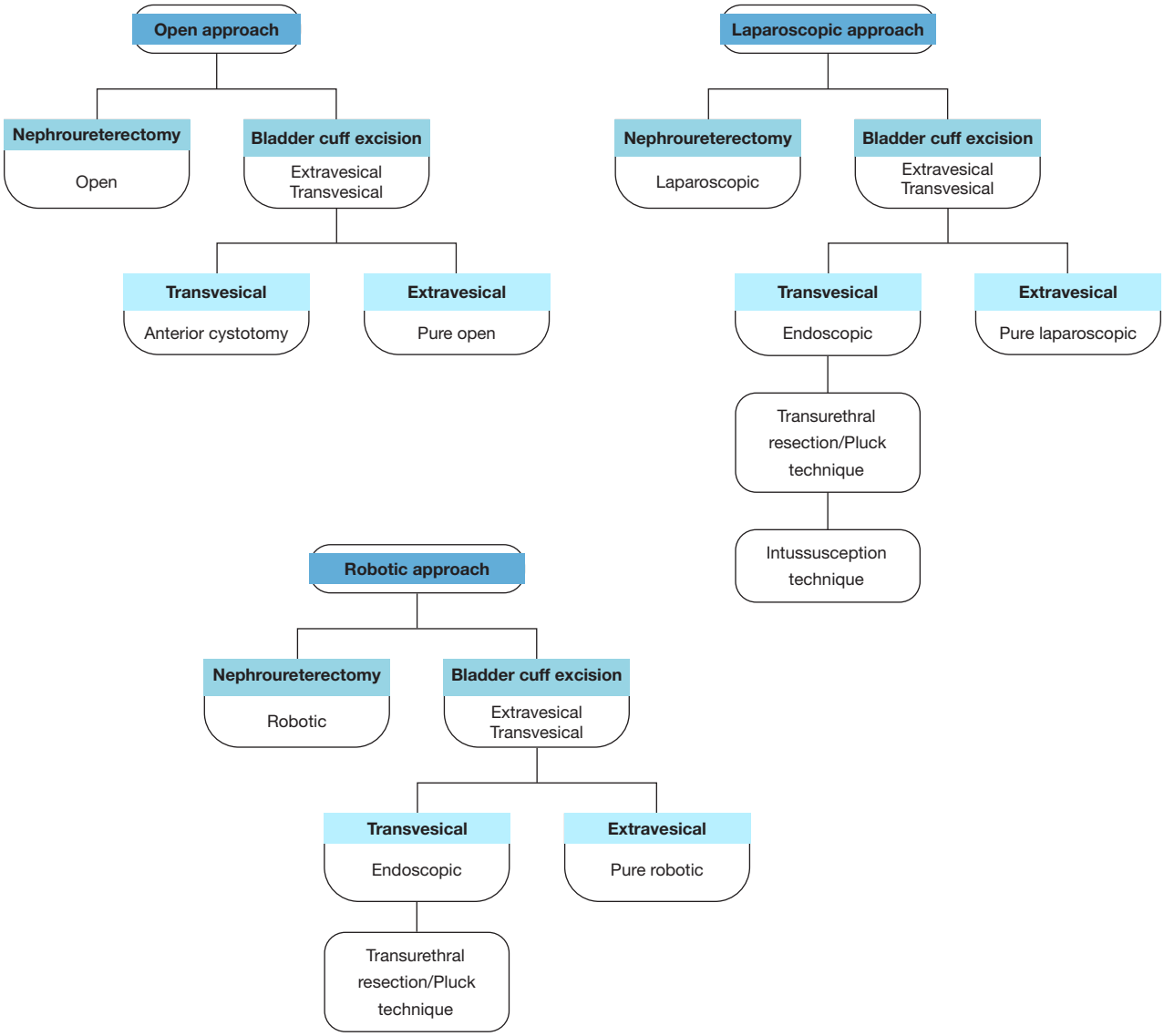

Figure 1 Management options and evolution for radical nephroureterectomy and BCE. BCE, bladder cuff excision.

no absolute contraindications to the use of open technique for managing UTUC, it may be relatively difficult in obese patients and patients with history of pelvic surgery or irradiation. Furthermore, while the open approach yields comparable oncological outcomes to minimally invasive approaches, it is associated with poorer peri-operative outcomes (24,34,35).

LNU

Laparoscopic techniques for urological procedures have been widely adopted, after its first description by Clayman *et al.* in 1991 (14). Given its minimally invasive nature and advantages like reduce post-operative pain, early recovery and better cosmesis, it has been the preferred method for performing nephrectomy (19,36). In 1993, Kerbl *et al.* presented successful outcomes of their first laparoscopic radical nephroureterectomy cases (37). However, adoption and recommendation took more time due to concerns, particularly regarding the distal ureter, bladder cuff excision (BCE) and bladder repair. These aspects of the procedure require advanced laparoscopic skills and pose an increased risk of breaching into the ureter or renal pelvis during dissections, which bears the risk of tumor seeding (38).

ONU is still listed as the mainstay treatment for high risk and non-organ confined UTUCs, according to the latest EAU guidelines (4). Numerous studies in the literature have demonstrated comparable oncological outcomes between open and minimally invasive/laparoscopic techniques for organ confined disease. Therefore, the extent of the disease and surgeons' laparoscopic experience are important factors in choosing an approach.

Robot assisted LNU: the beginning

In 2006, Nanigian *et al.* performed the first robotic distal ureterectomy, which involved a laparoscopic nephrectomy and distal excision using the Da Vinci™ system (Intuitive Surgical, Sunnyvale, CA, USA) (22). Initial case reports focused on combining techniques of open, laparoscopic and endoscopic approaches in the early stages of developing the robotic technique (39-41). In 2010, Eandi *et al.* performed the first total RAL-NU, where they described a lateral rectus port configuration for initial nephroureterectomy, and after kidney and ureter mobilization to iliac vessels the robot is undocked and patient repositioned for the distal ureterectomy. Pelvic configuration of the ports was done to access the distal ureter segment, ureterovesical junction, and bladder (42). With technological advancements in robotic platforms, the Da Vinci™ S system provided features like expanded depth and improved mobility of robotic instruments. Surgeons were no longer restricted to working within specific zones (upper tract, lower tract) and, for the first time, could use the robot in two different anatomical areas, avoiding longer surgical times and risks associated with re-docking the robot. Eun *et al.* published the first report of a total RAL-NU with concurrent multiple quadrant urinary tract management using the Da Vinci S platform in 2007 (23). In 2011, Hemal and collaborators (26) described a new technique that eliminated the need for patient repositioning, port reassignment, or redocking of the robotic arms (43). This novel port placement technique established a more effective, efficient, and reproducible method for RAL-NU. Since then, multiple different robotic techniques have been described (23,26,41,44-47) and, as result of the advent of da Vinci Xi, further advancement in controlling the movement of the robotic platform has allowed greater mobility within the abdominal and pelvic cavities, leading to the development of the techniques used nowadays (48).

As for the BCE technique, it has undergone significant changes since the introduction of the open technique in 1898. The transvesical needlescopic technique was described in 1999 (49), achieving the oncological goals of *en-bloc* resection but with limitations such as patient repositioning and a steep learning curve. Other hybrid laparoscopic-endoscopic techniques, such as laparoscopic stapling of the distal ureter and bladder cuff, transurethral resection of the ureteral orifice, and the intussusception technique (31,50,51), do not adhere to oncological principles. These techniques either leave tissue segments at risk of local recurrence, or involve transurethral removal of the ureter, posing a risk of tumor seeding (52).

Regarding lymph node dissection (LND), early series provide limited evidence regarding the importance of performing retroperitoneal lymph node dissection (RPLND) during nephroureterectomy. In 2007, Brausi and associates published an article emphasizing the importance of RPLND during the nephroureterectomy (53). More recently, a 2019 study by Zhai demonstrated that only T3–4 disease benefits from extended LND, which has an impact on disease free survival and overall survival (OS) (54). Several other studies have suggested improved survival when LND is performed (55). In 2013, an initial study compared LNU with RAL-NU, suggesting the latter as a viable option for managing UTUC. The study revealed that RAL-NU resulted in a higher frequency of LNDs and, as a consequence, RAL-NU had a longer operation time (298 *vs.* 251 minutes) and greater blood loss (380 *vs.* 233 mL) compared to LNU (56).

RAL-NU: the present

Minimally invasive surgery for the management of UTUC follows the same oncological principles as the open approach. These principles include complete *en-bloc* kidney and ureteral resection, avoiding entering the urinary tract, avoiding direct contact between instruments and tumor, and avoiding morcellation of the tumor (43,57). Regardless of the surgical approach, five main components should be ensured: nephrectomy, ureterectomy, BCE, LND, and intravesical administration of chemotherapeutic agent (58) (*Figure 2*).

Nephroureterectomy and BCE

The first robotic nephroureterectomy was performed in 2007 (23), followed by a modification in the technique in 2011 (26) to eliminate patient repositioning. This extirpative

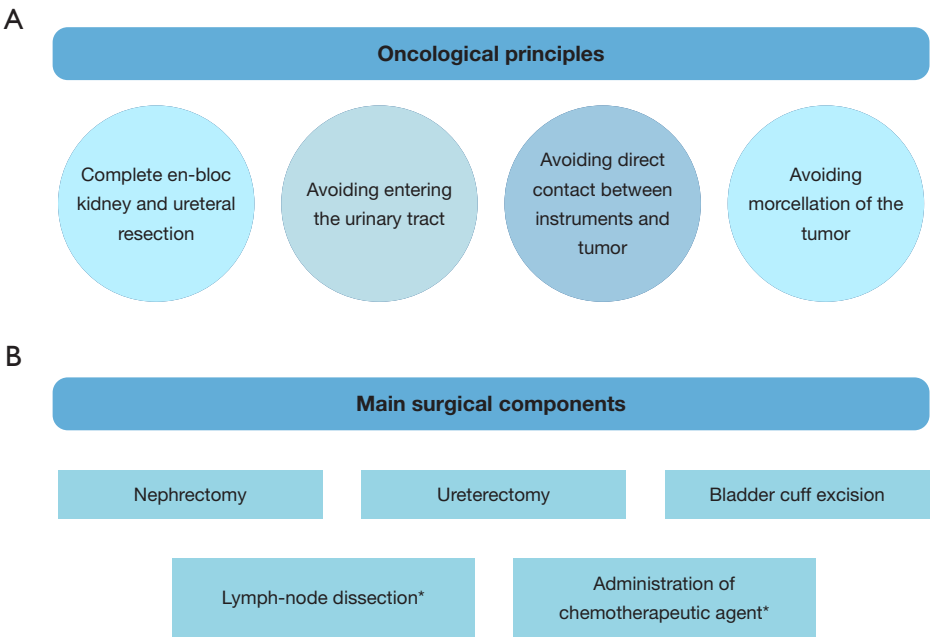

Figure 2 Key oncological principles that must be upheld during surgical interventions for UTUC, aiming to prevent recurrence and ensure positive cancer-related outcomes, and, essential surgical components that are universally necessary irrespective of the chosen approach. (A) Oncological principles: the principles guiding minimally invasive surgery for UTUC management mirror those of the open approach, encompassing complete en-bloc resection of the kidney and ureter, careful avoidance of urinary tract penetration, preventing direct instrument-tumor contact, and refraining from tumor morcellation. (B) Irrespective of the chosen surgical method, five key elements should be performed: nephrectomy, ureterectomy, excision of the bladder cuff, lymph node dissection, and intravesical delivery of a chemotherapeutic agent. *, in localized high-risk disease. UTUC, upper tract urothelial carcinoma.

portion of the procedure (nephroureterectomy/abdominal component) has been extensively studied in combination with other robotic procedures, such as partial and radical nephrectomy, yielding excellent long-term results that highlights the benefits of the minimally invasive robotic-assisted approach. The robot's easy hilar control, adequate visibility, and freedom of movement enables precise and efficient manipulation (59). Although the evidence for this procedure cannot be directly extrapolated due to intrinsic differences, some aspects of the technique are partially replicated in RAL-NU. Several studies have reported advantages of robotic approach in nephroureterectomy, demonstrating increased mobility and a simplified process for isolating the distal ureter and securing the bladder, thanks to the articulated robotic wrists (60,61).

Leaving the bladder cuff intact at the time of radical surgery is associated with a known recurrence rate 33–75% in the ureteric remnant (62,63). In 2015, the first series of cases involving pure RAL-NU and BCE was described, demonstrating satisfactory oncologic control at 12months of follow-up (64). Recent publications have compared the rate of complications comparing open, laparoscopic, and robotic approaches including BCE, and have found no significant difference in operation time, blood loss, length of hospital stay, and 90-day complications between the three groups (65,66). Currently, there are no randomized studies that have strong statistical evidence to recommend the use of one of the techniques over another. However, a recent retrospective study—with the largest study population to date—showed no difference in OS and cancer-specific survival (CSS) rates, as well as intravesical recurrence rates, when a robotic-assisted approach was used in patients undergoing radical nephroureterectomy and BCE.

LND

Despite the controversy surrounding LND over the years, both the EAU (67) and the NCCN (12) guidelines currently recommend considering lymphadenectomy based on to anatomical location. For cases involving primary disease

within the kidney, lymphadenectomy within the para-aortic and hilar lymph nodes is recommended, while cases involving primary disease within the ureter will require addition of pelvic lymph node removal. The utilization of lymphadenectomy templates provided by these guidelines has demonstrated an improved survival rate and reduced the likelihood of local cancer recurrence, especially in advanced-stage conditions (68). Additionally, achieving a high level of precision is crucial when performing template-based lymphadenectomy, particularly due to the complex surgical field surrounding the great vessels. Robotic systems offer increased control and greater dexterity, enabling more precise removal of lymph nodes, a higher number of resected lymph nodes, and a lower risk of complications (56,69,70). A study conducted by Clements *et al.* in 2018 revealed that the use of the robotic-assisted approaches increases the probability of successful lymphadenectomy, which itself is a predictor of improved survival (71). Moreover, visibility plays a vital role in performing this procedure, and the robotic system includes a high-definition camera that provide a magnified, 3D view of the surgical field, which can aid in the accurate identification and removal of lymph nodes (72).

Intravesical administration of chemotherapeutic agent

Between 22% and 47% of patients who undergo radical nephroureterectomy experience intravesical recurrence within two years after surgery (33,73). To determine which patients require intravesical adjuvant therapy, several studies have examined the risk of recurrence by evaluating prognostic factors such as tumor location (specifically the ureter), tumor size, surgical margins, and whether the initial procedure was performed laparoscopically (74).

Although LNU and RAL-NU yield similar oncological outcomes and shorter postoperative recovery times (4,75-77), a systematic review conducted by Seisen *et al.* in 2015 revealed an association between intravesical recurrence and the use of laparoscopic approach [hazard ratio (HR) 1.62; P=0.003] (78). This finding has contributed to the shift from the use of laparoscopic surgery to robotic specifically for this procedure. In a recent systematic review, it was demonstrated that a single-dose of intravesical chemotherapy instillation may reduce the risk of bladder cancer recurrence compared to no instillation over time [HR: 0.51 95% confidence interval (CI): 0.32, 0.82]. Additionally, factors such as surgical approach, pathological stage, and bladder management techniques were identified as significant factors affecting the outcome (79). This review was based on two studies, and one for them reported that in the multivariable Cox regression analysis laparoscopic surgical technique, along with others variables like advanced age, male gender, ureteral tumor location were all significantly associated with intravesical recurrence (P=0.04) (80).

Current evidence

In 2019, Lee *et al.* (24) conducted a single institution study involving 422 patients who underwent open, laparoscopic, or RAL-NU for non-metastatic UTUC. The study included 161 patients in the open group, 137 in the laparoscopic group, and 124 in RAL-NU group. The results demonstrated that RAL-NU and LNU had better perioperative outcomes compared to open surgery. Robotic-assisted surgery showed better oncologic outcomes in bivariate analysis, but these advantages were not observed in the multivariate analysis (81). Both laparoscopic and robotic approaches both had shorter length of stay (LOS), longer operative time, and less estimated blood loss compared to open surgery (all P values <0.001), with no differences in intraoperative or early postoperative complications rates. Regarding oncologic outcomes, RAL-NU demonstrated significantly longer progression-free survival (PFS), OS, and CSS compared to both LNU and ONU in bivariate analysis. However, these differences were not seen when taking into account others variables in the multivariate analysis (24). In the same year, Veccia *et al.* conducted a systematic review and meta-analysis of 80 studies on open, laparoscopic, and robotic nephroureterectomy (82). Their findings indicted that RAL-NU had superior perioperative outcomes without compromising oncologic success (66). The study revealed that intracorporeal BCE was performed for all RAL-NU procedures, but only in 50% of LNU. RAL-NU was also more commonly performed in patients with multifocal tumors (19%), but there were no differences in baseline characteristics. Operative time was shortest in the open group (224.98 min; 95% CI: 212.26, 237.69). RAL-NU had the lowest EBL of any group (163.31 mL; 95% CI: 88.94, 237.68). The rate of intraoperative complications was lowest in RAL-NU (2%), while the open group had the highest rates of transfusions (20%). There was no significant difference in overall or major complication rates among the different surgical techniques. Notably, RAL-NU had the shortest LOS of 5.35 days, while open surgery had the longest at 10.27 days. RAL-NU was more commonly

performed for high-grade pathology (70%), but there were no other differences in pathologic outcomes. There was no correlation between surgical technique and recurrence free survival (RFS) or CSS, except for one study that assessed these parameters for RAL-NU. Furthermore, no statistical difference was found among hand-assisted laparoscopic, open, and RAL-NU in terms of 2- and 5-year RFS and CSS. Hand-assisted laparoscopic nephroureterectomy (NU) had the lowest overall risk of recurrence (22%), metastasis (7%) and cancer-related death (3%), while ONU showed the lowest 5-year CSS (77%) (40,64).

In one of the most recent studies in 2021, Zeuschner *et al.* analyzed 131 radical nephroureterectomies (66 RAL-NU *vs.* 65 ONU) for UC of the upper urinary tract at a single tertiary referral center. The study revealed that RAL-NU had superior perioperative outcomes without compromising oncologic outcomes. With similar baseline characteristics, RAL-NU had less EBL (150 mL *vs.* 250, P=0.004) and fewer positive surgical margins (PSMs) (1.5% *vs.* 15.4%, P=0.004), with similar operating room (OR) time (188 *vs.* 178 min). The open surgery group experienced more complications (63.1% *vs.* 40.9%, P=0.011) and longer LOS (12 *vs.* 9 days, P<0.001). These differences remained significant after propensity score matching, except for the complication rate. The median follow up was 30.9 months. The 2-year PFS was 66.7% in RAL-NU and 55.3% in open surgery, but this difference was not statistically significant. The 2-year OS was 76.2% in RAL-NU *vs.* 68.4% in open, which was also not statistically significant. Regression analysis revealed that the surgical approach did not impact the PFS or OS (35).

In 2022, Veccia *et al.* published data collected from 17 centers worldwide regarding RAL-NU and LNU procedures performed between 2015 and 2019 (82). The study included 185 patients, and a multivariate analysis was conducted to evaluate a "tetrafecta" of variables (occurrence of BCE, LND, no complications, and negative surgical margins) to predict outcomes. The integration of robotics technology was found to potentially lead to the achievement of a "tetrafecta" outcome. RAL-NU had lower overall complications (24.9% *vs.* 42.9%; P=0.003) and a shorter LOS {3.5 [2–5] *vs.* 5 [4–7]; P<0.001} compared to LNU.

In a most recent study comparing LNU *vs.* RAL-NU, Huang *et al.* (83) conducted an observational retrospective study involving a total 231 patients. They found similar perioperative and oncological outcomes but superiority of RAL-NU in terms of LOS and intraoperative blood loss. The RAL-NU group had a reduced estimated blood loss compared to LNU (30 *vs.* 150 mL, P<0.001). Additionally, their LOS was shorter (8 *vs.* 9 days, P=0.009). However, there was no significant difference between the groups in terms of total operative time or postoperative catheter time. At a total follow-up time of 29 *vs.* 20 months, there was no significant differences in incidence of bladder recurrence, adjuvant chemotherapy, disease progression, local recurrence, distant metastasis, cancer-specific mortality rate, or overall mortality rate between the groups (82) (*Table 2*).

Conclusions

The adoption of robotic surgery for managing UTUC has grown exponentially over the years. A recent study by Bae *et al.* demonstrated that minimally invasive surgery (MIS) techniques were utilized in half of all radical nephroureterectomies performed in the USA. While the trend in LNU has leveled off, the number of RAL-NU has continued to rise (65). Despite the widespread adoption of robotic surgery in UTUC management, it is crucial to prioritize scientific rigor and conduct robust studies within this context, acknowledging the limitations imposed by the disease's prevalence.

Taking into account all currently available evidence discussed in this paper, we can summarize the reasons behind the increasing popularity of robotic surgery in UTUC and anticipate its continued growth. Comparing LNU to RAL-NU reveals an additional degree of freedom and technically easier manipulation of the tissues, along with instruments offering improved visualization and precision. These factors contribute to better patient outcomes. Furthermore, as previously mentioned, RAL-NU results in reduced blood loss and post-operative pain, shorter hospital stays, quicker recovery times, and the inherent benefit in cosmesis of MIS. Most importantly, the fact that a safe and effective lymphadenectomy can be performed using robotic surgery strongly supports its use. We consider that just like other urologic cancers, it is expected that robotic surgery will become the preferred method for NU as more medical facilities adopt this technique and new, well conducted studies are published to support future guideline recommendations.

Table 2 Current relevant evidence regarding approaches and outcomes of nephroureterectomy

Study, year (design)	Sample size, N	Study goal	Follow-up	Outcomes
Lee *et al.* 2019, (24), retrospective study	n=422: ONU =161, LNU =137, RAL-U =124	Compare the oncological and perioperative outcomes of different nephroureterectomy approaches in patients with non-metastatic UTUC	24 months (IQR, 10–59 months)	LNU and RAL-NU approaches involved significantly less blood loss (P=0.001), shorter hospital stay (P<0.001), and longer operation time (P<0.001) compared with the ONU approach No significant differences in intraoperative complications (ONU, 8.1%; LNU, 5.1%; RAL-NU, 7.3%; P=0.363) No significant differences early postoperative complications (ONU, 14.9%; LNU, 14.6%; RAL-NU, 13.7%; P=0.880) LNU and RAL-NU groups showed significantly less postoperative analgesic use (P=0.015) RAL-NU group showed significantly longer progression-free, cancer-specific, and overall survivals than the ONU approach group on univariate Kaplan-Meier analysis Surgery type was not significantly associated with survival outcomes per multivariate Cox proportional tests (all P values >0.05)
Zeuschner *et al.* 2021, (35), retrospective study	n=131: ONU =65, RAL-NU =66	Compare the perioperative and oncological outcomes of open and robot-assisted radical nephroureterectomies	30.9 months (range, 1.4–129.5 months)	RAL-NU had less blood loss (150 mL *vs.* 250, P=0.004) and less positive surgical margins (1.5% *vs.* 15.4%, P=0.004) at a comparable operating time (robotic 188 *vs.* 178 min) Any grade complications were more frequent after ONU (40.9% *vs.* 63.1%, P=0.011) The length of stay was shorter after RAL-NU (9 *vs.* 12 days, P<0.001) These differences remained significant in the propensity score matched analysis, except for the complication rates, which were still lower for the robotic approach, but no longer significant PFS at 2-year was: RAL-NU 66.7% *vs.* ONU 55.3% OS was (OS, 2-year: robotic 76.2% *vs.* open 68.4%). None of them significant In the Cox regression, the surgical approach did not impact the PFS or OS Lymph node metastases (HR 3.32, P=0.008) had the strongest impact on the PFS besides patient age (HR 1.51 per 10 years, P=0.025) and prior cystectomy (HR 2.42, P=0.026) in the multivariate analysis
Veccia *et al.* 2022, (82), retrospective study	n=877: RAL-NU =185, LNU =91	Compare the outcomes of robotic radical nephroureterectomy and laparoscopic radical nephroureterectomy within a large multi-institutional worldwide dataset	Low number of oncologic events after matching did not allow survival analysis	RAL-NU patients were more likely to undergo bladder cuff excision (81.9% *vs.* 63.7%; P<0.001) compared to the LNU group A statistically significant difference was found in terms of overall postoperative complications (24.9% *vs.* 42.9%; P=0.003) and LOS {3.5 [2–5] *vs.* 5 [4–7]; P<0.001} in favor of RAL-NU Pathology showed no statistically significant differences between the two groups. Patients in the multivariable analysis demonstrated that LNU was the only independent predictor negatively associated with achievement of "tetrafecta" (OR: 0.09; 95% CI: 0.02–0.45; P=0.003)
Veccia *et al.* 2020, (34), systematic review	80 studies, 87,291 patients included: ONU n=45,601, HALNU n=442, LNU n=31,093, RAL-NU n=10,155	Perform a systematic review and meta-analysis of the literature inherent robotic nephroureterectomy (RAL-NU) and to compare its outcomes with those of other NU techniques	N/A	RAL-NU was more likely to be performed in those patients with multifocal tumor location (proportion: 0.19; 95% CI: 0.14, 0.24) and high-grade disease (proportion: 0.70; 95% CI: 0.53, 0.68). Lowest EBL was recorded in the RAL-NU group (WM 163.31 mL; 95% CI: 88.94, 237.68) Highest EBL was in the ONU group (414.99 mL; 95% CI: 378.52, 451.46) Operative time was shorter for ONU (224.98 mL; 95% CI: 212.26, 237.69) RAL-NU had lower rate of intraoperative complications (0.02; 95% CI: 0.01, 0.05). ONU showed higher odds of transfusions (0.20; 95% CI: 0.15, 0.25) LOS was statistically significantly shorter for the RAL-NU group (5.35 days; 95% CI: 4.97, 5.82). LNU seemed to present lower risk of PSM (0.02; 95% CI: –0.01, 0.05), and lower risk of recurrence (0.22; 95% CI: 0.15, 0.30), metastasis (0.07; 95% CI: 0.05, 0.10), and cancer-related death (0.03; 95% CI: 0.01, 0.06) ONU showed the lowest 5 years cancer specific survival (proportion: 0.77; 95% CI: 0.74, 0.80) No correlation was found between the surgical technique and recurrence-free and cancer-specific survival

ONU, open nephroureterectomy; LNU, laparoscopic nephroureterectomy; RAL-NU, robot-assisted laparoscopic nephroureterectomy; UTUC, upper tract urothelial carcinoma; IQR, interquartile range; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; LOS, length of stay; OR, odds ratio; CI, confidence interval; HALNU, hand assisted laparoscopic; NU, nephroureterectomy; N/A, not applicable; EBL, estimated blood loss; WM, weighted mean; PSM, positive surgical margin.

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