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Robot-assisted nephroureterectomy for upper tract urothelial carcinoma—feasibility and complications: a single center experience

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ABSTRACT

Background: Robot-assisted nephroureterectomy (RANU) is the primary treatment for upper tract urothelial carcinoma (UTUC) at our hospital for patients with clinical stage less than T2, and for patients with invasive tumours, but unfit for major surgery.

Objective: To assess peri-operative conditions and outcomes of RANU at our unit, and to evaluate the safety of the procedure.

Methods: The medical records of all 166 patients undergoing RANU for suspected UTUC and followed for more than three months in a large university hospital in Sweden were reviewed retrospectively. After the exclusion of twenty patients because of previous cystectomy, simultaneous surgical procedure, or other tumour types than UTUC in the pathological report, 146 patients remained for the analyses. The primary endpoint was complication rate according to Clavien-Dindo at 90 days. Secondary endpoints were perioperative bleeding, violation of oncological surgical principles, hospital stay, and re-admission within 90 days.

Results: The median age was 75 [(Inter Quartile Range) IQR 70–80] years and 57% of the patients had an ASA score above 2. According to Clavien-Dindo, one patient had a grade 3 complication, and no patient had a grade 4–5 complication. The median blood loss was 50 (IQR 20–100) ml and the median hospital stay was 6 (IQR 5–7) days. Twelve patients were re-admitted to the hospital within 90 days (eight with urinary tract infection/haematuria, one with hematoma, and three with other diseases).

Conclusion: Robot-assisted nephroureterectomy is a safe procedure for patients with upper tract urothelial carcinoma, with a low risk of major surgical complications.

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Introduction

Upper tract urothelial carcinoma (UTUC) of the renal pelvis or ureter is a rare disease. The incidence of UTUC in Sweden in 2019 was 369 cases only, compared to 2970 cases of bladder cancer [1]. Standard surgical treatment for UTUC is nephroureterectomy with bladder cuff excision [2], but nephron-sparing options with segmental resections and endoscopic methods are alternatives for selected patients. Open surgery is associated with long-term morbidity related to the incisions required, and after flank incisions, almost one out of two patients suffer from flank bulges [3]. Therefore, decreased surgical trauma has been an argument for minimally invasive laparoscopic nephroureterectomy [4]. In other surgical procedures, such as radical prostatectomy and partial nephrectomy, robot-assisted surgery has also shown advantages of less bleeding, shorter recovery, and less post-operative pain compared to open surgery [5,6]. Consequently, robot-assisted nephroureterectomy (RANU) has been introduced for the treatment of UTUC. Until now, studies on RANU have been limited by small cohorts [7], although a few recently published studies including one systematic review indicate less morbidity and non-inferior oncological outcomes

[8–11]. However, these series are heterogeneous and various factors, such as inclusion criteria, the performance of lymph node dissection, and the use of adjuvant treatment differ between those studies.

This study seeks to evaluate the safety of RANU in a relatively large cohort with post-operative complications as a primary endpoint and perioperative bleeding, hospital stay, and re-admission within 90 days as secondary endpoints.

Materials and methods

Patients

Medical records of all patients ($n = 166$) who underwent RANU in our institution (Department of Urology, Skåne University Hospital, Malmö, Sweden), from the first procedure was performed in June 2008 until March 2021, with a follow-up time of more than three months were reviewed retrospectively. Information on patient characteristics, peri-operative conditions, and pathology reports were recorded. After the exclusion of twenty patients because of previous cystectomy, simultaneous

other surgical procedures, or other tumour types than UTUC in the pathological report, 146 patients remained for the analyses.

As part of standard practice at our institution, all patients with suspected upper tract urothelial carcinoma are discussed at a regional multi-disciplinary tumour board (MDT) following routine clinical workup with cystoscopy, voided urinary cytology, and CT-urography. Diagnostic ureteroscopy with biopsy was only considered in selected cases after discussion at the MDT, either if the diagnosis was unclear as recommended by EAU guidelines when imaging and cytology are not sufficient for diagnosis and/or risk stratification [2], or if endoscopic treatment was an option, i.e. in low-risk tumours. Those individuals that were diagnosed outside our referral center did not always apply to this diagnostic algorithm, i.e. could have undergone a diagnostic ureteroscopy before the MDT. RANU was the primary treatment for UTUC in the renal pelvis, upper ureter, or lower ureter in case of a non-functioning kidney of clinical stage less than T2 not suitable for nephron-sparing surgery as determined by the MDT [12]. Patients with locally advanced tumours (stage T2 and above) or clinical lymph node metastases underwent a preoperative PET-CT [13] and were considered for neoadjuvant or induction chemotherapy before nephroureterectomy with template-based lymph node dissection through an open approach, as part of a prospective multicenter study (Figure 1) [14]. However, patients unfit for major open surgery with suspicion of locally advanced tumours were in selected cases subjected to RANU.

Surgery

Initially, the Da Vinci Si[®] Surgical System (Intuitive Surgical, Inc.) was only used for the nephrectomy, while open bladder cuff surgery was performed with either an intravesical or extravesical approach through a Gibson or lower midline incision. When the Da Vinci Xi[®] system (Intuitive Surgical, Inc.) became available at our institution in 2011, enabling automatic change of surgical focus and operating table position without re-docking, we gradually shifted toward favoring robot-assisted laparoscopic extravesical bladder cuff

excision. Furthermore, incremental improvements to the procedure have been performed continuously, such as optimizing the position of the patient and the ports as well as optics, with the omission of the 0° lens for bladder cuff surgery allowing exclusive use of 30° optics throughout the procedure. Also, a post-operative percutaneous drainage tube is no longer a part of standard procedure. The urothelial carcinoma robotic surgery program was initiated by one primary surgeon with extensive experience in robotic and laparoscopic surgery. One additional primary surgeon with experience in open and laparoscopic surgery, as well as some robotic experience mainly as an assistant in kidney surgery and radical prostatectomies further developed the program, participating in 113/146 of the surgeries in the current series (AS). In all, seven surgeons were carrying out the procedures with the following volume distribution as primary surgeons; 2, 3, 10, 14, 15, 28, and 74. Eight patients with tumours in the lower ureter and non-functioning kidneys received a template-based unilateral iliac regional lymphadenectomy, of which four were performed robotically. In one additional patient, para-aortal lymph node metastases were found peri-operatively, and thus a robotic template-based para-aortal lymphadenectomy was performed.

Pathological examination

Specimens were staged according to the 2009 TNM classification and tumour grade was assessed according to the WHO 1999 system.

Endpoints

The primary endpoint was complication grade within 90 days according to Clavien Dindo [15]. Secondary endpoints were blood loss, violation of surgical principles (such as the inadvertent opening of the urinary tract or refraining from bladder cuff excision), length of stay, and unplanned readmission to the hospital within 90 days.

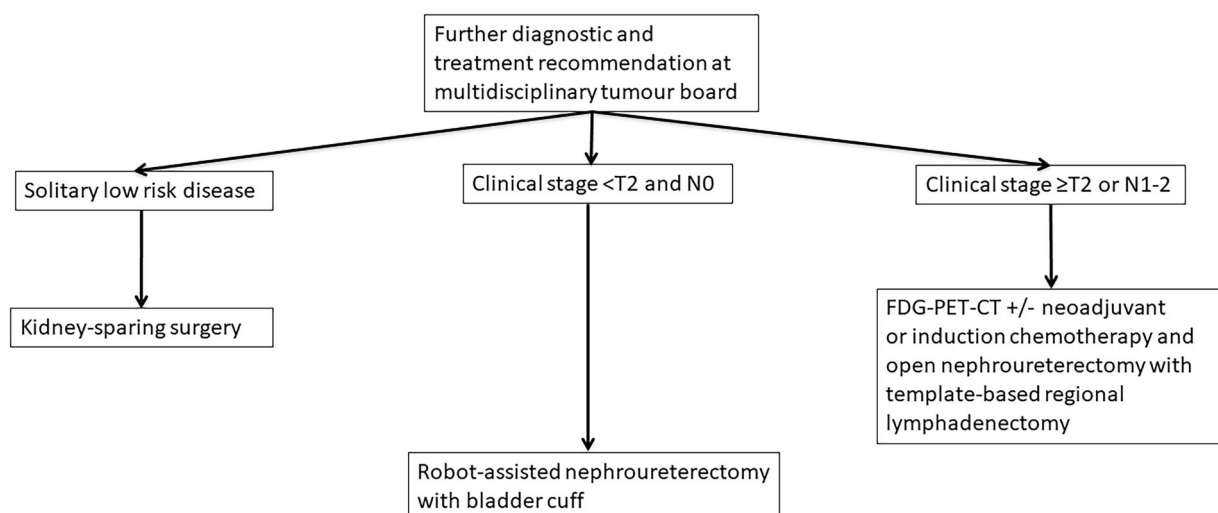


Figure 1. Treatment algorithm when selecting patients with upper tract urothelial carcinoma to different treatment modalities in the current series.

Statistics

Mainly descriptive statistics were applied. Distributions of patient and clinical tumour characteristics as well as peri-operative outcomes were computed using median and IQR (Inter Quartile Range, 25–75% percentile). The difference in the proportion of upstaging among patients with or without pre-operative ureteroscopy was performed with the chi-square test.

The Regional Ethical Review Board in Lund approved the study (Dnr 2013/106 and 2017/480).

Results

Between June 2008 and March 2021, 166 patients were operated on with RANU. After exclusion, 146 individuals remained for analyses (Figure 2). A majority [136/146 (93%)] of the patients were operated on in 2014 and later. The presence of comorbidities as assessed by ASA-score was 3 or higher in 83 (57%) of patients. Patient and clinical tumour characteristics are shown in Table 1. Three patients had tumours that could not be classified pre-operatively by radiology. In two of these patients, CT was performed without contrast because of kidney failure, and in the third patient, there was an abnormal contrast uptake in the kidney parenchyma but no contrast secretion to the renal pelvis. Voided and/or selective urine cytology was benign in 32 patients, showed atypical cells in 55 patients, malignant cells in 43 patients, and was not taken in 16 patients.

In 61/146 (42%) of the patients, a diagnostic ureteroscopy was performed. In 144 patients, no radiological signs of regional or distant tumour manifestations were seen, whereas two patients had radiological regional lymph node metastases. Both patients had severe co-morbidities, excluding them from open surgery with template-based lymph node dissection according to our treatment algorithm. One of these patients underwent a palliative procedure because of bleeding from the

tumour. The other patient with clinical para-aortic lymph node metastases underwent RANU with an intention to perform regional lymph node dissection if feasible without excessive anaesthesiologic risk, although this could not be achieved due to severe intraabdominal obesity.

Peri-operative data are shown in Table 2. No patient had a complication with a Clavien-Dindo grade higher than three, and only one grade three complication was observed in an 85-years old female patient with a BMI of 19 who developed a post-operative pneumothorax that was successfully treated with a thoracic drain. The pneumothorax was considered an anaesthesiologic complication related to ventilation and not a surgical incision into the pleura. Of the grade 2 complications ($n=39$), infection requiring antibiotic treatment was most common, followed by blood transfusion (28 and 5 patients, respectively). Estimated blood loss was 50 ml (IQR=inter quartile range 20–100 ml). The median hospital stay was 6 days (IQR 5–7 days). Twelve patients were re-admitted to the hospital within 90 days, because of urinary tract infection ($n=7$), haematuria ($n=1$), hematoma ($n=1$), suspected cerebral insult ($n=1$), atrial flutter ($n=1$), and psoriasis rash ($n=1$).

Ten patients were subjected to hybrid surgery with an open bladder cuff, mainly in the early study period in patients with advanced tumours in the lower ureter. In 14 patients (10%), excision of the bladder cuff was not performed (Figure 3). This was due to a palliative intent in one patient and to shorten the procedure in four patients with severe co-morbidity and extensive adhesions after previous pelvic surgery. In eight patients, the reason for refraining from bladder cuff excision was not stated in the medical records. Moreover, one patient had residual carcinoma *in situ* of the bladder, although repeated BCG induction therapy, but was considered unfit for simultaneous cystectomy. Therefore, to avoid introducing tumour cells from the bladder into the abdomen a bladder cuff was not excised. During the last three years of the study, bladder cuff excision was

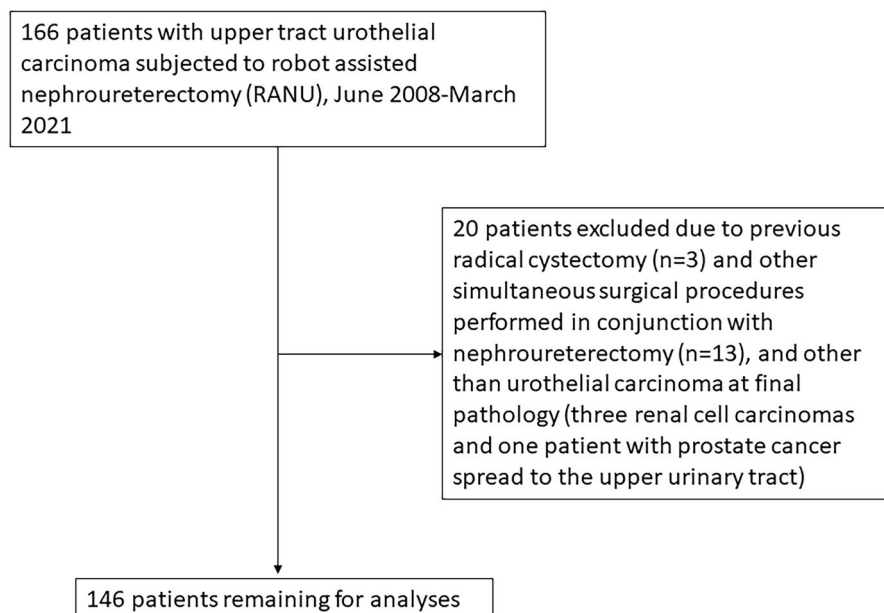


Figure 2. CONSORT-diagram describing the study cohort and exclusions.

Table 1. Patient and clinical tumour characteristics (IQR = inter quartile range and n = numbers) of all upper tract urothelial carcinomas (UTUC) subjected to robot-assisted nephroureterectomy (RANU) at Skåne University Hospital, Malmö, Sweden from June 2008 to March 2021.

n	146
Median age, years	75
IQR	(70–80)
Range	(44–89)
Female, n (%)	88 (60)
Male, n (%)	58 (40)
ASA score n (%)	
1	8 (5.5)
2	55 (38)
3	80 (55)
4	3 (2.1)
Clinical T-stage, n (%)	
≤T1	128 (88)
T2	8 (5.5)
T3	6 (4.1)
Tis	1 (0.7)
Tx	3 (2.1)
Tumour localisation, n (%)	
Renal pelvis	103 (71)
Ureter	31 (21)
Renal pelvis and ureter	12 (8.2)

Table 2. Peri- and post-operative outcomes after robot-assisted nephroureterectomy (IQR = inter quartile range and n = numbers).

Complication grade according to Clavien-Dindo, n (%)	
0	69 (47)
1	37 (25)
2	39 (27)
3	1 (0.7)
4	0
5	0
Median estimated blood loss, ml	50
IQR	(20–100)
Range	(0–500)
Median operation time, min	358
IQR	(301–416)
Range	(193–680)
Median hospital stay, days	6
IQR	(5–7)
Range	(3–16)
Re-admission within 90 d, n (%)	12 (8.2)

performed in 99 of 100 patients, all robotically. The aim of keeping the upper urinary tract intact throughout the procedure was not achieved in eight patients (5.5%) as perforation occurred during distal dissection of the ureter in five patients, perforation of the renal pelvis occurred in two patients and the specimen bag ruptured during extraction in one patient (Figure 3). Of these eight patients, three have died of urothelial cancer, of which all had tumour up-staging from ≤T1 to >T1 in the pathological report. One of the patients had positive margins where the ureter was fixed to the iliac artery. The other two patients relapsed with retroperitoneal lymph node metastasis, with one also having liver metastasis and ascites.

Pathological report data including grade and tumour multiplicity is available in Table 3, however, information on tumour size in the nephroureterectomy specimen was not uniformly reported and is therefore not known. Upstaging from ≤T1 to >T1 occurred in 51 (35%) of patients when comparing clinical and pathological stages in the nephroureterectomy specimen. The proportion of patients with up-staged tumours was similar among those subjected to preoperative ureteroscopy [19/61 (31%)] compared to those who did not [32/85 (38%)]

($p = 0.3$). In one patient, no tumour was found in the nephroureterectomy specimen. Preoperatively, this patient had a benign voided urinary cytology, blood flow from the right ostium at cystoscopy, and a contrast defect in the lower renal pelvis was observed with a corresponding contrast enhancement. This was interpreted as a pelvic tumour in both the primary radiology report and following radiological review during the MDT.

Positive surgical margins were detected in 12 patients (8.2%), four with carcinoma *in situ* and two with T2 in the distal resection margin. One of the patients with a T2 positive margin underwent partly open surgery to achieve an extended bladder cuff but despite this effort, non-radical resection was suspected perioperatively. Additionally, three patients with either stage T3 or T4 in the renal hilus, and three with T3 in the ureter, had positive surgical margins (one had a palliative nephroureterectomy for recurrent haematuria). Four of the patients with positive margins were clinically staged as T2 or higher but were subjected to RANU as they were considered unfit for major surgery including retroperitoneal template-based lymphadenectomy. One patient with a clinical T2 tumour in the most distal part of the ureter adjacent to the ostium and a non-functional kidney underwent RANU with extended bladder cuff excision and radical iliacal lymph node dissection, but the pathological report showed a larger, more advanced tumour with non-radical T3-tumour lengthwise the ureter and metastases in 10/23 lymph nodes with periglandular growth. Of the twelve patients with positive margins, three have died of urothelial cancer and three of other causes. One patient with T3 in the ureter received adjuvant chemotherapy and is disease free 6 years after the operation.

Discussion

Based on this study, with regards to surgical complications, RANU can be considered a safe, minimally invasive procedure with an exceedingly low risk of serious adverse events despite severe comorbidities. To our knowledge, this cohort is the largest to date and more than half of the patients had an ASA score of three or higher. Despite this, only one patient had a major complication within 90 days post-operatively.

The rate of major complications in the present series is similar to that reported in a recent single-center series [8] but smaller than the 90-day major complication rates reported in two contemporary series with patients operated with RANU (2.6 and 6%) [9,10]. The current study is limited by the retrospective study design. Therefore, a recording bias of complications in the medical records could not be ruled out. However, major complications of Clavien-Dindo 3–5 requiring intervention are likely to be recorded in the majority of the cases, considering that the chart review had access to the journal system for all regional hospitals. Furthermore, the continuous development of surgical techniques, such as the introduction of the Xi-platform eliminating the need for re-docking, and the increased use of the 30° lens throughout the procedure, is part of the learning curve of the surgeons in the present series.

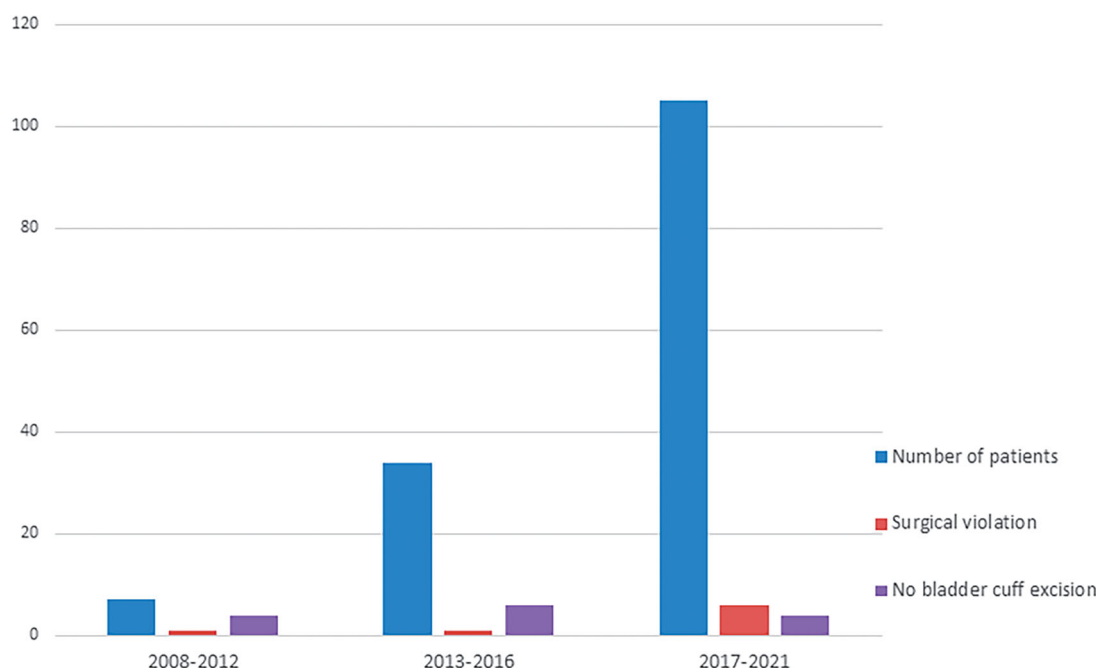


Figure 3. Violation of surgical principles stratified as refraining from bladder cuff excision and inadvertent opening of the upper urinary tract in relation to the number of patients operated with robot-assisted nephroureterectomy over time.

Table 3. Pathological report data from the nephroureterectomy specimen (n = numbers, Tis = tumour *in situ*, tumour grade according to WHO 1999, multiple tumours ≥ 2 tumours).

Pathological report data, n (%)	Stage	Grade 1	Grade 2	Grade 3	Multiple tumours
T0	1 (0.7)	0	0	0	0
Ta	46 (32)	2	33	11	7
T1	30 (21)	1	7	22	6
T2	12 (8.2)	0	2	10	4
T3	51 (35)	0	9	42	8
T4	2 (1.4)	0	0	2	1
Tis	4 (2.7)	0	0	4	n/a
Tumour localisation, n (%)					
Renal pelvis	86 (59)				
Ureter	28 (19)				
Renal pelvis and ureter	31 (21)				
Upstaged from $\leq T1$ to $> T1$, n (%)	51 (35)				
Upstaged per tumour localisation, n (%)					
Renal pelvis ($n = 86$)	31 (36)				
Ureter ($n = 28$)	7 (25)				
Renal pelvis and ureter ($n = 31$)	13 (42)				

Table 4. Stage migration between clinical tumour stage preoperatively (cT) and pathological tumor stage (pT) in the nephroureterectomy specimen.

	pT1 or less	pT2	pT3	pT4	Totals
cT1 or less	80	10	42	0	132
cT2	0	2	5	1	8
cT3	1	0	4	1	6
cT4	0	0	0	0	0
Totals	81	12	51	2	146

Long-term oncological outcomes are needed to elucidate if any oncological risks are associated with the minimally invasive technique compared to open surgery. The risk of port-site metastases in urothelial carcinomas [16,17] and inferior outcomes reported in the only randomized study comparing open and minimally invasive nephroureterectomy [18] are the main reasons for open surgery remaining the gold standard in the treatment of high-risk UTUC according to the European Association of Urology Guidelines [2]. Port-site metastasis or carcinomatosis related to tumour seeding

was not reported in any of the three patients with high-risk UTUC in this study, with peri-operative perforation of the urinary tract, who died of urothelial cancer relapse, but cannot be ruled out in this retrospective setting. The higher proportion of patients where surgical principles were violated during the initial part of the series, such as refraining from bladder cuff excision, is in line with a recent study reporting an association between surgical volume and both 90-day mortality and long-term survival [19]. During the last 5 years, 15% (260/1781) of all patients in Sweden with a newly diagnosed UTUC were discussed in our regional MDT, successively refining the treatment principles in the current patient series. For example, the stratification between perioperative template-based lymphadenectomy in conjunction with nephroureterectomy or RANU without lymph node dissection developed over time at the MDT. Similarly, the use of diagnostic ureteroscopy was reserved for a minority of the patients (61/146) following a discussion of whether further

diagnostic measures were necessary at the MDT [20]. Furthermore, with the advent of level III evidence supporting adjuvant chemotherapy for patients with suspected pathologically invasive or node-positive UTUC [21], we suggest estimation of split renal function be regularly performed preoperatively to determine if a patient will be eligible for chemotherapy following nephroureterectomy. The diversity of treatment options for UTUC makes preoperative decisions increasingly relevant [12].

Pre-operative urine cytology failed to detect malignant cells in 87/130 (67%) patients, although atypical cells were reported in 55/130 (42%) patients but were often difficult to consider unless re-evaluated urine cytology at the MDT, since the severity of atypia was not stated in the primary cytology report. Hopefully, the new Paris classification of urine cytology will improve the diagnostic value in future preoperative evaluations [22]. Our data suggest a 35%-risk of under-staging based on the final pathological analysis, which illustrates the challenge of clinical staging associated with UTUC. Due to the inherent selection of patients with clinical stage T1 or less in the current series, this is in line with 49% sensitivity for the detection of non-organ confined UTUC before nephroureterectomy in a recent report [23]. The risk of under-staging in the present study seems to be even higher in tumours located in both the renal pelvis and ureter, either as a single tumour growing continuously from the pelvis into the ureter or as two separate entities. Thus, we suggest that future studies investigating the association between tumour location both in the renal pelvis and ureter and upstaging are warranted. Selection of an optimal treatment modality from endoscopic ablation, segmental resection, RANU, and nephroureterectomy with template-based lymphadenectomy is hampered by such staging difficulties. These concerns were discussed in a review article by Seisen et al. where grade-based subgroup analyses revealed an increased risk of cancer-specific death in endoscopically treated patients with high-grade UTUC [24]. The increased risk of intravesical bladder recurrences associated with a diagnostic ureteroscopy further complicates the diagnostic considerations in UTUC [25].

Apart from the oncological concerns that are discussed above, the minimally-invasive technique can be safely applied for UTUC either as laparoscopic surgery [26] or RANU, although oncologically sound surgical principles for urothelial carcinoma must be applied. A randomised study comparing open nephroureterectomy and RANU in stage T3-disease with an oncological primary outcome with non-inferiority design in addition to evaluating per- and post-operative complications and patient-reported outcome measures is also lacking. Such a study would address the concerns raised by inferior cancer-specific survival in patients with T3-disease treated with laparoscopic nephroureterectomy compared to open nephroureterectomy [18].

Conclusions

We demonstrate the feasibility and safety of RANU with a low rate of post-operative complications in a cohort

comprised of elderly patients where a large proportion presented with significant comorbidities. The relatively low incidence of UTUC combined with the availability of different diagnostic and treatment modalities, the risk of under-staging, and the surgical learning curve for RANU, all underline the need for high-volume centers for establishing optimal diagnostic and treatment approaches.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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