ORIGINAL PAPER

Perioperative and oncological outcomes of laparoscopic and open radical nephroureterectomy for locally advanced upper tract urothelial carcinoma: a single-center cohort study

Jorge Correia, Gonçalo Mendes, Bernardo Texeira, Mariana Madanelo, Avelino Fraga, Miguel Silva-Ramos

Department of Urology, Centro Hospitalar Universitário do Porto, Porto, Portugal

Corresponding author
Jorge Correia
Porto University
Hospital Center
Department of Urology
Largo do Prof. Abel Salazar
4099-001 Porto, Portugal
phone: +35 191 046 6393
jorgericardocorreia@
gmail.com

Introduction Open radical nephroureterectomy (ONU) is the standard of care for treatment of upper tract urothelial carcinoma (UTUC), but laparoscopic radical nephroureterectomy (LNU) is increasingly being used due to better perioperative outcomes. However, its oncological safety remains controversial, in particular for advanced disease.
We aimed to compare perioperative and oncological outcomes between surgical approaches in locally advanced UTUC (≥pT3 and/or pN+).
Material and methods This study was a retrospective analysis of all 48 patients submitted to radical nephroureterectomy for advanced UTUC between 2006 and 2020 in our center.
Perioperative data were compared between groups. Bladder tumor-free survival (BTFS), metastasis-free survival (MFS) and cancer-specific survival (CSS) were estimated using Kaplan-Meier curves and compared with log-rank p test. Multivariable Cox regression model was used to evaluate their association with surgical approach.
Results Clinical and pathological characteristics were similar between groups. LNU had lower blood loss (p = 0.031), need for transfusion (p = 0.013) and length of hospital stay (p <0.001), with similar operative time (p = 0.860).
LNU was associated with better MFS (hazard ratio [HR]: 0.43, 95% confidence interval [CI] 0.20–0.93, p = 0.033) and CSS (HR: 0.42, 95%CI 0.19–0.94, p = 0.036). Median time to cancer death was 41 months for LNU and 12 months for ONU (log-rank p = 0.029). BTFS was similar between groups (HR: 0.60, 95%CI 0.17–2.11, p = 0.427). On multivariable Cox regression model, surgical approach wasn't significantly associated with MFS (p = 0.202), CSS (p = 0.149) or BTFS (p = 0.586).
Conclusions In our cohort of advanced UTUC, LNU did not result in inferior oncological control compared to ONU. The minimally invasive approach conferred an advantage in perioperative outcomes.

Key Words: laparoscopic nephroureterectomy ‹› open nephroureterectomy ‹› locally advanced ‹› upper tract urothelial carcinoma ‹› oncological outcomes

INTRODUCTION

Urothelial carcinomas of the upper urinary tract (UTUC) are rare and account for only 5–10% of all urothelial tumors [1]. Due to their aggressive biological behavior, approximately two-thirds present with invasive disease at diagnosis [2]. Open radical nephroureterectomy (ONU) with bladder cuff excision is considered the current standard of care for the treatment of non-metastatic UTUC [3]. However, ONU has been associated with significant morbidity and, since the first description by Clayman et al. of laparoscopic radical nephroureterectomy (LNU) [4], this minimally invasive

approach has been accepted as an alternative surgical treatment.

Although LNU has been shown to provide similar oncological outcomes with less morbidity in organ-confined UTUC [5–8], controversy still exists about its oncologic efficacy in locally advanced disease. With the sustained increase in use of laparoscopy, more complex cases of advanced UTUC have been approached by LNU, yet few studies have focused on the surgical choice in this particular disease setting.

The objective of our study was to compare the perioperative outcomes between ONU and LNU in locally advanced UTUC, and to evaluate the association of bladder-only recurrence, metastasis-free survival and disease-specific survival with each surgical approach.

MATERIAL AND METHODS

Study design and patient selection

In this observational retrospective, single-center, cohort study, we evaluated data on all consecutive patients submitted to radical nephouretrectomy for advanced UTUC ($\geq$pT3 and/or pN+) from May 2006 to January 2020. We excluded patients with concurrent or previous history of bladder cancer or contralateral upper urinary tract cancer, or evidence of metastatic disease other than regional lymph nodes. A total of 48 patients with locally advanced UTUC were identified based on histopathological staging, and open and laparoscopic approach was compared between groups. Perioperative and socio-demographic data, clinical and histopathological characteristics and survival outcomes were extracted from medical records.

Preoperative staging and surgical technique

All patients were evaluated preoperatively with chest and urography computed tomography (CT), cystoscopy, urinary cytology and biochemical blood work with creatinine.

Radical nephroureterectomy was performed by open or laparoscopic approach, based on patient and surgeon preference. ONU was performed according to standard criteria by either a midline excision, with dissection of the kidney and adjacent perirenal fat inside Gerota's fascia and the entire length of the ureter and bladder cuff removed en bloc, or by a combined two-incision approach, proceeding with nephrectomy through a flank incision and approaching the distal ureter through a lower quadrant Gibson incision.

LNU was performed in all patients by a transperitoneal approach, with a four-trocar technique. After completing nephrectomy and securing the kidney in an endobag, a Gibson incision was made to manage the distal ureter and bladder cuff and removing the specimen en bloc. No hand-assisted technique was used in any patient. Bladder cuff excision was made by either a conventional open extravesical cuff excision with removal of the entire intramural ureter through the lower quadrant incision, or, in a few cases, by endoscopic resection of the ureteric orifice by the Pluck technique.

A template-based lymph node dissection (LND) was not routinely performed, unless nodal involvement was suspected based on preoperative imaging or intraoperatively palpable enlarged lymph nodes.

From 2013, after publication of the first randomised controlled trial demonstrating the benefit of single post-operative instillation of intravesical chemotherapy in reducing the risk of bladder recurrence [9], intravesical mitomycin C (MMC) was administered in the peri-operative period whenever felt safe.

Pathological evaluation

All surgical specimens were processed according to standard pathological procedures. All lesions were confirmed to be urothelial carcinomas. Tumors were staged according to the 7th edition of Union for International Cancer Control TNM classification, and grading with the 2004/2016 World Health Organization/ International Society of Urological Pathology classification. Tumor location was defined as renal pelvis or ureter. When synchronous lesions were present on both locations, the location of the largest lesion was used. Tumor multifocality was defined as the presence of two or more synchronous lesions, pathologically confirmed to be urothelial carcinoma, in any location of the upper urinary tract. The presence of carcinoma in situ (CIS) or lymphovascular invasion (LVI) was documented and compared between groups.

Follow-up

Patients were followed every 3 months for the first 2 years after surgery, every 6 months thereafter until 5 years, and then yearly. Follow-up consisted of appropriate history and physical examination, cystoscopy and cytology. CT urography for the contralateral upper urinary tract and chest CT were performed every 6 months for the first 2 years, and then yearly. Oncological outcomes comprised bladder tumor-free survival (BTFS), metastasis-free survival (MFS) and cancer-specific survival (CSS). BTFS was de-

fined as recurrences within the bladder only, while MFS concerned recurrences in all sites other than the bladder (recurrence in the tumor bed, contralateral kidney, port-site metastasis, regional lymph nodes or distant metastasis). Survival outcomes were evaluated from the date of surgery to time of event or, when lost to follow-up, the last documented outpatient visit with his physician. Perioperative characteristics analyzed were estimated blood loss, need for transfusion, operative time and length of hospital stay.

While no patient received neoadjuvant chemotherapy, patients could have received adjuvant platinum-based combination chemotherapy based on physician's choice. Platinum-based chemotherapy or immunotherapy were also administered at the time of first metastasis.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and interquartile ranges (IQR) for variables with skewed distributions. Normal distribution was checked using Shapiro-Wilk test or skewness and kurtosis.

Univariate logistic regression was used to investigate the association between baseline patient and pathological characteristics and the surgical approach. Continuous variables were compared with the use of paired Student's t-test or Mann-Whitney test for variables with normal and skewed distribution, respectively. Categorical variables were compared with the use of Fisher's exact test or the chi-square test, as appropriate.

Kaplan-Meier survival curves were calculated for each type of surgical approach and log-rank (Mantel-Cox) test calculated for difference or equivalence between treatment groups, censoring patients without the event at their date of last follow-up. A multivariate Cox proportional hazards regression model was fit with time to bladder recurrence, time to first metastasis and time to cancer death as the dependent variables, and clinical and pathological characteristics as the independent variables.

All reported p values are two-sided, with a p value less than 0.05 indicating statistical significance. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS®), version 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographics and pathological characteristics of the cohort, stratified by surgical approach, are

Table 1. *Patients' demographic, clinical and pathological characteristics according to surgical approach*

	LNU (n = 22)	ONU (n = 26)	p value
Demographic characteristics			
Age (years)	75.0 ±10.9	74.4 ±12.6	0.778
Sex, n (%)			
Male	14 (63.6%)	18 (69.2%)	0.682
Female	8 (36.4%)	8 (30.8%)	
ASA score, n (%)			
<3	8 (36.4%)	10 (38.5%)	0.881
≥3	14 (63.6%)	16 (61.5%)	
GFR (ml/min/1.73 m²)	57.2 ±26.1	57.5 ±22.5	0.970
BMI (kg/m²) [IQR]	27.1 [25.4–29.0]	26.9 [23.2–29.0]	0.281
Clinical and pathological characteristics			
T stage, n (%)			
T3	18 (81.8%)	17 (65.4%)	0.202
T4	4 (18.2%)	9 (34.6%)	
N stage, n (%)			
Nx, N0	19 (86.4%)	23 (88.5%)	1.0
N1, N2	3 (13.6%)	3 (11.5%)	
LVI, n (%)	10 (45.5%)	17 (65.4%)	0.165
CIS, n (%)	3 (13.6%)	3 (11.5%)	1.0
Laterality, n (%)			
Right	11 (50%)	12 (46.2%)	0.790
Left	11 (50%)	14 (53.8%)	
Location, n (%)			
Renal pelvis	16 (72.7%)	23 (88.5%)	0.267
Ureter	6 (27.3%)	3 (11.5%)	
Tumor multifocality, n (%)	4 (18.2%)	6 (23.1%)	0.735
Distal ureter management			
Open extravesical	21 (95.5%)	22 (84.6%)	0.357
Endoscopic	1 (4.5%)	4 (15.4%)	
Post-operative MMC, n (%)	10 (45.5%)	0 (0%)	<0.001
Adjuvant chemotherapy, n (%)	8 (36.4%)	4 (15.4%)	0.094

ASA – American Society of Anesthesiologists; BMI – body mass index; CIS – carcinoma in situ; GFR – glomerular filtration rate; LNU – laparoscopic radical nephroureterectomy; LVI – lymphovascular invasion; MMC – mitomycin C; n – number of patients; ONU – open radical nephroureterectomy; IQR – interquartile range

Table 2. *Perioperative outcomes according to surgical approach*

Operative outcomes	LNU (n = 22)	ONU (n = 26)	p value
Operative time, min [IQR]	148 [110–187]	160 [98–203]	0.860
Estimated blood loss, ml [IQR]	125 [50–475]	500 [200–650]	0.031
Need for transfusion, n (%)	1 (4.5%)	9 (34.6%)	0.013
Length of hospital stay, days [IQR]	4 [4–5]	6 [5–7]	<0.001

LNU – laparoscopic radical nephroureterectomy; ONU – open radical nephroureterectomy; IQR – interquartile range

Table 3. *Multivariable Cox regression model predicting MFS and CSS after radical nephroureterectomy*

	MFS			CSS		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Surgical approach, LNU vs ONU	0.54	0.21–1.39	0.202	0.49	0.18–1.30	0.149
Age, years	0.98	0.94–1.02	0.281	0.98	0.94–1.03	0.390
Sex, male vs female	0.63	0.25–1.60	0.330	0.76	0.29–1.99	0.575
ASA score, ≥3 vs <3	0.72	0.31–1.69	0.453	1.05	0.40–2.78	0.923
T stage, T4 vs T3	2.52	0.98–6.47	0.054	2.88	1.03–8.04	**0.044**
N stage, N1–2 vs Nx–0	3.52	0.97–12.82	0.056	2.55	0.60–10.78	0.203
LVI, yes vs no	1.94	0.74–5.10	0.178	1.46	0.53–4.02	0.469
CIS, yes vs no	1.37	0.34–5.45	0.659	1.61	0.39–6.57	0.510
Location, renal pelvis vs ureter	0.83	0.25–2.72	0.761	0.86	0.25–3.01	0.813
Distal ureter, open extravesical vs endoscopic	0.76	0.16–3.65	0.734	1.32	0.26–6.75	0.738
Adjuvant chemotherapy, yes vs no	0.30	0.10–0.92	**0.035**	0.36	0.11–1.19	0.094

ASA – American Society of Anesthesiologists; CI – confidence interval; CIS – carcinoma in situ; CSS – cancer-specific survival; LNU – laparoscopic radical nephroureterectomy; LVI – lymphovascular invasion; MFS – metastasis-free survival; ONU – open radical nephroureterectomy
p values <0.05 are shown in bold type

shown in Table 1. Overall, 22 (46%) were treated with LNU and 26 (54%) with ONU. The mean age at the time of surgery was 75 years old, and the majority of patients in both groups were male (67% overall). Pathological characteristics were homogeneous between surgical approaches. Most patients had pT3 stage (73% overall) and node-negative disease (88%), with renal pelvis being the most common location of UTUC (81%). Patients submitted to LNU were more likely to have pT3 stage (82% vs 65%) and tumor in the ureter (27% vs 12%) than ONU group; however, those differences were not statistically significant (p = 0.202 and p = 0.267, respectively). The bladder cuff management most commonly used was the open extravesical approach, with slightly more patients in the ONU having endoscopic treatment (15% vs 5%, p = 0.357). All the 10 patients treated with intravesical MMC in the post-operative period had been submitted to LNU (p <0.001), and more patients in this group had also received adjuvant chemotherapy, though without statistical significance (36% vs 15%, p = 0.094). The operative time was similar between the two surgical choices (148 min vs 160 min, p = 0.860), with significant differences in the other perioperative outcomes (Table 2). Patients in the LNU group had significantly lower blood loss (125 ml vs 500 ml, p = 0.031) and need for transfusion (5% vs 35%, p = 0.013), and had their median length of hospital stay shortened by 2 days (p <0.001).

Over a median follow-up of 21 months (IQR 6–54; LNU 34 months and ONU 7 months), 28 metastases occurred: 11 in the LNU group and 17 in the ONU

Table 4. *Multivariable Cox regression model predicting BTFS after radical nephroureterectomy*

	BTFS		
	Hazard ratio	95% CI	p value
Surgical approach, LNU vs ONU	0.63	0.12–3.37	0.586
Age, years	1.07	0.95–1.21	**0.235**
Sex, male vs female	0.35	0.07–1.71	0.197
ASA score, ≥3 vs <3	0.72	0.01–0.69	0.023
T stage, T4 vs T3	0.63	0.04–9.23	0.736
LVI, yes vs no	5.87	0.48–71.89	0.167
CIS, yes vs no	1.55	0.09–27.54	0.766
Location, renal pelvis vs ureter	0.06	0.01–0.53	**0.012**
MMC, yes vs no	0.13	0.01–4.05	0.245

ASA – American Society of Anesthesiologists; BTFS – bladder tumor-free survival; CI – confidence interval; CIS – carcinoma in situ; LNU – laparoscopic radical nephroureterectomy; LVI – lymphovascular invasion; MMC – mitomycin C; ONU – open radical nephroureterectomy
p values <0.05 are shown in bold type

group. There were no recurrences on port site locations or in the contralateral upper tract. Figure 1A shows the probability of freedom from metastasis following nephroureterectomy according to the surgical approach. Median time to metastasis was 39.0 months (95% confidence interval [CI] not evaluable [NE] – NE) in the LNU group and 6.0 months (95% CI 4.3–7.7) in the ONU group (hazard ratio [HR] = 0.43, 95% CI 0.20–0.93, p = 0.033). The 3-year MFS was 55% (95% CI 44–65) for LNU and 35% (95% CI 25–43) for ONU (log-rank p = 0.014). There were 25 deaths due to UTUC
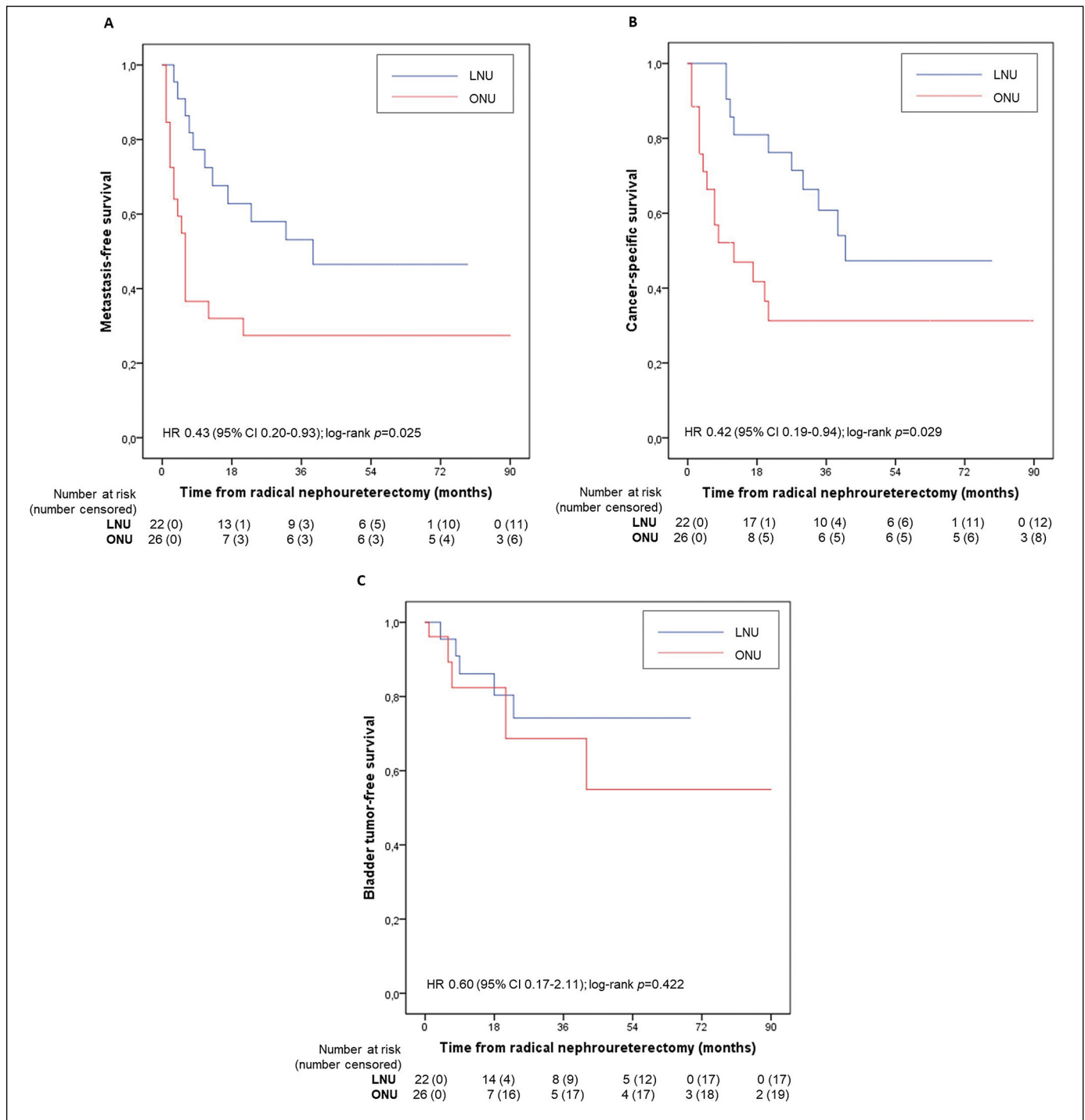
Figure 1. *Kaplan-Meier estimates of metastasis-free survival* **(A)**, *cancer-specific survival* **(B)** *and bladder tumor-free survival* **(C)** *following radical nephroureterectomy, comparing laparoscopic (LNU) and open radical nephroureterectomy (ONU).*

(10 LNU and 15 ONU). Median time to cancer-specific death for LNU was 41.0 months (95% CI NE-NE) and 12.0 months (95% CI NE – 25.9) for ONU, with 3-year CSS of 64% (95% CI 53–75) and 42% (95% CI 32–52) respectively (log-rank p = 0.008) (Figure 1B). The laparoscopic approach had 58% reduction in the relative risk of cancer death (HR = 0.42, 95% CI 0.19–0.94, p = 0.036). On multivariable Cox regression analysis (Table 3), adjusting for clinical and pathological confounders, surgical approach was not significantly associated with MFS (HR 0.54 LNU vs ONU, 95% CI 0.21–1.39, p = 0.202)

or CSS (HR 0.49 LNU vs ONU, 95% CI 0.18–1.30, p = 0.149). The only independent predictor of better MFS was adjuvant chemotherapy (HR 0.30, 95% CI 0.10–0.92, p = 0.035), although it was not significantly associated with CSS (HR 0.36, 95% CI 0.11–1.19, p = 0.094).

There was a similar number of intravesical recurrences in both groups (n = 5), with median time to bladder recurrence not reached in any (HR = 0.60, 95% CI 0.17–2.11, p = 0.427). There were no bladder recurrences in the patients staged as N+ or submitted to endoscopic management of the distal ureter. The 3-year BTFS was 77% (95% CI 67–87) for LNU and 85% (95% CI 70–99) for ONU (log-rank p = 0.639). On multivariable analysis, the type of surgical procedure was not as independent predictor of BTFS (HR = 0.63, 95% CI 0.12–3.37, p = 0.586) (Table 4).

DISCUSSION

Some previous studies have hypothesized that high-pressure peritoneum during LNU and lack of tactile feeling during tumor dissection could lead to increased tumor-cell spillage [10], and inferior oncological outcomes. However, a definitive association between laparoscopy and inferior survival was never proven, and the laparoscopic approach has been increasingly adopted in the surgical treatment of UTUC [11]. Due to the rarity of this disease and the difficulty in accrual for well-design prospective trials, reports about surgical choice are sparse and mainly based on retrospective observational studies. Although several trials have confirmed the oncological equivalence of LNU in localized UTUC, there are conflicting results for the laparoscopic approach in locally advanced disease and controversy still remains.

The perioperative safety of LNU has been well documented [12, 13] and confirmed in a recent meta-analysis [14]. In accordance with these studies, in our unique cohort of advanced UTUC patients, we found that LNU was associated with less blood loss, lower need for transfusion and shorter hospital stay, without an increase in operative time. In agreement with previous retrospective studies, we did not find any significant association between surgical approach and bladder recurrence, metastasis or cancer-specific death in locally advanced UTUC. Additionally, we did not observe any case of port-site metastasis, which is in accordance with the exceedingly low rates described in the literature (0–2.8%) [15].

The study by Simone et al. [16] is the only randomized prospective study to date comparing ONU and LNU. This was a small trial (40 LNU and 40 ONU) in which, interestingly, the sample size was calculated to show a difference in mean time to hospital discharge. In fact, the authors demonstrated the advantages of minimally invasive LNU in perioperative outcomes, allowing less blood loss and length of hospital stay. Moreover, when comparing oncological outcomes, the authors found no difference between the two approaches, with ONU only showing a survival benefit in a sub-analysis of pT3 stage and high-grade tumors. However, the study was likely underpowered to evaluate oncological outcomes in advanced UTUC, as this sub-analysis was based solely on 25 patients with pT3 stage (13 ONU and 12 LNU) and was not matched for other clinical and pathological characteristics. Moreover, while demonstrating the oncological inferiority of LNU in high-grade tumors, LNU is still considered the procedure of choice in this setting, with kidney-sparing strategies being considered as gold standard in low-grade disease. This led in fact the authors to conclude that the oncological outcomes had to be considered preliminary, given that sample size was not determined to evaluate survival benefits. Additionally, patients with regional lymph nodes were excluded, so the decision on choice of surgical approach in pN+ patients is still based entirely on retrospective evidence.

Several studies have confirmed the value of minimally invasive surgery in the management of UTUC and its oncological safety. Indeed, oncological outcomes after radical nephroureterectomy have not changed significantly in the past decades despite a considerable increase in the use of laparoscopy, from <5% before 2000 to approximately 50% in the first decade of this century, making it unlikely that surgical approach is one of the main determinants in recurrence or death [11]. This trend remained true even for non-organ confined disease (>pT3, and/or pN+) who underwent LNU. Favaretto et al. [12] in a retrospective study of 162 patients have shown that recurrences and CSS were similar between groups, even after adjusting for clinical and pathological characteristics on multivariable cox regression analysis. After stratifying patients by pathological stage, they have also demonstrated that MFS was similar in 52 patients with locally advanced disease (≥pT3). Similarly, in a single-center study with 102 patients, Waldert et al. [17] did not find any difference in recurrences between groups, with tumor stage and grade being independent factors for progression and disease-specific death, while type of surgery was not a significant prognosticator. Also, Walton et al. in a multicentric international cohort concluded that LNU was not predictive

of recurrence or death in ≥pT3 or pN+ disease [18]. A multi-institutional national study of the Japanese Urological Association from 348 institutions analyzed data on 379 ONU and 167 LNU with locally advanced disease (pT3/4 and/or pN+) [19] and found no difference in overall survival between groups, concluding that surgical approach was not associated with oncological outcomes. Similarly, in a multicentric study of locally advanced UTUC including 723 patients, Kim et al. [20] found no significant differences in 5-year CSS. To summarize all the available evidence, a recent updated meta-analysis by Piszczek et al. also revealed no significant differences in bladder recurrence, metastasis or death [21]. Furthermore, in a separate analysis for pT3/4 and pN+ populations, the authors observed similar oncological outcomes for both surgical approaches.

One potential limitation when interpreting the results of these retrospective studies is that LND was frequently omitted or only performed in a limited number of patients. We have also only performed LND when pre-operative imaging or intra-operative findings were suspicious. However, it has been demonstrated that template-based LND improves CSS and reduces recurrences [22], even in clinically and pathological node-negative disease [23]. Accordingly, in a study with 214 patients (114 LNU and 100 ONU), all undergoing regional LND, Abe et al. [24] demonstrated that the number of lymph nodes removed, and oncological outcomes were similar between the two approaches. Additionally, when analyzing only patients with pT3/4 disease (n = 83), they observed that oncological outcomes remained equivalent.

In line with previous studies [12, 16, 17], we found no evidence that LNU increases bladder recurrences. O'Brien et al. [9] demonstrated the value of post-operative MMC in the reduction of intravesical recurrences. Although the similar outcomes could be related to the fact that only LNU patients had administration of MMC after surgery, BTFS remained similar after adjustment in our multivariable model. Additionally, the distal ureter management is a crucial surgical step for the prevention of bladder recurrence, with the endoscopic approach being associated with increased recurrences [25]. Although in our cohort, 90% of patients had an open extravesical bladder cuff excision, the endoscopic approach was used slightly more frequently in ONU (15% vs 5%, p = 0.357). However, there were no cases of intravesical recurrence in the endoscopic approach, precluding it from further multivariable analysis and, therefore, no definitive conclusions can be made regarding this aspect. While LNU has

been associated with lower BTFS in some studies, this seems to mainly concern the pure laparoscopic bladder cuff excision, where the incomplete excision of the intramural ureter could lead to increased risk of local recurrence [26]. Conversely, in our study, as in others that used a conventional open extravesical approach after nephrectomy, there was no evidence that laparoscopy resulted in inferior outcomes. We acknowledge several limitations in our study. First, we recognize that our study is limited by its observational design and the results should be interpreted within the limits of retrospective data. Second, this was a single-center study with a small sample size. However, it was aimed to answer specifically the question of laparoscopy safety in advanced UTUC, only including patients with locally advanced disease (≥pT3 and/or pN+), which we believe make comparisons more homogeneous and reliable. Third, due to the long timespan, not all patients were treated with LND, and adjuvant chemotherapy and post-operative MMC, which are currently the standard of care. However, due to the rarity of this disease it is unlikely that prospective studies with a proper sample size will be conducted in the future reflecting all the current standard of care management, as evidence in this disease is rapidly evolving, particularly in the locally advanced stage.

CONCLUSIONS

In this cohort, composed exclusively by locally advanced UTUC, LNU did not result in inferior oncological outcomes in comparison to ONU. LNU demonstrated to be superior in perioperative outcomes due to its minimal invasiveness. Well-controlled prospective multicentric trials are needed to confirm LNU as an effective oncological therapeutic alternative in this setting.

AUTHORS' CONTRIBUTION

Concept and study design: J. Correia, M. Silva-Ramos
Methods and experimental work: J. Correia, G. Mendes, B. Teixeira
Results analysis and conclusions: J. Correia, G. Mendes, B. Teixeira, M. Madanelo, M. Silva-Ramos
Manuscript preparation: J. Correia, A. Fraga, M. Silva-Ramos

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021; 71: 7-33.

2. Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009; 115: 1224-1233.

3. Rouprêt M, Babjuk M, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2020. Eur Urol. 2021; 79: 62-79.

4. Clayman RV, Kavoussi LR, Figenshau RS, Chandhoke PS, Albala DM. Laparoscopic nephroureterectomy: initial clinical case report. J Laparoendosc Surg. 1991; 1: 343-349.

5. Rassweiler JJ, Schulze M, Marrero R, Frede T, Palou Redorta J, Bassi P. Laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: is it better than open surgery? Eur Urol. 2004; 46: 690-697.

6. Capitanio U, Shariat SF, Isbarn H, et al. Comparison of oncologic outcomes for open and laparoscopic nephroureterectomy: a multi-institutional analysis of 1249 cases. Eur Urol. 2009; 56: 1-9.

7. Taweemonkongsap T, Nualyong C, Amornvesukit T, et al. Outcomes of surgical treatment for upper urinary tract transitional cell carcinoma: comparison of retroperitoneoscopic and open nephroureterectomy. World J Surg Oncol. 2008; 6: 3.

8. Moschini M, Zamboni S, Afferi L, et al. Comparing oncological outcomes of laparoscopic vs open radical nephroureterectomy for the treatment of upper tract urothelial carcinoma: A propensity score-matched analysis. Arab J Urol. 2020; 19: 31-36.

9. O'Brien T, Ray E, Singh R, Coker B, Beard R. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). Eur Urol. 2011; 60: 703-710.

10. Micali S, Celia A, Bove P, De Stefani S, Sighinolfi MC, Kavoussi LR, Bianchi G. Tumor seeding in urological laparoscopy: an international survey. J Urol. 2004; 171(6 Pt 1): 2151-2154.

11. Adibi M, Youssef R, Shariat SF, et al. Oncological outcomes after radical nephroureterectomy for upper tract urothelial carcinoma: comparison over the three decades. Int J Urol. 2012; 19: 1060-1066.

12. Favaretto RL, Shariat SF, Chade DC, et al. Comparison between laparoscopic and open radical nephroureterectomy in a contemporary group of patients: are recurrence and disease-specific survival associated with surgical technique? Eur Urol. 2010; 58: 645-651.

13. Afferi L, Abufaraj M, Soria F, et al. A comparison of perioperative outcomes of laparoscopic versus open nephroureterectomy for upper tract urothelial carcinoma: a propensity score matching analysis. Minerva Urol Nephrol. 2022; 74: 49-56.

14. Liu G, Yao Z, Chen G, Li Y, Liang B. Open Nephroureterectomy Compared to Laparoscopic in Upper Urinary Tract Urothelial Carcinoma: A Meta-Analysis. Front Surg. 2021; 8: 729686.

15. Peyronnet B, Seisen T, Dominguez-Escrig JL, et al. Oncological Outcomes of Laparoscopic Nephroureterectomy Versus Open Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: An European Association of Urology Guidelines Systematic Review. Eur Urol Focus. 2019; 5: 205-223.

16. Simone G, Papalia R, Guaglianone S, et al. Laparoscopic versus open nephroureterectomy: perioperative and oncologic outcomes from a randomised prospective study. Eur Urol. 2009; 56: 520-526.

17. Waldert M, Remzi M, Klingler HC, Mueller L, Marberger M. The oncological results of laparoscopic nephroureterectomy for upper urinary tract transitional cell cancer are equal to those of open nephroureterectomy. BJU Int. 2009; 103: 66-70.

18. Walton TJ, Novara G, Matsumoto K, et al. Oncological outcomes after laparoscopic and open radical nephroureterectomy: results from an international cohort. BJU Int. 2011; 108: 406-412.

19. Miyazaki J, Nishiyama H, Fujimoto H, et al. Laparoscopic Versus Open Nephroureterectomy in Muscle-Invasive Upper Tract Urothelial Carcinoma: Subanalysis of the Multi-Institutional National Database of the Japanese Urological Association. J Endourol. 2016; 30: 520-525.

20. Kim SH, Song MK, Ku JH, et al. A retrospective multicenter comparison of conditional cancer-specific survival between laparoscopic and open radical nephroureterectomy in locally advanced upper tract urothelial carcinoma. PLoS One. 2021; 16: e0255965.

21. Piszczek R, Nowak Ł, Krajewski W, et al. Oncological outcomes of laparoscopic versus open nephroureterectomy for the treatment of upper tract urothelial carcinoma: an updated meta-analysis. World J Surg Oncol. 2021; 19: 129.

22. Dominguez-Escrig JL, Peyronnet B, Seisen T, et al. Potential Benefit of Lymph Node Dissection During Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Systematic Review by the European Association of Urology Guidelines Panel on Non-muscle-invasive Bladder Cancer. Eur Urol Focus. 2019; 5: 224-241.

23. Lenis AT, Donin NM, Faiena I, et al. Role of surgical approach on lymph node dissection yield and survival in patients with upper tract urothelial carcinoma. Urol Oncol. 2018; 36: 9.e1-9.e9.

24. Abe T, Kondo T, Harabayashi T, et al. Comparative study of lymph node dissection, and oncological outcomes of laparoscopic and open radical nephroureterectomy for patients with urothelial carcinoma of the upper urinary tract undergoing regional lymph node dissection. Jpn J Clin Oncol. 2018; 48: 1001-1011.

25. Xylinas E, Rink M, Cha EK, et al. Impact of distal ureter management on oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol. 2014; 65: 210-217.

26. Seisen T, Granger B, Colin P, et al. A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. Eur Urol. 2015; 67: 1122-1133. ■