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Comparison Between Laparoscopic and Open Radical Nephroureterectomy in a Contemporary Group of Patients: Are Recurrence and Disease-Specific Survival Associated with Surgical Technique?

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Abstract

Background—Open radical nephroureterectomy (ORN) is the current standard of care for upper tract urothelial carcinoma (UTUC), but laparoscopic radical nephroureterectomy (LRN) is emerging as a minimally invasive alternative. Questions remain regarding the oncologic safety of LRN and its relative equivalence to ORN.

Objective—Our aim was to compare recurrence-free and disease-specific survival between ORN and LRN.

Design, setting, and participants—We retrospectively analyzed data from 324 consecutive patients treated with radical nephroureterectomy (RN) between 1995 and 2008 at a major cancer

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center. Patients with previous invasive bladder cancer or contralateral UTUC were excluded. Descriptive data are provided for 112 patients who underwent ORN from 1995 to 2001 (pre-LRN era). Comparative analyses were restricted to patients who underwent ORN ($n = 109$) or LRN ($n = 53$) from 2002 to 2008. Median follow-up for patients without disease recurrence was 23 mo.

Intervention—All patients underwent RN.

Measurements—Recurrence was categorized as bladder-only recurrence or any recurrence (bladder, contralateral kidney, operative site, regional lymph nodes, or distant metastasis). Recurrence-free probabilities were estimated using Kaplan-Meier methods. A multivariable Cox model was used to evaluate the association between surgical approach and disease recurrence. The probability of disease-specific death was estimated using the cumulative incidence function.

Results and limitations—Clinical and pathologic characteristics were similar for all patients. The recurrence-free probabilities were similar between ORN and LRN (2-yr estimates: 38% and 42%, respectively; $p = 0.9$ by log-rank test). On multivariable analysis, the surgical approach was not significantly associated with disease recurrence (hazard ratio [HR]: 0.88 for LRN vs ORN; 95% confidence interval [CI], 0.57–1.38; $p = 0.6$). There was no significant difference in bladder-only recurrence (HR: 0.78 for LRN vs ORN; 95% CI, 0.46–1.34; $p = 0.4$) or disease-specific mortality ($p = 0.9$). This study is limited by its retrospective nature.

Conclusions—Based on the results of this retrospective study, no evidence indicates that oncologic control is compromised for patients treated with LRN in comparison with ORN.

Keywords

Laparoscopy; Nephroureterectomy; Recurrence; Survival; Transitional cell carcinoma; Urothelial carcinoma

1. Introduction

Open radical nephroureterectomy (ORN) with excision of the distal ureter and bladder cuff is considered the current standard of care for the treatment of nonmetastatic upper tract urothelial carcinoma (UTUC) [1]. However, ORN has been associated with significant morbidity. Laparoscopy has been shown to be equally effective as open surgery for some urologic malignancies while resulting in less perioperative morbidity [2]. In 1991, Clayman et al first described the technique of laparoscopic nephroureterectomy (LRN), and since then it has emerged as an accepted minimally invasive treatment alternative to ORN. However, the oncologic efficacy of LRN and its equivalence to ORN have not been established. UTUC is a biologically aggressive malignancy with a high potential for disease recurrence and eventual death. Some investigators have hypothesized that tumor dissection and high-pressure pneumoperitoneum during LRN are associated with a higher risk of bladder and/or local recurrence as well as port-site metastasis [3]. The differential effect of LRN versus ORN on oncologic outcomes after radical nephroureterectomy (RN) remains controversial. Although several recent studies suggested comparable oncologic results between ORN and LRN in well-selected patients [4–10], others reported a higher risk of intravesical disease recurrence with LRN as compared with ORN [11–13].

We hypothesized that there is no difference in clinical outcomes between ORN and LRN when performed by expert surgeons. To test this hypothesis, we studied the effect of surgical approach on bladder-only recurrence, any recurrence, and disease-specific survival at a single cancer center with genitourinary surgeons and pathologists.

2. Materials and methods

2.1. Patient selection and technique

In this study approved by the institutional review board, we retrospectively reviewed all the prospectively collected data on 324 consecutive patients treated with RN at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1995 and 2008. The first LRN was performed in our institution in 2002. Because the aim of the study was to assess the differential effect of surgical approach on oncologic outcomes, we restricted our analyses to patients who underwent ORN or LRN from 2002 to 2008. Additional descriptive data are provided for the cohort of patients who underwent ORN between 1995 and 2001 (historical control group). We excluded patients who underwent previous or concurrent radical cystectomy ($n = 46$), had prior contralateral UTUC ($n = 4$), or had metastatic UTUC prior to RN ($n = 3$), leaving 274 patients for analysis.

RN was performed by genitourinary surgeons at MSKCC according to the standard criteria, that is, dissection of the kidney with the entire length of the ureter and adjacent segment of the bladder cuff. The indication for lymph node dissection was at the discretion of each surgeon. The hilar and regional lymph nodes adjacent to the ipsilateral great vessel generally were resected, which included paracaval for right side and paraortic for left side above bifurcation. For patients with distal ureter tumors, lymph node dissection was performed including common, external, and internal iliac and obturator nodes. Extended lymphadenectomy (including retrocaval and interaortocaval for right side and interaortocaval for left side) was not routinely performed unless the patient was otherwise suspected of locally advanced disease (pT3/pT4 or node positive). Choice of method (laparoscopic vs open) mainly depended on patient and surgeon preference. Laparoscopic technique was performed by a transperitoneal approach in 35 patients and a retroperitoneal approach in 18. No hand-assisted technique was used in these patients. Bladder cuff excision for LRN patients was done by open technique in 40 patients, laparoscopically in 11, or transurethrally (ie, resection of the ureteric orifice) in 2. During ORN the bladder cuff was resected using a completely extravesical approach.

2.2. Pathologic evaluation

Surgical specimens were processed according to standard pathologic procedures at our institution. All specimens were histologically confirmed to be urothelial carcinomas. UTUC was defined as urothelial carcinoma in the renal pelvis or calices as well as tumors located within the ureter. Tumors were staged according to the 2002 American Joint Committee on Cancer/Union Internationale Contre le Cancer TNM classification. Tumor grading was assessed according to the 1998 World Health Organization/International Society of Urologic Pathology consensus classification [14].

2.3. Follow-up regimen

Patients were followed every 3 mo for the first year, every 4 mo for the second year, every 6 mo from the third through the fifth years, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiograph, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Since 2001, computed tomography (CT) urograms have been the standard imaging modality for evaluating the abdomen and pelvis for urothelial recurrence. Bone scans, chest CT, and magnetic resonance imaging were performed when clinically indicated.

Disease recurrence was defined as any documented recurrence—by radiograph, endoscope, or pathology—in the bladder, contralateral kidney, operative site, regional lymph nodes, or distant metastases. Cause of death was determined by chart review corroborated by death certificate. Most patients who were identified as having died of UTUC had progressive widely disseminated metastases at the time of death.

2.4. Statistical methods

Univariate logistic regression was used to investigate the association between baseline patient characteristics (age, body mass index [BMI], and American Society of Anesthesiologists [ASA] grade) and surgical approach. Multivariable regression models were used to investigate the association between surgical approach and operative outcomes, controlling for the effects of age, BMI, and ASA. Linear regression was used for the outcomes of blood loss and operative time, logistic regression was used for any transfusion, and quantile regression was used for length of stay.

Recurrence-free probabilities were estimated using Kaplan-Meier methods, censoring patients without disease recurrence at their date of last follow-up. Survival time was calculated from the date of RN. A multivariable Cox proportional hazards regression model was used to evaluate the association between surgical approach and disease recurrence, controlling for the effects of age, ASA, pathologic stage and grade, nodal status, pathologic carcinoma in situ, and prior history of bladder cancer. Analyses were repeated for the outcome of bladder-only recurrence, where patients without bladder recurrence were censored at their date of last follow-up. The probability of disease-specific death was estimated using the cumulative incidence function, accounting for the competing risk of death from other causes. All covariates adjusted for in the multivariable models were prespecified before any data analysis. All reported *p* values are two sided, and statistical significance was set at <0.05 . Statistical analyses were conducted using Stata v.11.0 (StataCorp, College Station, TX, USA).

3. Results

In the cohort of 274 patients who underwent RN without prior or concurrent radical cystectomy, 95 (35%) had primary non-muscle-invasive bladder cancer (NMIBC; Table 1). Those with primary bladder cancer were more likely than patients with primary UTUC to have an ASA class of 3 (57% vs 42%); there were no other differences between the two groups.

In comparison with the historical ORN cohort, the contemporary ORN cohort was more likely to have a lymph node dissection (81% vs 50%) and shorter operative times (median: 164 vs 225 min), but a similar blood loss and a higher rate of transfusion (26% vs 16%); median length of hospital stay decreased from 7 to 5 d.

Comparisons between ORN and LRN focused on the contemporary group of patients who underwent surgery between 2002 and 2008: 109 (67%) had ORN and 53 (33%) had LRN (Table 2). Patients in the LRN group were slightly older (median: 73 vs 71 yr of age) and were also more likely to have an ASA class of 3 (58% vs 48%); however, these differences were not statistically significant (both $p = 0.4$). Pathologic outcomes were also similar between the surgical approaches. Although a lymph node dissection was performed less often in LRN patients (70% vs 81%), there was no significant difference in the number of nodes evaluated ($p = 0.9$). A median of eight nodes was evaluated for each group (interquartile range: 4–15 for both groups; range: 1–39 for open and 1–46 for laparoscopic). We observed significant differences in blood loss, operative time, and length of hospital stay between the groups (all $p < 0.04$, on univariate and multivariable analyses). Patients treated with LRN had a significantly longer operative time (mean difference: 86 min; 95% confidence interval [CI], 61–111 min), and less blood loss (mean difference: –141 ml; 95% CI, –237 to –45 ml); a smaller proportion of LRN patients were transfused (absolute risk difference: –9%; 95% CI, –22% to 4%), although this difference was not statistically significant. The median length of stay was shortened by 2 d with laparoscopic surgery (Table 3).

The median follow-up for patients without recurrence was 23 mo. Overall, 99 of 162 patients experienced disease recurrence of any type: 70 in the ORN group and 29 in the LRN group. The most common type of disease recurrence was within the bladder (51 ORN patients and 15 LRN patients). Figure 1 shows the probability of freedom from recurrence following RN, stratified by surgical approach. The recurrence-free probabilities were similar between groups ($p = 0.9$ by log-rank test). The 2-yr probability of freedom from any recurrence was 38% (95% CI, 28–47%) for the ORN and 42% (95% CI, 27–56%) for the LRN group. Figure 2 shows the probability of freedom from recurrence following RN, stratified by pathologic stage; the recurrence-free probabilities were similar between the groups regardless of pathologic stage. On multivariable analysis, surgical approach was not significantly associated with any recurrence (adjusted hazard ratio [HR]: 0.88 for laparoscopic vs open; 95% CI, 0.57–1.38; $p = 0.6$) or bladder-only recurrence (adjusted HR: 0.78; 95% CI, 0.46–1.34; $p = 0.4$; Table 4). The 2-yr probability of freedom from bladder recurrence was 50% (95% CI, 40–60%) for the ORN group and 61% (95% CI, 45–74%) for the LRN group. Exclusion of patients with previous NMIBC did not change the statistical or clinical significance of the findings; the proportion of patients with previous NMIBC was the same for both groups (36%).

In the ORN group, there were 26 deaths from UTUC and 10 deaths from other causes. In the LRN group, there were nine deaths from UTUC and six deaths from other causes. Figure 3 shows the cumulative incidence of disease-specific death, stratified by surgical approach; the cumulative incidence of disease-specific death was similar between groups ($p = 0.9$).

The 2-yr cumulative incidence of disease-specific death was 14% (95% CI, 9–22%) for the ORN group and 18% (95% CI, 8–31%) for the LRN group.

4. Discussion

Some investigators have suggested that tumor manipulation during LRN may lead to increased gravitational migration of tumor cells and eventual implantation in the bladder. In addition, the high-pressure environment required for the laparoscopic procedure could allow tumor cells to spread through pressurized aerosolization [3]. It is known that the development of secondary bladder cancer after primary UTUC can occur in up to 50% of the patients, mainly due to tumor cells seeding [15]. Furthermore, port-site tumor cell implantation has also been reported as a possible concern with LRN [16]. However, these potential risks of LRN are controversial and need testing.

In accordance with many previous studies, we found no statistically significant difference in any recurrence, bladder-only recurrence, and disease-specific death between patients treated with ORN and those with LRN [4–10]. In a single-center study with 140 patients, Greco et al did not find any difference in recurrence rates between ORN and LRN [4]. Also in a single-center study with 102 patients, Waldert et al were unable to show any difference in recurrence rates between groups [6]. Interestingly, in a multicenter study with 1003 patients, Kamihira et al reported that hand-assisted retroperitoneal LRN was an independent risk factor for bladder-only recurrence compared with pure LRN [11]. All cases in our study were pure LRN; therefore we could not address this issue. In a large single-center series analyzing 385 RNs, Huang et al found that LRN had a significantly greater risk of bladder-only recurrence in the univariate analysis; however, multivariable analysis failed to characterize treatment modality as an independent risk factor for recurrence [12]. The only randomized prospective study comparing LRN and ORN did not find any differences concerning bladder-only recurrence. However, the study's conclusions were limited by the small number of patients in each arm and one single surgeon performing both techniques [17].

In agreement with previous retrospective studies [6,8,9], we did not find any significant association between surgical approach and disease-specific death. Our 2-yr cumulative incidence of disease-specific death was 14% for the open group and 18% for the laparoscopic group. In a single-center series of 224 patients, Manabe et al did not find any significant difference in disease-specific survival or overall survival between ORN and LRN [9]. In a multi-institutional study with 1249 patients, Capitanio et al found a difference in the univariate analysis favoring LRN; however, this was explained by a selection bias with regard to tumor size, stage, and other features favoring LRN patients. After adjustment for the effect of tumor stage, no significant difference was found between ORN and LRN [8]. Similarly, in a single-center series of 240 patients, Terakawa et al found a slightly lower disease-specific survival rate in LRN patients with high-grade disease; however, surgical procedure was not an independent prognostic factor in multivariable analysis [18]. Whereas the single-center studies were limited by small sample size, the multicenter studies lacked centralized pathologic evaluation and heterogeneity in disease severity and treatment. Moreover, many studies spanned 20 yr, with changes in disease management. In the only

prospective randomized study published in the literature, the authors found lower rates of metastasis-free survival and cancer-specific survival in patients treated with LRN, after adjusting for pT3 category and high-grade disease; for organ-confined disease, there was no difference between groups [17]. The authors labeled their results preliminary because of the small number of patients.

The present study has several limitations, including its retrospective nature. We included patients with previous NMIBC, which is a known risk factor for bladder recurrence; however, we identified exactly the same proportion of patients with previous bladder tumor in both groups. Nevertheless, the small numbers of LRN patients and the short follow-up limit generalizations of our findings. Despite these limitations our study has some strengths, such as centralized pathologic review and standardized follow-up. Moreover, clinical and pathologic characteristics were similar between the LRN and ORN groups, avoiding the selection bias commonly seen with the introduction of new surgical techniques. Ninety-two percent of patients had bladder cuff control done by the open technique. The homogeneity of this approach avoids confounding when analyzing bladder recurrence rates. Most of our patients had undergone lymphadenectomy, which is not commonly seen in other series of LRN.

5. Conclusions

Based on our retrospective analysis of trained genitourinary oncologic surgeons, no evidence indicates that oncologic control is compromised for patients treated with LRN in comparison with ORN. Despite a well-controlled design, our study lacks a sufficient number of patients treated with LRN as well as a longer follow-up. Well-controlled multi-institutional randomized trials are needed to validate LRN as an oncologically efficacious procedure for patients with UTUC.

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Take-home message

Laparoscopic radical nephroureterectomy does not seem to increase the risk of bladder recurrence, any recurrence, or cancer-specific mortality compared with open radical nephroureterectomy in patients with upper tract urothelial carcinoma.

Fig. 1.
Kaplan-Meier estimates of recurrence-free probabilities following nephroureterectomy, stratified by surgical approach.

Fig. 2. Kaplan-Meier estimates of recurrence-free probabilities following nephroureterectomy comparing open and laparoscopic radical nephroureterectomy, stratified by pathologic stage.

Fig. 3.
Cumulative incidence of disease-specific death following nephroureterectomy, stratified by surgical approach.

Table 1

Patient characteristics according to primary cancer type

	Primary UTUC (<i>n</i> = 179)	Primary bladder cancer (<i>n</i> = 95)
Baseline characteristics		
Age at surgery, yr (IQR)	72 (63–77)	70 (65–77)
BMI (IQR)	27 (24–30)	27 (24–30)
ASA score, <i>n</i> (%)		
1	6 (3)	1 (1)
2	97 (54)	40 (42)
3	75 (42)	54 (57)
Pathologic characteristics		
Pathologic stage, <i>n</i> (%)		
pT1	90 (50)	49 (52)
pT2	37 (21)	21 (22)
pT3	52 (29)	25 (26)
Pathologic grade, <i>n</i> (%)		
Low	39 (22)	20 (21)
High	137 (77)	71 (76)
NA/Unknown	3 (2)	4 (4)
Nodal status, <i>n</i> (%)		
Not done (NX)	60 (34)	33 (35)
Negative (N0)	101 (56)	49 (52)
Positive (N1, N2)	18 (10)	13 (14)
Pathologic CIS, <i>n</i> (%)	44 (25)	31 (33)

ASA = American Society of Anesthesiologists; BMI = body mass index; CIS = carcinoma in situ; IQR = interquartile range; NA = not applicable; UTUC = upper tract urothelial carcinoma.

Table 2

Patient characteristics according to surgical approach

	Historical cohort: surgery, 1995–2001	Contemporary cohort: surgery, 2002–2008		<i>p</i> value*
	All ORN (<i>n</i> = 112)	ORN (<i>n</i> = 109)	LRN (<i>n</i> = 53)	
Baseline characteristics				
Age at surgery, yr (IQR)	71 (63–77)	71 (64–76)	73 (67–78)	0.5
BMI (IQR)	27 (24–30)	27 (24–29)	27 (25–31)	0.6
ASA grade, <i>n</i> (%)				0.4
1	3 (3)	3 (3)	1 (2)	
2	62 (56)	54 (50)	21 (40)	
3	46 (41)	52 (48)	31 (58)	
Prior history of bladder cancer, <i>n</i> (%)	37 (33)	39 (36)	19 (36)	1.0
Pathologic characteristics				
Pathologic stage, <i>n</i> (%)				–
pT1	57 (51)	56 (51)	26 (49)	
pT2	30 (27)	18 (17)	10 (19)	
pT3	25 (22)	35 (32)	17 (32)	
Pathologic grade, <i>n</i> (%)				–
Low	41 (37)	13 (12)	5 (9)	
High	68 (61)	94 (86)	46 (87)	
NA/Unknown	3 (3)	2 (2)	2 (4)	
Nodal status, <i>n</i> (%)				–
Not done (NX)	56 (50)	21 (19)	16 (30)	
Negative (N0)	49 (44)	71 (65)	30 (57)	
Positive (N1, N2)	7 (6)	17 (16)	7 (13)	
Pathologic CIS, <i>n</i> (%)	28 (25)	32 (29)	15 (28)	–

ASA = American Society of Anesthesiologists; BMI = body mass index; CIS = carcinoma in situ; IQR = interquartile range; LRN = laparoscopic radical nephroureterectomy; NA = not applicable; ORN = open radical nephroureterectomy.

* *p* values are given to compare characteristics of patients receiving open or laparoscopic surgery from 2002 to 2008.

Table 3

Operative characteristics according to surgical approach

	Historical cohort: Surgery, 1995–2001	Contemporary cohort: Surgery, 2002–2008		Contemporary LRN vs contemporary ORN cohort
	All ORN (<i>n</i> = 112)	ORN (<i>n</i> = 109)	LRN (<i>n</i> = 53)	
				Mean difference (95% CI)
				<i>p</i> value*
Operative outcomes				
Estimated blood loss, ml (IQR)	250 (175–438)	250 (200–400)	200 (150–300)	–141 (–237 to –45)
Operative time, min (IQR)	225 (173–300)	164 (126–210)	265 (230–310)	86 (61–111)
Transfused, <i>n</i> (%)	18 (16)	28 (26)	9 (17)	–9 (–22 to 4)
Length of hospital stay, d (IQR)	7 (5–8)	5 (4–6)	3 (3–4)	–2 (–4 to –0.2) [‡]

CI = confidence interval; IQR = interquartile range; LRN = laparoscopic radical nephroureterectomy; ORN = open radical nephroureterectomy.

* Adjusted for age, body mass index, and American Society of Anesthesiologists grade.

[†] Difference in median.

Table 4

Multivariable Cox regression models predicting disease recurrence (any recurrence and bladder-only recurrence) in patients treated with radical nephroureterectomy for upper tract urothelial carcinoma

	Any recurrence			Bladder-only recurrence		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Age, per 10 yr	0.87	0.72–1.05	0.15	0.84	0.68–1.04	0.11
ASA						
<2	Reference	Reference		Reference	Reference	
2	1.03	0.67–1.57	0.9	0.86	0.53–1.41	0.6
Pathologic stage						
pT1	Reference	Reference	0.002	Reference	Reference	0.6
pT2	1.45	0.82–2.56		1.39	0.75–2.57	
pT3	2.31	1.44–3.70		1.06	0.58–1.93	
Pathologic grade						
Low	Reference	Reference		Reference	Reference	
High	1.39	0.74–2.62	0.3	1.27	0.67–2.42	0.5
Nodal status						
Not done	Reference	Reference	0.3	Reference	Reference	0.04
Negative	0.66	0.40–1.10		0.65	0.37–1.14	
Positive	0.80	0.40–1.63		0.25	0.08–0.74	
Pathologic CIS						
No	Reference	Reference		Reference	Reference	
Yes	1.00	0.64–1.57	0.99	0.93	0.55–1.57	0.8
Previous bladder cancer						
No	Reference	Reference		Reference	Reference	
Yes	1.04	0.68–1.58	0.9	1.18	0.72–1.91	0.5
Surgical approach						
ORN	Reference	Reference		Reference	Reference	
LRN	0.88	0.57–1.38	0.6	0.78	0.46–1.34	0.4

ASA = American Society of Anesthesiologists; CI = confidence interval; CIS = carcinoma in situ; LRN = laparoscopic radical nephroureterectomy; ORN = open radical nephroureterectomy.