Oncology: Renal/Upper Tract/Bladder

ONCOLOGICAL CONTROL FOLLOWING LAPAROSCOPIC NEPHROURETERECTOMY: 7-YEAR OUTCOME

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ABSTRACT

Purpose: Proof of the oncological safety of laparoscopic nephroureterectomy (LNU) relies on truly long-term outcome being at least equivalent to that of open surgery. We compared the long-term oncological outcome of laparoscopic versus open nephroureterectomy (ONU) in patients with upper tract transitional cell carcinoma (TCC).

Materials and Methods: Between April 1992 and January 1999, 26 LNUs and 42 ONUs were performed at our hospital for suspected upper tract TCC. Hospital medical records were retrospectively reviewed to assess preoperative staging, pathology and followup.

Results: There were 4 patients excluded from study (1 who underwent LNU and 3 ONU) since the histological diagnosis was other than TCC. Median followup for the laparoscopic and open groups was 101 and 96 months, respectively. There was local recurrence in 2 patients (8%) after LNU and in 6 patients (15.4%, p = 0.3) after ONU. TCC recurred in the contralateral kidney or ureter in 2 LNU cases (8%) and 1 ONU case (2.6%, p = 0.3). There was bladder recurrence in 7 patients (28%) following LNU compared with 15 patients (42%, p = 0.2) after open nephroureterectomy. The 1 and 5-year metastasis-free survival rates were 80% and 72% for LNU compared with 87.2% and 82.1% for ONU (p = 0.33 and 0.26). Upper tract tumor grade and stage influenced the incidence of metastatic and contralateral disease, but not the incidence of local or bladder recurrence.

Conclusions: In the surgical management of upper tract TCC, the laparoscopic approach does not affect long-term oncological control. Tumor stage and grade are important prognostic factors in the development of metastases and cancer specific mortality.

KEY WORDS: laparoscopy; carcinoma, transitional cell; kidney, ureter

Laparoscopic nephrectomy has gained wide acceptance in the management of benign surgical diseases of the kidney and renal cell carcinoma. The aggressive nature of upper tract transitional cell carcinoma (TCC) and the high risk of recurrence have caused many to be reluctant to treat this disease laparoscopically. To date the reported worldwide experience with laparoscopic radical nephroureterectomy is limited, particularly with respect to long-term cancer control.[1] Upper tract TCC has a high propensity to recur in the bladder and with systemic metastases. Proof of the oncological safety of laparoscopic nephroureterectomy relies upon truly long-term outcome being at least equivalent to that of open surgery. We report on the 7-year median followup of laparoscopic nephroureterectomy and compare its oncological outcome with that of open nephroureterectomy.

MATERIALS AND METHODS

Patients undergoing open or laparoscopic nephroureterectomy for suspected upper tract transitional cell carcinoma between April 1992 and January 1999 were included in the study. Patients with tumors of the upper ureter or renal pelvis and calices had initial transurethral resection of the intramural ureter. Laparoscopic nephroureterectomy was always performed using a transperitoneal approach. The initial laparoscopic dissection in patients with tumors in the renal pelvis or upper ureter was similar to that of a routine laparoscopic radical nephrectomy, with early identification of the ureter which was clipped in continuity with Ligaclips (Ethicon Endo-surgery, Inc., Cincinnati, Ohio) before mobilization of the kidney. The ureter was mobilized into the pelvis beyond the bifurcation of the common iliac artery and down to the resected end at the bladder wall. The specimen was then removed intact in an impermeable laparoscopic catchment bag. Patients with tumors of the distal ureter were treated with initial laparoscopic mobilization of the kidney and ureter into the pelvis, followed by formal open cystotomy, and combined extra and transvesical dissection to mobilize the distal ureter and remove the kidney, ureter and bladder cuff en bloc. Patients undergoing open nephroureterectomy had preliminary mobilization of the kidney and proximal ureter followed by extra or transvesical mobilization of the lower ureter and bladder cuff, depending on tumor location and surgeon preference.

Hospital medical records were retrospectively reviewed to assess preoperative staging, pathology and followup. Length of followup was determined by the time between surgery and most recent surveillance, either flexible cystoscopy or upper

tract imaging. Statistical analysis was performed using SPSS version 11.0 (SPSS, Inc., Chicago, Illinois). Continuous variables were compared with the independent t test (parametric data) and the Mann-Whitney U test (nonparametric data). Dichotomous variables were analyzed using Pearson's chi-square test and Fisher's exact t test.

RESULTS

A total of 26 laparoscopic and 42 open nephroureterectomies were performed. There were 2 patients in the open nephroureterectomy (ONU) group and 1 in the laparoscopic nephrourectomy (LNU) group who had incomplete ureterectomy. In addition, 4 patients were excluded (1 LNU and 3 ONU) from study since pathological diagnosis was not TCC. Pathology revealed patients with inverted papilloma and ureteritis cystica in the ONU group. In addition, in 1 patient undergoing ONU on the basis of a filling defect on excretory urography no tumor was identified. One patient in the LNU group had a renal cell carcinoma. Another patient in the LNU group had no tumor identified on histopathological sectioning, however she had previous biopsy proven TCC treated ureteroscopically, and subsequently recurrence developed in the bladder and contralateral upper tract. This case was included in the cohort, leaving 25 LNU and 39 ONU cases available for comparison. Four patients (15%) in the laparoscopic group required open conversion with tumors of the renal pelvis or upper calix, and pathology revealed a renal cell carcinoma (in a patient excluded from study), G2 Ta, G3 T3 and G3 T1 tumors. Conversion occurred after preliminary transurethral resection of the ureteral orifice and laparoscopic mobilization of the upper ureter, lower pole of the kidney and pedicle, and so patients were analyzed on an intent to treat basis in the laparoscopic group.

There were a larger number of ureteral tumors treated in the open nephroureterectomy group (table 1) and otherwise patient features were comparable between the 2 groups. Pathological features are summarized in table 2. One patient in the ONU group had positive lymph nodes at surgery and died of metastatic disease 12 months later.

Median followup for the laparoscopic and open groups was 100.5 (range 41 to 138) and 96 (range 46 to 136) months, respectively. Followup was complete for laparoscopic and open nephroureterectomy groups. There was local recurrence in 1 patient (4%) following LNU, a G3 pT3 tumor of the renal pelvis in the renal bed as well as systemic metastases to the liver and lungs. There were 6 local recurrences in the ONU group (15%, p = 0.32), which included patients whose initial tumors were in the renal pelvis (3), upper ureter (2) and lower ureter (1). All of these patients had high grade invasive disease except 2 with G1 pTa tumors who had an incomplete ureterectomy and recurrence in the lower ureter. Both patients were cured surgically, in contrast with the other patients with local recurrence who all died of TCC. There were no port site or wound recurrences. Metastatic disease occurred in 7 patients (28% LNU and 18% ONU, p = 0.26).

	No. Laparoscopic (%)	No. Open (%)	p Value
Grade:			
1	5 (20)	4 (10)	
2	6 (24)	20 (51)	0.22
3	13 (52)	15 (38)	
Stage:			
a	10 (40)	21 (54)	
1	7 (28)	7 (18)	0.11
2	4 (16)	2 (5)	
3	3 (12)*	9 (23)	
Associated ca in situ	3 (12)	6 (15)	0.53

TABLE 2. *Pathological features*

* There was 1 patient in the LNU group with biopsy proven T0 lesion.

There were 2 patients (8%) with recurrence in the contralateral upper tract following LNU compared with 1 after ONU in whom liver metastases also developed (3%, p = 0.34). Upper tract tumor grade and stage influenced the incidence of contralateral disease. If the 2 patients in the ONU group with pTa tumors who had recurrence in the ureteral stump after incomplete ureterectomy were excluded from study, then advanced stage is also associated with increased risk of local recurrence (p = 0.02).

After LNU there was bladder recurrence in 7 patients (28%). In the ONU group 3 patients had previous or simultaneous cystectomy, with bladder recurrence affecting 15 of the remaining 36 patients (42%, p = 0.21). There were 7 patients (2 LNU, 5 ONU) in whom recurrence developed in their native bladder and who underwent previous treatment for bladder TCC before nephroureterectomy. Bladder recurrence tended to be of similar grade but lower stage than the upper tract lesion. All bladder recurrence was within 3 years of nephroureterectomy and 91% was within 2 years. Mitomycin bladder instillations prevented further recurrence in 8 of 12 patients (67%) while a further 3 required cystectomy for invasive tumor or recurrent carcinoma in situ. There were no factors identified which increased the risk of bladder recurrence.

Additional treatment was given to 11 (44%) and 16 (40%) patients after LNU and ONU, respectively. This treatment included intravesical instillations for bladder recurrence, radiotherapy, cystectomy, chemotherapy, nephrostomy drainage, ureteroscopic laser ablation for contralateral recurrence and small bowel bypass for obstructing peritoneal metastases.

The 1-year metastasis-free survival rates were 80% and 87.2% for LNU and ONU, respectively (p = 0.33). Disease specific and overall survival at median 7 years of followup for LNU was 72% and 56%, compared with 82% and 59% for ONU (p = 0.26 and 0.51). Median predicted survival for laparoscopic and open nephroureterectomy was the same at 79 months (95% CI 61, 97 and 64, 95, respectively, Kaplan-Meier p = 0.982, see figure). Advanced tumor stage and grade increased the risk of metastases and death (table 3).

TABLE 1. *Preoperative data*

	Laparoscopic		Open		p Value
No. pts	25		40		–
No. male/female	12/13		24/16		0.31
Mean age (range)	69.5 (42–92)		69.4 (43–88)		0.87
Operative side (lt/rt)	15/10		18/21		0.32
Mean mm tumor size (range):					
Pelvis/calices	37	(10–70)	34	(12–70)	0.67
Ureter	21	(3–40)	30	(13–50)	0.42
No. tumor sites (%):					
Renal pelvis/calices	18	(72)	14	(36)	
Proximal ureter	2	(8)	5	(13)	0.026
Distal ureter	3	(12)	17	(44)	
Multifocal	1	(4)*	3	(7)	

* There was 1 patient in the LNU group with biopsy proven T0 lesion.
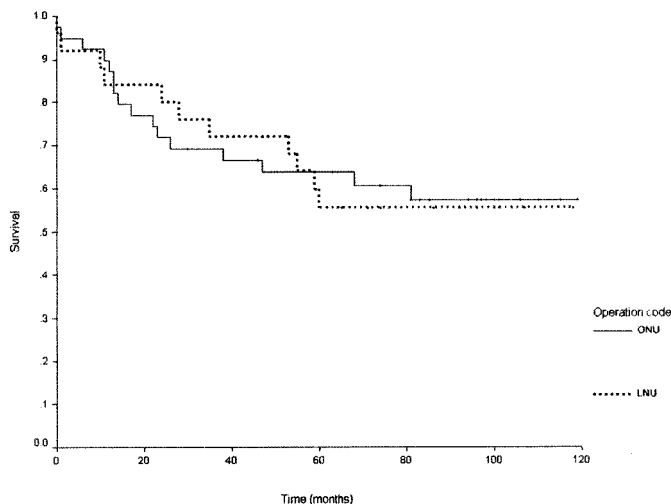
Survival following laparoscopic and open nephroureterectomy

TABLE 3. *Survival by tumor grade and stage*

Tumor Grade/Stage	1-Yr Metastasis-Free Survival (%)	5-Yr Metastasis-Free Survival (%)	Overall Survival (%)
G1	100	89	67
G2	100	100	69
G3	64	54	43
pTa	100	97	71
pT1	86	86	64
pT2	83	50	50
pT3	42	33	17

DISCUSSION

The Washington University group described the first LNU in 1991.[2] Subsequent experience with the technique has demonstrated a number of advantages compared to the open technique with decreased postoperative pain, lower transfusion requirement, shorter hospital stay and earlier convalescence.[3–6] The aggressive nature of TCC and its uncommon incidence has delayed the widespread acceptance of laparoscopic techniques in the surgical management of upper tract TCC. As a result there are few publications regarding truly long-term outcome following laparoscopic nephroureterectomy. Hattori et al recently published 5-year metastasis-free survival rates of 87% following retroperitoneoscopic nephroureterectomy,[1] but outcome in other studies is either actuarial or too short to confirm the oncological safety of LNU.[7–9]

We acknowledge that there were more ureteral tumors, particularly lower ureteral, removed with ONU in the study. This reflects referral patterns as the laparoscopic procedure evolved. This should not affect comparison of local recurrence rates between LNU and ONU since the rate of local recurrence was not influenced by primary tumor site in our study. Indeed, 2 of the tumors that recurred locally did so because of incomplete ureterectomy in the ONU group. More importantly the LNU and ONU groups were equivalent with respect to the grade and stage of tumor removed, which was shown to affect development of metastases and survival.

Operative technique for laparoscopic nephroureterectomy is best considered in terms of 2 separate procedures, nephrectomy and distal ureterectomy. Approach to the kidney and upper ureter follows standard technique as practiced for laparoscopic radical nephrectomy for renal cell carcinoma,[10] although the ureter is identified and clipped before extensive renal mobilization. Some centers prefer the retroperitoneoscopic approach for nephroureterectomy.[1,8] However, most would agree that the transperitoneal approach affords more working space and, thus, better access. A number of different approaches to the distal ureter have been described with varying degrees of oncological safety.[11] A number of cases of local recurrence have been described with use of the "pluck" technique, and presumably this occurs due to seeding at the point where the nonoccluded ureter and adjacent bladder cuff are dismembered from the bladder.[12–14] While using minimally invasive techniques is commendable in an effort to decrease postoperative morbidity, they should never be used at the expense of well established oncological principles. We tailor the approach to the ureter according to the level of the tumor, with distal lesions being removed with an open technique. The low rate of local recurrence in the current study justifies this policy.

Patients undergoing LNU who required open conversion were analyzed on an intent to treat basis given that the initial surgical approach, particularly with respect to management of the lower ureter, was thought most likely to affect oncological outcome independent of tumor factors. This analysis could be criticized as overlooking some oncological advantage conveyed to patients who required open conversion. However, of the 3 patients included in the LNU group for comparison, 1 died of local and metastatic recurrence, bladder recurrence developed in 1 and the last patient died of unrelated disease. As already noted there were no cases of wound recurrence in patients undergoing LNU or ONU. Therefore, it seems highly unlikely that any oncological benefit is derived from open conversion.

Surprisingly, tumor stage and grade did not appear to affect the rate of local recurrence. This was probably due to the effect of incomplete ureterectomy, with low grade and stage lesions recurring in the ureteral stump. When the data were reanalyzed with these patients excluded from study, higher stage did predict local recurrence. Other studies have defined local treatment failure as occurring in patients who have undergone radical extirpative surgery alone, with similarly low rates of local disease associated with advanced stage on multivariate analysis.[15] No port site metastases occurred in the laparoscopic group, which can be attributed to the use of a robust laparoscopic catchment bag (15 mm EndoCatch, Auto Suture, Tyco, Norwalk, Connecticut), good trocar fixation and avoiding specimen morcellation.[16]

The incidence of metastases and bladder recurrence falls within the expected range[17] and was equivalent between ONU and LNU. The incidence of contralateral disease was higher than expected with LNU, but was not significantly different compared to ONU. Advanced stage and grade were associated with an increased risk of contralateral tumor, underlining the importance of upper tract surveillance in these patients. Predictors of bladder recurrence could not be identified. Our survival data confirm that most deaths occur due to metastases, reflecting the aggressive nature of the disease. Advanced stage and grade are confirmed as predictors of metastatic recurrence and death.[18]

CONCLUSIONS

Laparoscopic nephroureterectomy has well established advantages compared to the open approach in terms of decreased blood loss, fewer complications, and shorter hospital stay and convalescence. Given that long-term oncological control is equivalent to open surgery, laparoscopic nephroureterectomy for pelvic or upper ureteral tumors, or laparoscopically assisted nephroureterectomy for lower ureteral tumors should be considered a suitable option for upper tract transitional cell carcinoma.

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