

Laparoscopic vs open radical nephroureterectomy for upper urinary tract urothelial cancer: oncological outcomes and 5-year follow-up

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OBJECTIVE

To compare the oncological outcomes of laparoscopic radical nephroureterectomy (LNU) vs open NU (ONU) for upper urinary tract transitional cell carcinoma (TCC).

PATIENTS AND METHODS

Between July 1999 and January 2003, we performed 70 LNUs and 70 ONUs for TCC of the upper urinary tract. ONU was reserved for patients with previous abdominal surgery

or with severe cardiac and/or pulmonary problems. Demographic data, tumour staging and histological grading and rates of metastasis were recorded and compared.

RESULTS

For LNU and ONU the mean operative durations were 240 min and 190 min, respectively. The definitive pathology showed a high incidence of tumour stage pT2 G2 in both LNU and ONU groups. The median follow-up was 60 months. In the LNU group, the 5-year disease-free survival (DFS) was 75%: 100% for pTa, 88% for pT1, 78% for pT2, and 35% for pT3 ($P < 0.001$). In

the ONU group, the 5-year DFS was 73% (LNU vs ONU, $P = 0.037$): 100% for pTa, 89% for pT1, 75% for pT2 and 31% for pT3 ($P < 0.001$).

CONCLUSION

The results of our long-term controlled study support the use of LNU as an effective alternative to ONU in the therapy of upper urinary tract urothelial cancer.

KEYWORDS

upper urinary tract urothelial cancer, laparoscopy, port-site metastasis, oncological outcomes

INTRODUCTION

During the last 10 years, laparoscopy has gained widespread acceptance among urologists, and has been applied in the treatment of most urological pathologies.

The first laparoscopic nephroureterectomy (LNU) was performed in 1991 by Clayman *et al.* [1] on an 82-year-old man with low-grade TCC of the upper urinary tract. Subsequently, numerous published studies [2–20] have reported oncological and functional outcomes after LNU and open NU (ONU) for urothelial carcinoma of the upper urinary tract, with attention to operative duration, estimated blood loss, need for transfusion, complications, pathological stage and grade of the tumour, and incidence of tumour recurrence.

Nevertheless, the question of whether LNU is oncologically safe in the management of

upper urinary tract urothelial carcinoma remains unanswered. In the present study, we attempted to answer this question, reporting our experience and 5-year follow-up in 70 patients who underwent LNU, compared with 70 patients who underwent ONU, for urothelial cancer of the upper urinary tract.

PATIENTS AND METHODS

In July 1999, we initiated a study to evaluate the feasibility of LNU and its outcomes in comparison with ONU. Between July 1999 and January 2003, we performed 70 LNUs and 70 ONUs for urothelial carcinoma of the upper urinary tract. Preoperatively, all the patients underwent an IVU, CT, and cystoscopy with cytology. Ureterorenoscopy with biopsy and cytology was performed in cases of diagnostic doubt. The ONU was reserved for patients with previous abdominal surgery or with severe cardiac and/or pulmonary problems. Demographic data,

tumour stage, histological grade and rate of metastases, were recorded and compared. All surgical procedures were performed by a single surgeon (P.F.) who has had extensive experience with both LNU and ONU, thus reducing the 'learning-curve' effect in this study.

The median follow-up was 60 months in both groups. Follow-up was calculated from the date of surgery to the date of the most recent documented examination. No patient was lost to follow-up. For all patients, a physical examination and cystoscopy were performed every 3 months in the first year, every 6 months in the second and in the third years, and yearly thereafter. Urine cytology was performed on the same schedule, but only for high-grade lesions. Imaging (IVU or retrograde pyelography if the patient was not a candidate for injection of contrast medium) of the contralateral kidney was performed yearly, while CT or MRI was performed every

6 months in the first and second years, and yearly in the third, fourth and fifth years. A bone scan was performed only in patients with symptoms of bone pain.

Data were expressed as mean (percentage and range if appropriated); statistical significance was accepted at $P < 0.05$. Survival rates were calculated by the Kaplan–Meier method. Comparisons between groups were made using either one-way ANOVA with Bonferroni *post hoc* test or Wilcoxon signed-rank test. Differences between the groups for every other variable were determined by Student's *t*-test.

LNU TECHNIQUE

After the induction of general anaesthesia, a nasogastric tube and transurethral catheter were placed to decompress the stomach and bladder. The patient was secured to the operating table in a full-flank position. A transperitoneal approach was used in all patients. A Veress needle was inserted peri-umbilically to establish a CO₂ pneumoperitoneum. With an initial intra-abdominal pressure of 12–15 mmHg, a 12-mm trocar was placed supra-umbilically after removal of the Veress needle. An endoscopic 0° camera was introduced and after inspection of the abdominal cavity three additional trocars were inserted under direct vision: two 12-mm trocars in the ipsilateral mid-clavicular line and a 10-mm trocar between the xyphoid and the first port. Occasionally, a fifth trocar (5-mm) was used in the anterior axillary line below the umbilicus. The intra-abdominal pressure was lowered to 10–12 mmHg and maintained at this level. The peritoneum was incised along the Toltdt's line using electro-surgical scissors and grasping forceps. After mobilization of the colon, the ureter was identified above its crossover of the iliac vessels and clipped without dissection to prevent urine spillage. The renal hilum was exposed and the renal vessels were carefully dissected. The renal artery was ligated between two clips and the renal vein was secured with a vascular stapler or, when small, divided between clips. Dissection of the remaining fat and connective tissue was continued for complete mobilization of the kidney. Then the ureter was mobilized and dissected caudally into the pelvis, without changing the position of the patient. Two additional (5 and 10-mm) trocars were placed in the lower abdomen (midline 5 cm below the umbilicus and in the right or

in the left lower abdomen) and dissection was continued caudally until the detrusor muscle fibres were identified at the vesico-ureteric junction. After a 1-cm area of bladder adventitia around the vesico-ureteric junction was dissected out with electro-surgical scissors, the ureteric end with a bladder cuff was transected using a laparoscopic LigaSure™ System (Covidien formerly Tyco Healthcare Germany GmbH, Neustadt/Donau, Germany). Additional sutures were not required on the bladder wall. Two suction drains were placed through the trocars in the perivesical space and in the perirenal space. The camera was moved to the 12-mm working-trocar and an EndoCatch® (Covidien) bag was introduced through the camera port. After entrapment of the kidney and ureter in the organ sack, the bag was removed through an extended 6-cm skin incision along the linea alba. Morcellation of the organ was not performed. Finally, the abdominal pressure was decreased to 5 mmHg and after 5 min the abdominal cavity was examined for bleeding. The trocars were removed under laparoscopic visualization and the fasciae of the extended incision and of the other trocar sites were closed with interrupted absorbable sutures. The skin was approximated with clips.

ONU TECHNIQUE

To reach the retroperitoneal space, a lumbar skin incision was performed and angled down toward the pelvis. The entire kidney, along with all perinephric fat and Gerota's fascia, was fully mobilized after clamping the ureter. The renal hilum was exposed and the renal vessels were carefully dissected. The renal artery and vein were both ligated with zero silk and 4/0 vascular polypropylene suture ligature on an RB needle. The ureter was then mobilized and dissected caudally into the pelvis. The entire distal ureter, including the intramural portion and the ureteric orifice, was removed; 1 cm of bladder mucosa was included circumferentially around the ureteric orifice. The defect in the bladder wall at the ureteric hiatus was closed in two layers from outside the bladder with interrupted 2/0 or 3/0 absorbable suture on muscle, and 4/0 suture on the mucosa. Two flat suction drains were placed in the perivesical space and in the perirenal space.

RESULTS

The mean age of patients who underwent LNU and ONU for the upper urinary tract TCC was

66.4 years and 67.2 years, respectively. Of these 140 patients, 64 were women and 76 were men. The mean body mass index was 24.8 kg/m² in the LNU and 25.9 kg/m² in the ONU groups. Tumours were located in the upper third (kidney and renal pelvis) in 89 patients (63%), in the middle third (ureter) in 28 patients (20%) and in the lower third (distal ureter) in 23 patients (17%) (Table 1). The mean (range) operative duration for LNU and ONU was 240 (180–300) min and 190 (160–220) min, respectively ($P < 0.05$).

The mean catheterization time was 3 (2–4) days and 4.5 (3–6) days in the LNU and ONU groups, respectively, after performing cystography. No bladder leakage was reported after LNU using a laparoscopic LigaSure™ System (Covidien).

The definitive pathology showed high incidence of pT2 G2 tumour in both the LNU and ONU groups. There was no pT4-tumour (Table 1).

Bladder recurrence developed in three patients (4.3%) in the LNU group, with a pT2 high-grade tumour, 14 months (on average) after surgery. In the ONU group, five patients (7.1%) developed a pT2 high-grade tumour recurrence, 12 months (on average) after surgery. All recurrences were localized at the ipsilateral bladder half of the upper tract from where the primary tumour arose. However, all recurrences were localized at the lateral [3] and posterior [5] bladder wall, but not closed at the excised ureteric opening site. There was no tumour seeding of port sites after laparoscopic surgery. Negative surgical margins were obtained in all but one patient in the ONU group. This patient presented with a pT3 G3 tumour, developed lung-metastases 7 months after surgery, and died after two cycles of chemotherapy with gemcitabine plus cisplatin. Progression was related to stage: 0% for pTa, 14% for pT1, 17% for pT2 and 57% for pT3; and to grade: 0% for G1, 6% for G2 and 51% for G3.

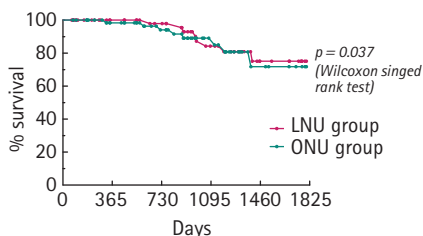
The 5-year disease-free survival (DFS), calculated according to the Kaplan–Meier method, was 75% in the LNU group and 73% in the ONU group ($P = 0.037$; Fig. 1). DFS in the LNU group was classified by tumour stage: 100% for pTa, 88% for pT1, 78% for pT2 and 35% for pT3 ($P < 0.001$, overall). In the ONU group, the 5-year DFS classified by tumour stage was: 100% for pTa 89% for pT1,

Variable	LNU	ONU	TABLE 1
N	70	70	The patients' characteristics and pathological data
Mean:			
Age, years	66.4	67.2	
Body mass index, kg/m ²	24.8	25.9	
N:			
Men/women	33/37	43/27	
Left/right kidney	31/39	27/43	
Location of the tumour (patients):			
Kidney and renal pelvis	47	42	
Ureter	10	18	
Distal ureter	13	10	
Pathological results			
Mean (range) kidney weight, mg	80 (50–110)	140 (80–200)	
N (patients):			
Tumour stage:			
pTa	13	14	
pT1	17	16	
pT2	39	37	
pT3	1	3	
pT4	0	0	
Tumour grade:			
G1	15	17	
G2	47	45	
G3	8	8	
Surgical margins:			
Negative for tumour	70	69	
Positive for tumour	0	1	

of peripelvic or periureteric soft tissue, renal parenchyma, or regional lymph nodes at the time of initial diagnosis. The standard treatment for infiltrative TCC of the upper urinary tract consists of two different procedures: nephrectomy and removal of lower end ureter with bladder cuff.

The safety and efficacy of laparoscopy for upper urinary tract urothelial cancer have been discussed for many years, particularly with regard to oncological outcome and the rate of tumour seeding [3–13,16–20]. Discussion has focused on whether laparoscopy is associated with an higher risk of peritoneal dissemination and port-site metastases [6,7]. The controversy in the mid-1990s concerning the formation of port-site metastasis was triggered by reports of an alarmingly high incidence of port-site metastasis; however, the validity of these findings is questionable. Laparoscopic removal of some urological malignancies, such as prostate cancer and RCC, has been shown to be safe and effective, without risks for port-site metastasis and tumour cell dissemination. Until now, these questions have not been answered definitively for urothelial cancer of the upper urinary tract.

FIG. 1. The 5-year DFS rates for both groups.

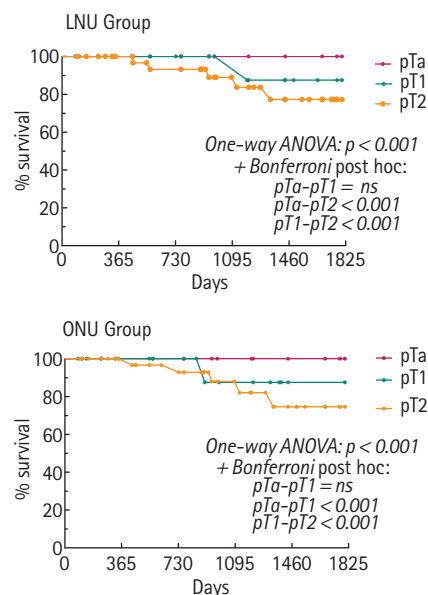


75% for pT2 and 31% for pT3 ($P < 0.001$, overall; Fig. 2).

DISCUSSION

TCC of the upper urinary tract is relatively uncommon, accounting for 2–10% of all urothelial tumours and, unlike other urological malignancies (prostate and RCC), is unique, as its cells can be shed via urine to implant in a raw wound. About 30% of these patients have tumours invading the musculature of the renal pelvis or the ureter, and an additional 30% have an involvement

FIG. 2. The 5-year DFS rates for both groups according to tumour stage.



The incidence of port-site metastases after LNU for TCC of the upper urinary tract is declining because of improvements in surgical technique. To date, only 11 port-site metastases have been reported [19]. Large series of LNU with short- and intermediate-term follow-up show a DFS rate of 59–95% [3–5,8–20]; with the rates of local recurrence and distant of 0–13% and 0–59%, respectively (Table 2).

Rassweiler *et al.* [3] reported an incidence of local recurrence of 0–15% after both ONU and LNU, describing a 5-year DFS rate of 81% after LNU and of 63% after ONU. In the multicentre study reported by Ozsahin *et al.* [18], the local recurrence rate after ONU was 22%. Gill *et al.* [11] reported a cancer-specific survival rate of 97% in 42 patients who underwent a LNU vs 87% in 35 patients who underwent an ONU. They concluded that the short-term oncological and survival data of LNU were comparable to those of ONU. In another study, Matin and Gill [17] evaluated recurrence and survival following LNU with various forms of bladder cuff control. They reported that the rate of recurrence in a group of patients whose surgery included the use of a laparoscopic stapling device was higher

TABLE 2 Recent studies on oncological outcomes in LNU for TCC

Reference	N	Follow-up, months	Positive margins, %	Local recurrence, %	Metastatic disease, %	Tumour stage >pT2, %	DFS, %	Cancer-specific survival, %
Schatteman <i>et al.</i> 2007 [12]	100	20	1	13	16	34	76	88
Rassweiler <i>et al.</i> 2004 [3]	23	–	–	0	17	17	81	89
Gill <i>et al.</i> 2000 [11]	42	11.1	–	0	8.6	–	–	97
Jarrett <i>et al.</i> 2001 [15]	25	>12	4	8	16	–	75	92
Matin <i>et al.</i> 2005 [17]	60	23	8	12	12	45	–	–
Bariol <i>et al.</i> 2004 [5]	25	101	–	4	28	–	72	72
Muntener <i>et al.</i> 2007 [13]	39	74	10	5	59	8	59	68
Klinger <i>et al.</i> 2003 [16]	19	22	0	0	5	26	95	95

than that of the group in which the surgical method involved cystoscopically secured detachment and ligation, thus showing an association between type of surgical technique and recurrence rate.

The present 5-year DFS rates (75% LNU group and 73% ONU group) were comparable with published rates (Table 2, Figs 1,2). There was local recurrence of a pT2 high-grade tumour in the bladder of three patients (4.3%) in the LNU group, 14 months (on average) after surgery. In the ONU group, five patients (7.1%), had a pT2 high-grade tumour recurrence, 12 months (on average) after surgery. One patient, who underwent ONU, had presented with a pT3 G3 tumour, developed metastatic disease 7 months after surgery, and died 15 months after surgery, having received two cycles of chemotherapy.

The resection of the distal ureter with bladder cuff was performed with a laparoscopic LigaSure® system, a computer-controlled bipolar diathermy system designed to optimally seal vessels of <7 mm in diameter. All the vessels <7 mm were sealed tightly with this device [14]. There were no postoperative haemorrhages, lymphatic leakage, or lymphoceles. Moreover no stones (which can be associated with a laparoscopic stapler) formed in the present study group. With this technique we obtained a precise excision of the complete bladder cuff without breach of the urinary system, thus preventing spillage, and enabling the removal of the entire specimen *en bloc*.

In conclusion, we conducted a long-term evaluation of LNU. The present results support the use of LNU, from an oncological standpoint, as a reasonable and effective

alternative to ONU in the therapy of upper urinary tract urothelial cancer.

CONFLICT OF INTEREST

None declared.

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Abbreviations: (L)(O)NU, (laparoscopic) (open) radical nephroureterectomy; DFS, disease-free survival.