Laparoscopic vs open partial nephrectomy for T1 renal tumours: evaluation of long-term oncological and functional outcomes in 340 patients

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What's known on the subject? and What does the study add?

- Whereas open nephron-sparing surgery (NSS) represents the 'gold standard' in the surgical therapy of T1 renal tumours, with the advances in laparoscopic surgery, the refinement of intracorporeal suturing and the availability of haemosealant substances, the laparoscopic approach to NSS is increasingly used. Laparoscopic partial nephrectomy (LPN), however, is currently performed in just a few high-volume reference centres, and its diffusion has been limited by the steep learning curve. Conversely, robot-assisted LPN is emerging as a promising procedure, able to tackle the technical difficulties of LPN and leading to a broader diffusion of minimally invasive treatment of small renal masses.
- Our study provides long-term follow-up outcomes concerning surgical and oncological outcomes and a detailed evaluation of the renal function in patients affected by T1 renal cancers who underwent LPN and OPN. We showed that LPN could be safely performed in the therapy of T1 renal cancer, without impairing renal function.

Objective

- To evaluate the long-term oncological and functional outcomes of laparoscopic partial nephrectomy (LPN) compared with open partial nephrectomy (OPN) for pT1 renal tumours.

Patients and Methods

- In this retrospective single-centre study, 340 consecutive patients underwent LPN and OPN for localized, incidentally discovered, renal masses of <7 cm (cT1).
- The patients were matched for age, sex, body mass index, American Society of Anesthesiology score, tumour side (right or left kidney) and tumour characteristics (RENAL nephrometry score).
- Demographic data, peri- and postoperative variables, including operating time, estimated blood loss, complications, hospital stay, renal function, histological tumour staging and grading, and metastasis rates were collected and analysed.

Results

- The median (SEM) operating time for LPN and OPN was 145.3 (45.4) min and 155.2 (35.6) min, respectively ($P = 0.07$). The median (SEM) warm ischaemia time was 11.7 (2.2) min in the LPN and 14.4 (1.9) min in the OPN group ($P = 0.03$).
- The median (SEM) RENAL nephrometry scores for LPN and OPN were 5.9 (1.6) and 6.1 (0.3), respectively ($P = 0.11$).
- During follow-up, the biochemical markers of glomerular filtration were completely normalized, showing the absence of renal injury and there was no significant difference in glomerular filtration rate between the groups, with median (SEM) rates of 79.8 (3.0) mL/min/1.72m^2 for the LPN and 80.2 (2.7) mL/min/1.72m^2 for the OPN group at 5-year follow-up.
- The 5-year overall survival and cancer-specific survival rates, calculated using the Kaplan–Meier method, were 94% and 91% in the LPN group, and 92% and 88% in the OPN group.

Conclusion

- LPN and OPN provide similar long-term oncological outcomes in the therapy of T1 renal cancer. With regard to renal function, no damage to the kidney was found after LPN and OPN, with a complete normalization of renal function at the 5-year follow-up in both groups.

Keywords

kidney cancer, partial nephrectomy, laparoscopy, oncological and functional outcomes

Introduction

Radical nephrectomy (RN) has been considered the standard surgical therapy and the only curative treatment for localized RCC for many decades. The widespread use of modern imaging methods has led to the earlier diagnosis and improved staging of RCC, resulting in a marked increase in the number of renal tumours detected incidentally in patients with no urological symptoms [1]. These tumours are often of lower grade and stage and the need for RN for such asymptomatic locally confined lesions has therefore been questioned. Nephron-sparing surgery (NSS) offers a good alternative for small renal lesions (<4 cm) [1,2]. Although open NSS represents the 'gold standard' in the surgical therapy of T1 renal tumours [1], recently, the advances in laparoscopic surgery, the refinement of intracorporeal suturing, and the availability of haemosealant substances have meant that the laparoscopic approach to NSS has been increasingly used. Despite this, laparoscopic partial nephrectomy (LPN) is currently performed in only a few high-volume reference centres, and its diffusion has been limited by the steep learning curve. Conversely, robot-assisted LPN is emerging as a promising procedure, able to tackle the technical difficulties of LPN and leading to a broader diffusion of minimally invasive treatment of small renal masses [3].

One crucial point with regard to NSS remains warm ischaemia time (WIT), which can potentially affect short- and long-term renal function [1,2]. The main challenge presented by NSS is the preservation of renal function. In recent years, evidence has shown that a minor loss of kidney function can increase life expectancy, reducing cardiovascular morbidity. Thus, the goal of preserving as much parenchyma as possible has become the priority [1,2,4]. Because it is generally less invasive than an open surgical technique, laparoscopy may be preferable if it can be shown to achieve the same results, with the same safety for the patient.

The objective of the present study was to investigate if LPN presents the same surgical and oncological safety as open partial nephrectomy (OPN), without impairing the renal function, in the treatment of T1 renal tumours.

Patients and Methods

This was a retrospective single-centre study including 340 patients who underwent partial nephrectomy (PN) between May 2000 and November 2010 and who were matched for age, sex, body mass index (BMI), American Society of Anesthesiology (ASA) score, tumour side (right or left kidney) and tumour characteristics (RENAL nephrometry score: tumour size-[R]adius, location and depth-[E]xophytic or endophytic; nearness to the renal sinus fat or collecting system [N]; anterior or posterior position [A], and polar vs non-polar location [L]). This provided comparative information on the surgical, oncological, and long-term renal function outcomes of laparoscopic and open NSS.

A total of 170 patients underwent LPN and 170 patients comprised a historical control group of patients who underwent OPN. OPNs were performed between May 1999 and April 2005 and LPNs were performed between May 2005 and November 2010.

The study was approved by the institutional review board. Written informed consent was obtained from all patients.

All operations were performed for localized incidentally discovered renal masses of <7 cm (cT1); all indications were elective. Before surgery, all patients underwent renal ultrasonography and CT to give detailed information about tumour size, location, extent of parenchymal infiltration and proximity to the pelvicalyceal system.

Patients with severe heart failure (New York Heart Association Functional Classification III–IV), chronic renal insufficiency and/or with an ASA score of ≥3 were excluded from the study. Demographic data, peri- and postoperative variables, including operating times, estimated blood loss, WIT, complications, hospital stay, renal function, histological tumour staging and grading, and metastasis rates were collected and analysed. All complications occurring ≤30 days after surgery were recorded and defined according to the modification of the Clavien system by Dindo et al. [5].

The RENAL nephrometry score was used to assess the characteristics of the tumours in both groups [6]. All operations were performed by two surgeons (F.G. and P.F.), who had completed at least 90 LPNs and OPNs each before the beginning of the study, thus reducing the learning-curve effect.

The median (SEM) follow-up period was 45.7 (18.4) months for LPN and 54.3 (13.1) months for OPN and no patients were lost to follow-up. Follow-up was calculated from the date of surgery to the date of the most recent documented examination. In all patients a physical examination and ultrasonography were performed every 3 months in the first year, every 6 months in the second and third years and yearly thereafter. CT or MRI was performed every 6 months in the first and second years, and yearly in the third, fourth and fifth years after surgery.

To prevent ischaemic damage, all patients received proper hydration and mannitol infusion (0.25 g/kg) 10 min before clamping. After unclamping, 20 mg i.v. furosemide was injected.

Surgical Technique: LPN

In all patients a transperitoneal approach was used. A Veress needle was inserted peri-umbilically to establish the pneumoperitoneum, using carbon dioxide. With an initial intra-abdominal pressure of 12–15 mmHg, a 12-mm trocar was placed supra-umbilically after removal of the Veress needle. The endoscopic 0° camera was introduced and three other trocars were inserted under direct vision: two 12-mm trocars in the ipsilateral midclavicular line and a 10-mm trocar were placed just between the xyphoid and the first port. Occasionally, a fifth trocar (5-mm) was used in the anterior axillary line below the umbilicus. Then, the intra-abdominal pressure was lowered to 10–12 mmHg and maintained at this level.

After mobilization of the colon, the ureter was identified above its cross over the iliac vessels. The renal hilum was exposed and the renal vessels were carefully dissected. The kidney was mobilized within Gerota's fascia and defatted, maintaining perirenal fat over the tumour. The renal artery was clamped with one laparoscopic bulldog clamp. The tumour was excised with cold scissors in a near-bloodless field. Targeted excisional biopsies of the tumour bed were sent for frozen section in case of suspicion regarding margin status.

The collecting system was repaired with a running 2-0 polyglactin 910 suture on CT-1 needle. Renal parenchymal repair was performed with three to five interrupted sutures. A PDS-clip was secured on the suture to prevent it from pulling through. Another Hem-o-Lok clip was applied to the suture flush with the opposite renal surface, compressing the kidney [7]. The bulldog clamp was then removed and fibrin glue was applied to the cut renal parenchymal surface. The *en bloc* specimen was extracted in an Endocath II bag (Covidien, formerly Tyco Healthcare Germany GmbH, Neustadt/Donan, Germany) and a flat suction drain was placed in the pararenal space.

Since 2008, we have adopted an early unclamping technique so as to minimize the WIT [8]. In patients undergoing LPN with an early unclamping, only the initial collecting system suturing was performed under ischaemia, with the renal parenchymal repair of the bolstered renorrhaphy being performed in the re-vascularized kidney.

Surgical Technique: OPN

An extraperitoneal thoraco-abdominal incision was performed over the 11th or 12th rib and the middle and anterior portions of the skin incision angle down toward the pelvis. The entire kidney was fully mobilized and defatted, maintaining perirenal fat over the tumour. The renal hilum was exposed and the renal artery was clamped with a bulldog clamp. The tumour was excised with cold scissors in a near-bloodless field. Targeted excisional biopsies of the tumour bed were sent for frozen section in case of suspicion regarding margin status.

The collecting system was repaired with a running 2-0 polyglactin 910 suture on a CT-1 needle. Renal parenchymal repair was performed with interrupted, horizontal mattress suture (0- polyglactin 910) on a CTX needle, placed over a pre-prepared Tabotamp (Johnson & Johnson Medical GmbH, Norderstedt, Germany) that was positioned over the cut surface of the kidney. The bulldog clamp was then removed and fibrin glue was applied to the cut renal parenchymal surface. A flat suction drain was placed in the pararenal space.

Measurements

The function of the kidney was evaluated by measuring serum creatinine and serum cystatin C levels (biochemical markers of glomerular filtration) at various times. Measurements were taken preoperatively (24 h before surgery: T0), after the placement of the trocars/after the cut (T1), after clamping of the renal vessels (T2), and at 6, 12, 24, 48, 72 and 96 h after surgery (T3-T8), then at 1, 3, and 6 months after surgery (T9-11), and also at 1, 2, 3, 4 and 5 years after surgery (T12-T16). We also evaluated, GFR preoperatively, at 24 h after surgery and at the end of follow-up. Estimated GFR (eGFR) was calculated using the modification of diet renal disease equation. To evaluate the effects of the procedure on the operated kidney, the patients underwent radionuclide renal scintigraphy with ^{99m}Tc-MAG3 before surgery and at 1 year after surgery.

Statistical Analysis

Statistical analysis was performed using SigmaPlot® software version 11.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as the median (SEM) values or as a percentage of baseline, and a P value of <0.05 was considered to indicate statistical significance. Fisher's exact test was applied to evaluate statistical between-group differences in pathological stages. For statistical analyses, the results of serum variables were calculated as the median (5%, 25%, 75% and 95% percentile). For comparison of paired values within the same group, the Friedman test (non-parametric) was used, followed by the Wilcoxon log-rank test for comparison of continuous variables.

The 5-year overall survival (OS) and local recurrence-free survival rates for local and distant relapse in pT1 stage RCC were estimated using the Kaplan–Meier method with log-rank test statistics.

Results

Baseline Characteristics

The baseline characteristics of the patients are shown in Table 1. No statistical differences were reported in either group for age, sex, BMI, ASA score, tumour side (right or left kidney), RENAL nephrometry score and preoperative renal function. The median RENAL nephrometry scores for LPN and OPN were 5.9 (1.6) and 6.1 (0.3), respectively ($P = 0.11$).

Intra- and Postoperative Outcomes

The median operating times for LPN and OPN were 145.3 (45.4) min and 155.2 (35.6) min, respectively ($P = 0.07$), with a median WIT of 11.7 (2.2) min in the LPN and 14.4 (1.9) min in the OPN group ($P = 0.03$; Table 2). The median complication rate was 4.1% in the LPN and 5.9% in the OPN group ($P = 0.04$). Two patients (1.2%) required postoperative blood transfusions (Clavien grade 2) in the LPN group and four (2.4%) in the OPN group ($P = 0.03$). Urine leakage occurred in three patients (1.7%) after LPN and in five patients (2.9%) after OPN.

After LPN, management was non-surgical in all cases (Clavien grade 1). After OPN, management was non-surgical in two patients, while three patients required an endoscopic intervention (Clavien grade 3), placing a mono-J-stent that was removed 1 week after performing retrograde pyelography.

One 73-year-old patient in the OPN group had a pulmonary embolism 4 days after surgery but fully recovered (Clavien grade 2). Two patients (1.2%) developed a postoperative haematoma in the flank after LPN, which did not require intervention (Clavien grade 1). There were no grade 4 or 5 complications and no conversion to radical nephrectomy was necessary.

Renal Function

The serum creatinine and cystatin C levels rose during and after surgery (Figs 1,2). They remained slightly above the initial values 4 days after surgery (median creatinine level of 84 µmol/L in the LPN group vs 86 µmol/L in the OPN group; median cystatin C level of 1.3 mg/L in the LPN group vs 1.5 mg/L in the OPN group; $P = 0.08$). At 5 years after surgery the values were completely normalized, showing the absence of renal injury (median creatinine level of 81 µmol/L in the LPN group vs 85 µmol/L in the OPN group ($P = 0.08$); median cystatin C level of 1.2 mg/L in the LPN group vs 1.2 mg/L in the OPN group). At the 1-year follow-up median renal function, evaluated by a renal scintigraphy performed in 147 patients (86.5%) of the LPN group and in 139 patients (81.8%) of the OPN group, was found to be 43.05 (3.21) and 42.93 (3.74)%,

Table 1 Preoperative patient data.

Variable	LPN	OPN	*P*
N	170	170	
Median (SD) age, years	55.6 (13.1)	56.1 (11.6)	0.11
No. of men/women	112/58	117/53	0.16
Median BMI, kg/m^2	27.2	26.9	0.18
Left/right kidney, *n/n*	92/78	98/72	0.14
Median (SEM) tumour size, cm	2.8 (1.9)	2.9 (1.4)	0.13
Median (SEM) RENAL nephrometry score	5.9 (1.6)	6.1 (0.3)	0.11
Median (SEM) preoperative renal function at renal scintigraphy, %	49.05 (2.63)	48.83 (3.12)	0.08
Median (SEM) preoperative GFR, mL/min/1.72m^2	89.4 (16.2)	90.3 (13.6)	0.09
Median (SEM) ASA score	2.1 (0.9)	2.2 (0.6)	0.12

Table 2 Intra- and postoperative patient data.

Variable	LPN	OPN	*P*
N	170	170	
Median (SEM) operating time, min	145.3 (45.4)	155.2 (35.6)	0.07
Median (SEM) estimated blood loss, mL	157.5 (123.1)	240.2 (135.4)	0.02
Median (SEM) WIT, min	11.7 (2.2)	14.4 (1.9)	0.03
Range, min	7–14	8–21	
Intake, days	1.4	2.7	0.07
Complication rates, %	4.1	5.9	0.04
Median (SEM) hospital stay, days	4.5 (2.1)	6.6 (3.8)	0.01
Median (SEM) postoperative renal function at renal scintigraphy, % (at 1-year-follow-up)	43.05 (3.21)	42.93 (3.74)	0.08
Median (SEM) GFR at 24 h after surgery, mL/min/1.72m^2	81.3 (2.3)	82.9 (3.2)	0.09
Median (SEM) GFR at 5-year follow-up, mL/min/1.72m^2	79.8 (3.0)	80.2 (2.7)	0.09

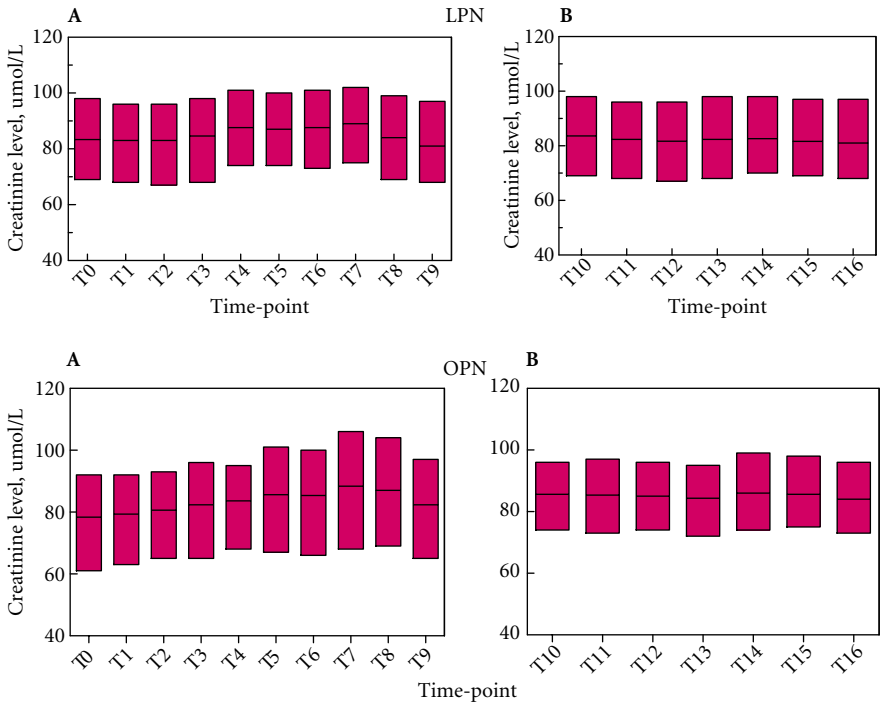


Fig. 1 Creatinine levels before, during and after **A**, LPN and **B**, OPN (μmol/L). T0, preoperative (24 h before surgery); T1, after the placement of the trocars/after the cut; T2, after clamping of renal vessels; T3, 6 h after surgery; T4, 12 h after surgery; T5, 24 h after surgery; T6, 48 h after surgery; T7, 72 h after surgery; T8, 96 h after surgery; T9, 1 month after surgery; T10, 3 months after surgery; T11, 6 months after surgery; T12; 1 year after surgery; T13, 2 years after surgery; T14, 3 years after surgery; T15, 4 years after surgery; T16, 5 years after surgery.

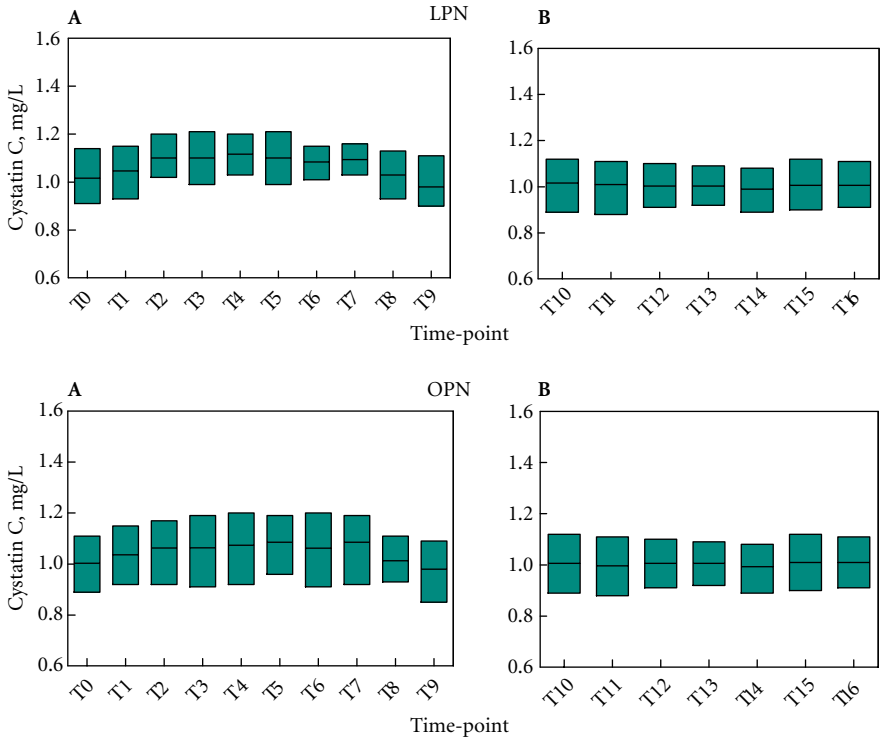


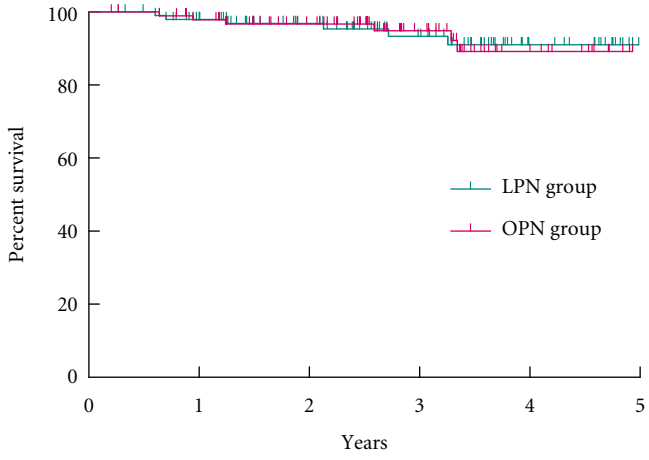
Fig. 2 Cystatin C levels before, during and after **A**, LPN and **B**, OPN (mg/L). T0, preoperative (24 h before surgery); T1, after the placement of the trocars/after the cut; T2, after clamping of renal vessels; T3, 6 h after surgery; T4, 12 h after surgery; T5, 24 h after surgery; T6, 48 h after surgery; T7, 72 h after surgery; T8, 96 h after surgery; T9, 1 month after surgery; T10, 3 months after surgery; T11, 6 months after surgery; T12; 1 year after surgery; T13, 2 years after surgery; T14, 3 years after surgery; T15, 4 years after surgery; T16, 5 years after surgery.

respectively ($P = 0.08$). The postoperative eGFR (24 h after surgery) was 81.3 (2.3) mL/min/1.72m^2 after LPN and 82.9 (3.2) mL/min/1.72 m^2 after OPN ($P = 0.09$). At the 5-year follow-up, there was no significant difference in eGFR between the groups (LPN: 79.8 (3.0) mL/min/1.72 m^2; OPN: 80.2 (2.7) mL/min/1.72m^2; $P = 0.09$). No kidney was postoperatively lost because of warm ischaemic injury.

Table 3 Pathological results.

	LPN	OPN	*P*
N	170	170	
Tumour stage, *n*			
pT1a	143	136	0.11
pT1b	27	34	0.12
Tumour grade, %			
G1	63	62	0.14
G2	31	29	0.15
G3	6	9	0.12
Median (SEM) tumour size, cm	3.1 (2.1)	3.4 (1.4)	0.11
Cell type, %			
clear-cell	79	80	0.21
chromophobe	16	15	0.22
oncocytoma	2	3	0.22
angiomyolipom	3	2	0.22
Positive margins (%)	1.2	1.7	0.09

Fig. 3 5-year overall survival after LPN and OPN ($P = 0.08$).



Oncological Outcomes

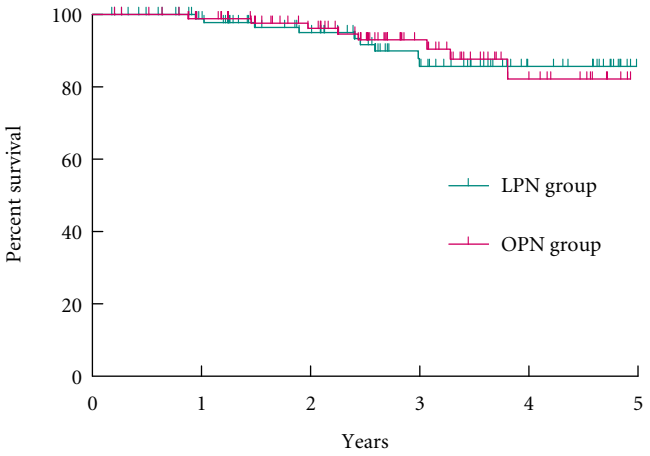
The definitive pathological results showed a high incidence of clear-cell tumours in both groups. Surgical margins were positive in two patients (1.2%) in the LPN group and in three patients (1.7%) in the OPN group with clear-cell carcinoma ($P = 0.09$; Table 3). In one patient after LPN a tumour seeding to the port site developed 24 months after surgery.

The 5-year OS and cancer-specific survival (CSS) rates, calculated using the Kaplan–Meier method, were 94% and 91% in the LPN group, and 92% and 88% in the OPN group ($P = 0.08$ and $P = 0.07$; Figs 3,4).

Discussion

Nephron-sparing surgery was initially reserved for patients at high risk of developing renal failure after kidney surgery to treat renal cancer. Several series have shown OPN to be equivalent to open RN in terms of long-term cancer-free

Fig. 4 5-year cancer-specific survival after LPN and OPN ($P = 0.07$).



survival with unilateral renal involvement, unifocal disease and a tumour size of <4 cm [2,4,7–9].

Van Poppel et al. [2], in a randomized prospective phase III trial, reported equivalent oncological outcomes after NSS and RN, and suggested that NSS may be considered to be an acceptable approach for small asymptomatic RCC. Fergany et al. [9] reported a 10-year CSS of 100% in patients who underwent NSS for localized RCC. Lesage et al. [10] concluded that a better health-related quality of life is achieved after PN than after RN and LPN has now emerged as an attractive minimally invasive treatment alternative for selected patients with small renal tumours [11–29].

The anatomical characterization of renal tumours before PN is fundamental for correct evaluation of the outcomes. Kutikov et al. [6] published the first anatomical characterization to evaluate the predictable difficulty of NSS. In the present study, all patients were matched for age, sex, BMI, tumour side (right or left kidney) and RENAL nephrometry score, which ensured the two groups were similar.

The more widespread use of grading schemes in reporting complications has facilitated standardization to some degree. Dindo et al. [5] proposed a modification of the Clavien system of surgical complications. When we applied this system to the present data, although not significantly different, the number of grade 3 complications was slightly higher in the OPN group because of a higher frequency of ureteric stenting. The overall complication rates for LPN range from 5 to 33% and for OPN from 4.1 to 38.6% [3,14–26,28,29]. These values are similar to the complication rates in the present study.

The median WIT was 11.7 (2.2) min in the LPN and 14.4 (1.9) min in the OPN group. The lower WIT in the LPN group can be explained by the use of an early unclamping

technique. This is an advantage of the laparoscopic technique, where the presence of the pneumoperitoneum, with an intra-abdominal pressure set at 15–20 mmHg, avoids possible bleeding from small vessels, allowing resection of the tumour even with unclamped renal vessels.

Renal function is assessed by history, physical examination, ^{99m}Tc-MAG3 and serum creatinine determinations. Long-term monitoring of creatinine levels is indicated if renal function is impaired pre- or postoperatively [1,27]. The diagnosis of acute kidney injury is usually based on changes in serum creatinine, but such measurements are a poor marker of acute deterioration in kidney function. Serum cystatin C is one of the serum and urinary biomarkers that allows an early and accurate diagnosis of acute kidney injury [30]. We evaluated postoperative renal function by measuring biochemical markers of glomerular filtration (serum creatinine, serum cystatin C) at various times after surgery and by assessing eGFR by renal scintigraphy. In the present study there was no significant difference between the LPN and OPN groups in the creatinine- and cystatin C-course during and after surgery and during follow-up where the renal function values normalized. Even the radiological control showed normal renal function in both groups at the 1-year follow-up. At the end of the follow-up, there was no significant difference in the eGFRs between the groups.

The oncological data showed a high incidence for clear-cell tumours; there were positive surgical margins in three patients (1.2%) in the LPN group and in two patients (1.7%) in the OPN group. Nevertheless the positive margins were not a risk factor for CSS, as recently reported by Bensalah et al. [28]. In one patient, after LPN, a tumour seeding to the port site developed 24 months after surgery, owing to a rupture of the specimen during the procedure and not to positive margins [31].

The 5-year OS and CSS rates were 94% and 91% in the LPN group, and 92% and 88% in the OPN group, demonstrating the oncological validity of the laparoscopic procedures.

There are a several limitations to the present study that should be acknowledged. Firstly, this was a retrospective study, which led to an inherent selection bias that could not be overcome. Another limitation of the present study is the different follow-up period for each group; however, in the >90 patients who underwent a LPN with a 5-year follow-up, kidney cancer mortality did not differ from the outcomes of those who underwent OPN. Moreover, the present results showed that any statistical difference could be identified for creatinine and eGFR levels between 1- and 5-year follow-ups. Thus, we could hypothesize that patients with normal creatinine and eGFR at 1-year follow up after NSS, would not require a further and rigorous long-term follow-up for renal function.

In conclusion, laparoscopic and open NSS provide similar long-term oncological outcomes in the therapy of T1 renal cancer. Moreover, positive surgical margins did not appear to be a risk factor for CSS. With regard to renal function, no damage to the kidney was found after LPN or OPN, and there was a complete normalization of renal function at the 5-year follow-up in both groups.

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Conflict of Interest

None declared.

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Abbreviations: PN, partial nephrectomy; RN, radical nephrectomy; LPN, laparoscopic PN; OPN, open PN; NSS, nephron-sparing surgery; WIT, warm ischaemia time; BMI, body mass index; ASA, American Society of Anesthesiology; eGFR, estimated GFR; OS, overall survival; CSS, cancer-specific survival.