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Francesco Porpiglia, Riccardo Bertolo, Daniele Amparore, Valerio Podio*, Tiziana Angusti*, Andrea Veltri* and Cristian Fiori

*Division of Urology, University of Turin, 'San Luigi Gonzaga' Hospital and *Division of Radiology and Nuclear Medicine, 'San Luigi Gonzaga' Hospital, Orbassano, Turin, Italy*

Objectives

To examine differences in postoperative renal functional outcomes when comparing clampless with conventional laparoscopic partial nephrectomy (LPN) by using renal scintigraphy, and to identify the predictors of poorer postoperative renal functional outcomes after clampless LPN.

Patients and Methods

Between September 2010 and September 2012, 87 patients with renal masses suitable for LPN were prospectively enrolled in the study. From September 2010 to September 2011, LPN with renal artery clamping was performed and from September 2011 to September 2012 clampless LPN (no clamping of renal artery) was performed. Patients who underwent clampless LPN were unselected and consecutive, and the procedure was performed at the end of surgeon's learning curve. Patients were divided into two groups according to warm ischaemia time (WIT): group A, conventional LPN and group B, clampless-LPN (WIT = 0 min). Demographic and peri-operative data were collected and analysed and functional outcomes were evaluated using biochemical markers and renal scintigraphy at baseline and at 3 months after surgery. The percentage loss of renal function, evaluated according to renal scintigraphy, was calculated. Chi-squared and Student's *t*-tests were carried out and regression analysis was performed.

Results

Group A was found to be similar to group B in all variables measured except for WIT and blood loss ($P < 0.001$). The percentage reduction in renal scintigraphy values was not significantly different between the groups (reductions of 5% in group A and 6% in group B for split renal function [SRF] and 12% in group A and 17% in group B for estimated renal plasmatic flow [ERPF]; $P = 0.587$ and $P = 0.083$, respectively). Multivariate analysis in group B showed that the lower the baseline values of SRF and ERPF, the poorer the postoperative functional outcome of the treated kidney.

Conclusions

In our experience, even clampless LPN was not found to be functionally harmless. The patients who benefitted most from a clampless approach were those with the poorest baseline renal function.

Keywords

laparoscopy, partial nephrectomy, renal ischaemia, renal scintigraphy, clampless, zero ischaemia

Introduction

Partial nephrectomy has become the preferred treatment for T1 clinical stage renal tumours (<7 cm) [1]. A bloodless field is essential for achieving the best surgical outcomes, and the conventional partial nephrectomy technique includes clamping of the renal artery. The side effect of this is renal ischaemia, which can produce a certain level of ischaemic damage to the kidney. The critical threshold at which such damage is initiated has been extensively studied and is widely thought to be ~25 min [2–4]. Nevertheless, recent studies have shown that each minute of ischaemia is crucial in determining the extent of renal damage [5,6] and this has prompted urological surgeons to introduce new techniques aimed at reducing warm ischaemia time (WIT) [7,8]. A desire to achieve the maximum reduction in WIT has led to the concept of partial nephrectomy without renal artery clamping. Laparoscopic partial nephrectomy (LPN), performed using a clampless technique, was introduced with the aim of completely avoiding renal ischaemia and so potentially avoiding postoperative loss of renal function. Whether avoiding renal artery clamping achieves a reduction in related renal damage compared with conventional LPN with clamping of the renal artery is still under investigation. The currently

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available studies were designed to include the variables serum creatinine (SCr) and/or estimated GFR, which could potentially limit crucial information on postoperative functional outcomes because the contralateral kidney may mask biochemical changes, if functioning normally.

The primary aim of the present study was to examine the differences in postoperative renal functional outcomes by comparing clampless with conventional LPN using renal scintigraphy variables. The secondary aim of the study was to look for any predictors of poorer postoperative renal functional outcomes in patients who underwent clampless LPN.

Patients and Methods

Between September 2010 and September 2012, patients diagnosed with a renal mass suitable for a nephron-sparing surgical approach underwent LPN and were prospectively enrolled in the present study. Renal functional follow-up was performed using renal scintigraphy. Before enrolling in the study, patients provided written informed consent and the study was approved by our institutional ethics committee. A single surgeon, skilled in laparoscopic renal surgery (with >200 procedures carried out), performed the key steps of all surgeries (resection and renorrhaphy phases). Specifically for the purpose of this study, from September 2011 all LPNs were performed using the clampless technique. Patients were divided into two groups according to the intra-operative management of the renal artery: group A included patients treated by conventional LPN (with clamping of renal artery); group B included patients who underwent clampless LPN (WIT = 0 min). Preoperative assessment included abdominal CT and renal scintigraphy using radionuclide 99mTc-mercapto-acetyl triglycine 3.

Inclusion Criteria

All patients who were candidates for LPN with renal tumours <7 cm and who had baseline split renal function (SRF) assessed by renal scintigraphy in the range of 45–55% in the treated kidney were enrolled. Only patients for whom WIT was <25 min were considered.

Exclusion Criteria

Patients with a single or horseshoe-shaped kidney and/or kidney scars observed on preoperative CT were excluded. In addition, patients with complications that could affect kidney function, such as significant bleeding causing severe hypotension, kidney infection or a condition in addition to the treatments investigated in the present study, were excluded.

Surgical Technique

Conventional LPN was performed according to a previously described technique [9]. The clampless approach differed from conventional LPN as follows: neither the renal hilum nor the renal artery were clamped, but the renal artery was accurately dissected up to its initial branches; carbon dioxide pressure was raised to 20 mmHg during excision of the lesion; and the tumour was slowly dissected by cold scissors and a suction device. During the resection, any emerging vessel from the resection bed was selectively coagulated by bi-polar forceps or clipped using Hem-o-lok (Teleflex, Wayne, PA, USA) and/or Absolok (Ethicon EndoSurgery, Cincinnati, OH, USA) clips. No dedicated anaesthetic procedures (such as calibrated hypotension) were used in any case. Renorrhaphy was performed in all cases by running suture of the medulla and cortex, both secured by Hem-o-lok clips. In all cases, Floseal (Baxter, Deerfield, IL, USA) and Tachosil (Nycomed, Zurich, Switzerland) were used on the closed parenchymal defect to reduce the risk of postoperative bleeding.

Measurements

For each patient, we prospectively collected the following variables in a dedicated database: demographic data, including age, gender, body mass index and comorbidities as classified by Charlson's comorbidity index [10]; preoperative variables, including American Society of Anesthesiologists score, clinical tumour size at preoperative CT and the side and location as classified using the PADUA score [11]; peri-operative data, including retro-/transperitoneal approach and operating time, WIT, estimated blood loss and intra-operative complications; pathological data, including positive surgical margin rate and average thickness of peri-tumoural healthy tissue excised; and postoperative complications as classified by the Clavien system [12].

Evaluation of Renal Function

Serial measurements were used to assess SCr and eGFR, and SRF and estimated renal plasmatic flow (ERPF) were evaluated using 99mTc-mercapto-acetyl triglycine 3 renal scintigraphy. All renal scintigraphy was performed at our institution and read by a dedicated nuclear medicine doctor. Measurements were conducted preoperatively and at 3 months postoperatively. Because a normal range does not exist for SRF and ERPF calculated by renal scintigraphy and there is variability among patients, we created a new variable: baseline weighted differential (b-WD) [4], representing the percentage reduction in SRF or ERPF, taking into consideration their baseline values. This variable was used in our statistical analyses to eliminate possible confounding by different scintigraphic baseline values for patients in the preoperative setting as follows: b-WD for SRF = (SRF 3 months after surgery – baseline SRF)/baseline SRF and b-WD for ERPF = (ERPF 3 months after surgery – baseline ERPF)/baseline ERPF. These variables are referred to as percentage of SRF/ERPF lost hereafter.

Pathology Assessment

A dedicated uro-pathologist analysed fresh-tissue specimens from the operating room and defined primary tumour extent in accordance with TNM classification 2009 [13]. A mean value for peri-tumoural healthy tissue thickness was obtained [14]. Histological subtypes and grading were defined in accordance with the WHO [15] and Fuhrman classification systems [16], respectively. A positive surgical margin was defined as cancer cells at the inked parenchymal excision surface level [14].

Statistical Analysis

Sample size was calculated to recognise significant differences ($P < 0.05$) of ~5% between the percentages of ERPF lost in groups A and B, with an adequate power (1 – ß = 80%). This condition required 38 + 38 (= 76) observations. Because of the possibility of patients dropping out or being lost to follow-up, extra patients were enrolled. Mean values and standard deviations were used to report continuous variables, while frequencies and proportions were used for categorical variables. Mean values for continuous variables were compared using the Student's *t*-test, after verifying that the analysed variables were approximately normally distributed. The chi-squared test was used for frequencies and proportions. Multivariable linear regression analysis was used to identify independent predictors of loss of renal function (e.g. percentage of SRF/ERPF lost) in group B among variables previously tested using a univariable model. Only variables that could potentially influence postoperative renal function were included in the multivariable analysis. All tests were two-sided; P value <0.05 were considered to indicate statistical significance. Statistical analysis was performed using STATISTIC 7 (Statsoft Inc.).

Results

A total of 102 LPNs were performed during the study period. Thirteen patients did not participate in the study because they did not provide the informed consent to undergo baseline renal scintigraphy and subsequent postoperative functional follow-up. Two patients were excluded because they had either a solitary ($n = 1$) or a horseshoe-shaped kidney ($n = 1$). Of the 87 patients included in the analysis, 44 underwent conventional LPN and composed group A and 43 patients underwent clampless LPN and composed group B. No patient in group A had WIT >25 min. Demographic, peri-operative data, pathological data and complications are shown in Table 1. In group B, one patient (2.4%) with central angiomyolipoma underwent conventional LPN instead, as renal artery clamping was required because of severe bleeding. This event was recorded as an intra-operative complication and the patient was excluded from the functional analysis. We recorded five (11.9%) medical postoperative complications (fever, $n = 3$; bronchitis, $n = 2$); none were Clavien grade > III. Results of clampless technique were compared with the those for conventional LPN (Table 1). Group A was similar to group B in terms of demographic and preoperative variables. Mean ± SD PADUA scores were 6.9 ± 1.2 and 7.0 ± 1.5 for groups A and B, respectively ($P = 0.713$). The mean ± SD WIT was 18.0 ± 5.8 min in group A and all patients in group B had WIT of 0 min ($P < 0.001$). The remaining peri-operative variables were similar, except for estimated blood loss, which was higher in

Table 1 Demographic, peri-operative and postoperative data stratified by group.

	Group A (WIT ≤25 min): *n* = 44	Group B (WIT = 0 min): *n* = 42	*P*
Age, mean (SD), years	57.5 (12.3)	60.6 (12.8)	0.255
Male patients, *n* (%)	29 (65.9)	30 (71.4)	0.584
BMI, mean (SD), kg/m^2	27.0 (3.6)	26.6 (3.4)	0.598
CCI, mean (SD)	1.4 (1.6)	1.3 (1.5)	0.766
ASA score ≥3, *n* (%)	21 (47.7)	21 (50.0)	0.832
Right-sided, *n* (%)	22 (50.0)	23 (54.7)	0.664
Transperitoneal approach, *n* (%)	19 (43.2)	17 (40.5)	0.800
CT scan size, mean (SD), cm	3.4 (1.1)	3.6 (1.4)	0.462
PADUA score, mean (SD)	6.9 (1.2)	7.0 (1.5)	0.713
Operating time, mean (SD), min	117.3 (32.3)	121.1 (31.1)	0.580
WIT, mean (SD), min	18.0 (5.8)	0	<0.001
WIT, range, min	8–25	–	–
EBL, mean (SD), mL	152.4 (117.6)	290.6 (179.7)	<0.001
Intra-operative complications, *n* (%)	0 (0)	1 (2.4)	0.304
Postoperative complications, *n* (%)	3 (6.8)	5 (11.9)	0.417
Thickness of the peri-tumoural healthy tissue rim, mean (SD), mm	3.9 (2.9)	4.3 (3.1)	0.538
Malignant lesions, *n* (%)	35 (79.5)	33 (78.6)	0.919
PSMs, *n* (%)	0 (0)	1 (2.4)	0.304

BMI, body mass index; CCI, Charlson's comorbitidy index; ASA, American Society of Anesthesiologists; WIT, warm ischaemia time; EBL, estimated blood loss; PSM, positive surgical margin.

Table 2 Functional results stratified according to warm ischaemia time.

	Group A (WIT ≤25 min): *n* = 44	Group B (WIT = 0 min): *n* = 42	*P*
SCr, mean (SD), mg/dL			
Baseline	0.95 (0.25)	0.95 (0.19)	1.000
3 months after surgery	0.98 (0.13)	0.96 (0.20)	0.582
*P**	*0.482*	*0.815*	
eGFR, mean (SD), mL/min			
Baseline	93.2 (21.4)	89.0 (17.5)	0.719
3 months after surgery	91.7 (22.7)	88.4 (17.3)	0.206
*P**	*0.750*	*0.875*	
SRF, mean (SD), %			
Baseline	49.4 (4.7)	49.8 (5.3)	0.712
3 months after surgery	47.2 (4.9)	48.6 (5.3)	0.206
*P**	*0.034*	*0.302*	
ERPF, mean (SD), mL/min*1.73 m^2			
Baseline	191.9 (38.8)	182.0 (49.7)	0.305
3 months after surgery	172.5 (39.0)	174.7 (44.8)	0.413
*P**	*0.022*	*0.793*	
Baseline vs 3 months after surgery			***P***
b-WD SRF, mean (SD)	−0.06 (0.08)	−0.05 (0.09)	0.587
b-WD ERPF, mean (SD)	−0.17 (0.15)	−0.12 (0.11)	0.083

**Student's t-test: baseline vs 3 months after surgery. WIT, warm ischaemia time; SCr, serum creatinine; eGFR, estimated GFR; SRF, split renal function; ERPF, effective renal plasmatic flow; b-WD: baseline-weighted differential.*

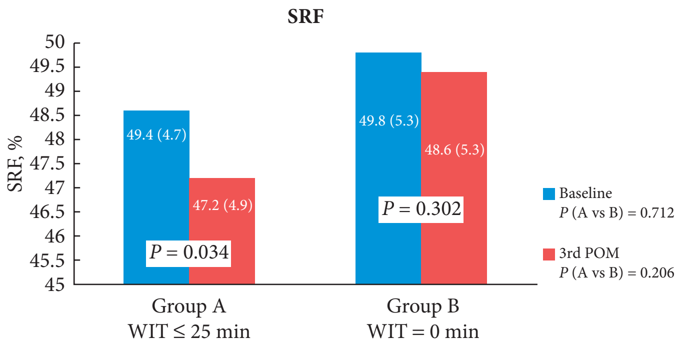
Table 3 Multivariate linear regression model performed in group B using (A)[(3 months after surgery SRF–baseline SRF)/baseline SRF] and (B) [(3 months after surgery ERPF–baseline ERPF)/baseline ERPF] as dependent variables, respectively.

(A) SRF b-WD	**d.f.**	**β**	**β standard error**	***P***
Intercept	1			0.007
CT-scan size (cm)	1	0.223	0.168	0.193
PADUA score	1	0.175	0.167	0.303
Baseline SRF	1	−0.371	0.143	0.013
(B) ERPF b-WD	**d.f.**	**β**	**β standard error**	***P***
Intercept	1			0.007
Baseline SRF	1	−0.327	0.167	0.135
Baseline ERPF	1	−0.233	0.158	0.030

SRF, split renal function; ERPF, estimated renal plasmatic flow; b-WD, baseline-weighted differential; d.f., degrees of freedom.

group B (group A: 152.4 ± 117.6; group B 290.6 ± 179.7; $P <$ 0.001). Nevertheless, this was not reflected in differences in transfusion rates between the groups (no transfusion was reported in either group). No differences were noted between the groups in postoperative complications. Positive surgical margin rates and thickness of peri-tumoural healthy tissue excised were also similar. Renal function results are shown in Table 2 and Figs 1–3. Groups A and B were similar at baseline assessment of renal function. No differences were observed in SCr and eGFR, and mean values were also similar in the two groups at 3 months after surgery. Conversely, in group A, SRF and ERPF values at 3 months after surgery were significantly lower than their baseline values ($P = 0.034$ and $P = 0.022$, respectively), without being significantly different from the mean values 3 months after surgery in group B (Figs 1,2).

Fig. 1 Split renal function (SRF): group A, laparoscopic partial nephrectomy (LPN) with warm ischaemia time (WIT) ≤25 min, columns on the left; group B, LPN with WIT = 0 min, columns on the right. Blue columns show baseline median values of both groups; red columns show median values of both groups 3 months after surgery. No differences in median SRF values were recorded when comparing group A with group B at either baseline ($P = 0.712$) or 3 months after surgery ($P = 0.206$). No differences in SRF were found when comparing baseline values with those 3 months after surgery in group A ($P = 0.034$). In group B, the mean SRF 3 months after surgery was significantly lower than its baseline value ($P = 0.302$). POM, postoperative month.



Consistent with these results, percentages of SRF and ERPF lost were not significantly different between the groups (SRF: −6% in group A and −5% in group B; ERPF: −17% in group A and −12% in group B; $P = 0.587$ and $P = 0.083$, respectively), although a trend towards a greater reduction was observed in group A for both functional variables (Fig. 3). In regression analysis performed in group B (see Table 3), only unmodifiable factors, such as CT scan size ($P = 0.012$), baseline SRF ($P = 0.004$) and PADUA score ($P = 0.022$), were predictive of a higher percentage

Fig. 2 Estimated renal plasmatic flow (ERPF): group A, laparoscopic partial nephrectomy (LPN) with warm ischaemia time (WIT) ≤25 min, columns on the left; group B, LPN with WIT = 0 min, columns on the right. Blue columns show baseline median ERPF for both groups; red columns show median ERPF for both groups 3 months after surgery. No differences in median ERPF values were recorded when comparing group A with group B at either baseline (*P* = 0.305) or 3 months after surgery (*P* = 0.413). No differences were found when comparing baseline EPRF values with those 3 months after surgery in group A (*P* = 0.022). In Group B, the mean ERPF value 3 months after surgery was significantly lower than its baseline value (*P* = 0.793). POM, postoperative month.

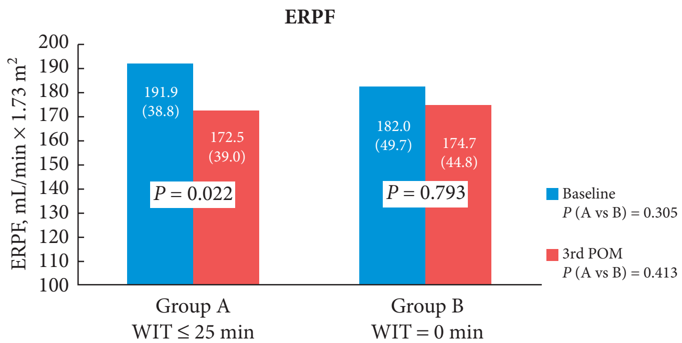
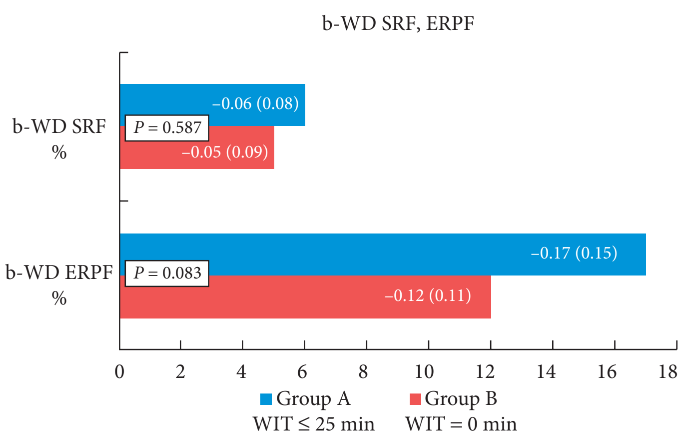


Fig. 3 Baseline-weighted differential (b-WD) for split renal function (SRF) and estimated renal plasmatic flow (ERPF): group A, warm ischaemia time (WIT) ≤25 min, is shown in light grey; group B, WIT = 0 min, is reported in dark grey. b-WD values for SRF and ERPF were not significantly different between the groups.



of SRF lost in the univariate analysis. Baseline SRF ($P = 0.004$) and ERPF ($P = 0.014$) were predictive of a higher percentage of ERPF lost. In multivariate analysis, baseline SRF was found to be the only independent factor predictive of a higher percentage of SRF loss ($P = 0.014$). Accordingly, baseline ERPF was the only independent factor predictive of a higher percentage of ERPF loss ($P = 0.049$).

Discussion

Recent studies on partial nephrectomy functional outcomes have reported that renal damage and subsequent loss of renal function occur even in cases with low WIT, demonstrating that each minute is crucial when the renal artery is clamped [5,6,17]. Based on these findings, an innovative LPN technique was introduced with the aim of saving kidneys from ischaemia, and the first clampless LPN was described [18,19]. A modified technique was then proposed [20,21], incorporating pharmaceutically induced intra-operative hypotension [22,23] and segmental renal artery clamping. The intra-operative reduction in blood pressure included in this technique is not always feasible, however, given the possible vascular comorbidities of patients [24,25]. Indeed, Gill et al. [26] furthered this research by developing a super-selective vascular micro-dissection and tumour devascularisation technique (the so-called 'zero ischaemia technique'). In our institution a few selected lesions have anecdotally been treated using the clampless approach, but since September 2011, we have systematically approached each clinical stage T1 renal mass using clampless LPN to obtain a consecutive series of patients evaluable in terms of post-partial nephrectomy renal functional outcomes without the confounder of ischaemia time. It is known that loss of renal function after partial nephrectomy is a multifactorial process related to unmodifiable factors (age, comorbidities and preoperative renal function) and modifiable factors (duration of ischaemia and sacrifice of unaffected nephrons). While designing the present study, we believed that eliminating the impact of ischaemia would have facilitated studies on other variables responsible for modifications in renal function after partial nephrectomy. Indeed, in this setting quantification of loss of renal function is difficult, especially when analysing patients with approximately normal baseline renal functions; SCr and eGFR are commonly used, but a functioning contralateral kidney may influence the results. By contrast, renal scintigraphy has been shown to be a reliable tool for measuring loss of renal function after partial nephrectomy [3,4,6]. In the present study, we evaluated a consecutive series of 87 patients who underwent LPN. Beginning in September 2011, all LPNs were performed using a clampless approach. The choice was dictated by the fact that, excluding a randomised study, this was the best way to limit other selection biases that could potentially occur in choosing candidates for clampless LPN. In this way, we collected a consecutive cohort of patients undergoing a clampless technique without selecting them. The aim of the study was to compare functional results of clampless LPN with those of clamped LPN to eventually find some differences between these approaches that could justify the higher risks of complications associated from the apparently more challenging procedure of clampless LPN. Patients were divided into 'clamped' and 'clampless' groups: group B (WIT >1 min) and group A (WIT = 0 min). WIT was <25 min in all the clamped procedures. Patients who underwent the clampless LPN were similar to those who underwent a clamped LPN in all peri-operative variables except for estimated blood loss, which was higher in the clampless group as expected, although this was not reflected in differences in transfusion rate. One case of complex angiomyolipomas in the clampless consecutive series required intra-operative clamping of renal artery because of consistent bleeding and was excluded from our analysis. We believe that such lesions are at higher risk of conversion to a clamped approach but accurate dissection of the renal artery before beginning the resection should facilitate prompt clamping, if required, without compromising the safety of the procedure. We considered the time point of 3 months after surgery to be sufficient for scintigraphic evaluation; in a previous study [4], we showed using a 4-year long scintigraphic follow-up that renal damage is detectable by renal scintigraphy within 3 months postoperatively, then remains stable over time. The previously created variable b-WD, which represents the percentage of SRF and ERPF lost relative to their baseline values, was used in statistical analyses to eliminate the possible confounder of different scintigraphic baseline values. In previous multivariate analyses, WIT was the main factor explaining postoperative loss of renal function, and we were concerned it could conceal the statistical influence of other variables in a multivariate model. Interestingly, in the present study, group B could be used for a multivariable analysis that eliminates the statistical weight of WIT; in clampless patients, the independent factor that increased the percentage of loss in the studied scintigraphic variables (SRF and ERPF) was the baseline value of the variable itself, which confirmed that kidney quality during the preoperative assessment is crucial in predicting functional outcomes after LPN and, in our experience, this is true even in case of clampless LPN. In the present analyses, we found that patients in the clampless group (group B) experienced a lower loss of renal function as evaluated using percentages of SRF and ERPF lost (SRF: group A, −6%; group B, −5%; ERPF: group A, −17%; group B, −12%), confirming the results of a previous report by Hung et al. [27]; however, the differences were not statistically significant: patients in group A were similar to those in group B; for this reason, at the end of our analysis, we could approximate groups A and B inside one group only.

Based on these findings, a surgeon would have to modulate LPN on the basis of a patient's baseline renal function; for good preoperative renal function, conventional LPN with WIT <25 min may be the optimum technique, and the risk of a more challenging clampless LPN may be unnecessary, while for patients with poorer baseline renal function, it is crucial to minimise WIT by using a clampless approach (or other techniques), if feasible, to reduce the inexorable loss of renal function after partial nephrectomy compared with the baseline.

The present study highlights the fact that loss of renal function after LPN is not correlated to WIT and baseline renal function only; we found a loss of renal function even in patients who underwent the clampless technique and who had normal renal function at baseline, suggesting that the suture technique (e.g. through suture damage) and the quantity of removed healthy parenchyma could play a crucial role.

The present study has some limitations. Although it was conducted prospectively, a larger sample size would be required to confirm our findings. The patients included in the clampless group were unselected, but they underwent LPN in the later part of surgeon's learning curve for LPN. Notwithstanding these limitations, to our knowledge, this study is the first to investigate renal functional outcomes using renal scintigraphy in a consecutive series of patients who underwent clampless LPN. Our analysis of this group of patients allowed us to evaluate functional outcome irrespective of WIT. Patients who benefitted most from the clampless approach seemed to be patients with compromised baseline function; therefore, surgeons should preoperatively assess the renal function of a patient in order to determine the most suitable WIT for him/her and then choose the best surgical technique to achieve the aim.

In conclusion, in our experience, clampless LPN was a safe procedure: meticulous dissection of the renal artery before performing tumour resection allows prompt clamping if required without compromising the safety of the procedure. With regard to functional evaluation, which was the primary aim of the present study, we observed some renal functional compromise even in patients undergoing clampless LPN. Patients who benefitted mostly from a clampless approach were those with poorer baseline renal function. As ischaemia was rendered a non-factor in this group, it is likely that this incremental functional loss was primarily driven by volume loss or by renorrhaphy-related damage. Future studies should evaluate renal volume data alongside scintigraphy data to better inform this debate, and definitive conclusions need to be drawn about the clinical significance of such minimal damage.

Conflict of Interest

Nothing to declare.

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Correspondence: Francesco Porpiglia, Division of Urology, Department of Clinical and Biological Sciences, University of Turin, 'San Luigi Gonzaga' Hospital, Regione Gonzole 10, 10043 Orbassano (Turin), Italy.

e-mail: porpiglia@libero.it

Abbreviations: LPN, laparoscopic partial nephrectomy; WIT, warm ischaemia time; SCr, serum creatinine; eGFR, estimated GFR; b-WD, baseline-weighted differential; SRF, split renal function; ERPF, estimated renal plasmatic flow.