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20 April 2024

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Abstract

Background

Renal scintigraphy may allow long-term monitoring of ischemic damage after partial nephrectomy (PN).

Objective

Evaluate use of renal scintigraphy for evaluating long-term effects of warm ischemia on renal function in patients with a normal contralateral kidney.

Design, setting, and participants

We prospectively examined kidney function of 54 patients who underwent laparoscopic PN (LPN). Minimum follow-up time was 4 yr.

Intervention

LPN was performed with warm ischemia by transperitoneal or retroperitoneal approach.

Measurements

Demographic, perioperative, and pathologic data and postoperative complications were registered. Split renal function (SRF) and effective renal plasma flow (ERPF) were evaluated by renal scintigraphy preoperatively, at 3 and 12 mo postoperatively, then yearly. Baseline weighted differentials (b-WDs) of both SRF and ERPF in the affected kidney were calculated between baseline condition and every time point. Multivariate linear regression was used to find independent variables for increased b-WDs at 3 and 48 mo. *P* values <0.05 were considered significant.

Results and limitations

The SRF and ERPF of kidneys treated by LPN decreased significantly at month 3 and subsequently remained stable through the duration of follow-up. Conversely, neither serum creatinine nor estimated glomerular filtration rate changed significantly during follow-up. The regression model showed statistical significance at month 3 for warm ischemia time (WIT) and age, whereas at 48 mo, statistical significance was reached by WIT alone. No new onset of cardiovascular disease was registered. No evidence of local recurrence was recorded with computed tomography scan. Our study may be underpowered due to small sample size; however, this is one of the largest long-term prospective series using renal scintigraphy to evaluate the renal function after LPN.

Conclusions

WIT contributes to irreversible kidney damage observed at month 3 that does not appear to worsen.

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1. Introduction

Elective partial nephrectomy (PN) is considered the gold standard of treatment for renal tumors ≤7 cm [1]. Most surgeons prefer the use of vascular clamping to improve visualization of the tumor limits, facilitating complete tumor resection and minimizing the risk of positive surgical margin (PSM). A bloodless field allows precise surgical closure of the collecting system and parenchymal defects [2]. The most common method used to perform ischemia is clamping of the renal artery with or without the renal vein (warm ischemia). Warm ischemia time (WIT) was identified as the most important surgery-related factor affecting renal function in patients who underwent PN [3]. Moreover, ischemic damage and postischemic renal failure may be involved in hypertension development and cardiovascular diseases (CVDs) [4].

Although every minute counts when the renal hilum is clamped [5], data suggest that safe WIT ranges between 20 and 25 min [5], [6] and [7].

Few studies have evaluated the long-term effect of WIT on treated kidney function in patients who underwent elective PN [8], [9], [10] and [11]. Moreover, most of the available studies evaluated kidney function using serum creatinine (SCr) and/or estimated glomerular filtration rate (eGFR), underestimating the importance of the normal contralateral kidney in masking biochemical changes. Renal scintigraphy (RS) is the only method that allows clinicians to quantify real changes in the amount of renal-function loss of the treated kidney [12] and [13]. To contribute to this discussion, we planned the present prospective study with two aims. The first was to evaluate the long-term effect of WIT on renal function, using split renal function (SRF) and effective renal plasmatic flow (ERPF) estimated by radionuclide technetium Tc 99m–mercaptoacetyl-triglycine (^{99m}Tc-MAG-3) RS, in a series of patients who underwent elective LPN for renal tumors. The second aim was to identify the predictors of renal damage following LPN.

2. Patients and methods

We prospectively enrolled all patients who underwent LPN between July 2004 and December 2007. All patients signed a written informed consent approved by the ethics committee of our center. Abdominal computed tomography (CT) scan and RS using radionuclide 99mTc-MAG-3 were performed preoperatively in every patient.

2.1. Inclusion criteria

We enrolled all patient candidates for LPN of renal tumors ≤4 cm, with baseline eGFR (modification of diet in renal disease [MDRD] formula) ≥60 ml/min [4] (stage I/II chronic kidney disease [CKD] according to the Kidney Disease Outcomes Quality Initiative), and baseline SRF ranging from 45% to 55% in the treated kidney. Only patients with minimum follow-up of 4 yr were included in the analysis.

2.2. Exclusion criteria

Patients with a solitary or horseshoe-shaped kidney and/or kidney scars at the preoperative CT scan were excluded. In addition, patients who experienced complications potentially affecting kidney function, such as significant bleeding (causing severe hypotension), urinary fistula, kidney infection, or any other condition different from the intervention itself were excluded from the analysis.

2.3. Intervention

All patients underwent LPN performed by a single surgeon using the technique described previously [14]. In all cases, the renal artery alone was clamped with a bulldog clamp and declamped at the end of the renal parenchyma reconstruction.

2.4. Measurements

For each patient, we prospectively collected the following variables in a dedicated database: demographic data including comorbidities classified according to Charlson comorbidity index (CCI) [15], and clinical tumor size, side, and location according to the RENAL nephrometry score [16]; perioperative data; pathologic data; and postoperative complications classified according to the Clavien system [17]. Moreover, CCI and new onset of CVDs were recorded at each time point. Body mass index (BMI) also was recorded to assess whether LPN influenced patients' body build, a possible confounder of eGFR assessment [13].

Patients with a final diagnosis of renal cell carcinoma were generally observed every 3 to 4 mo for the first year after LPN and every 6 mo from the second through the fifth years. Oncologic follow-up consisted of a history, a physical examination, and an abdominal evaluation using ultrasound or CT scan. Elective bone scan, chest CT, and magnetic resonance imaging were performed when clinically indicated.

2.5. Evaluation of renal function

SCr and eGFR (abbreviated MDRD formula) were assessed by serial measurements; SRF and ERPF were evaluated by ^{99m}Tc-MAG-3 RS. All renal scintigraphies were performed at our institution and read by a dedicated nuclear-medicine doctor. The measures were conducted preoperatively, at the 3rd and 12th postoperative months (POMs), and then yearly for a minimum of 4 yr.

A normal range does not exist for SRF and ERPF calculated by RS and there is variability among patients, so we created a new variable called *baseline weighted differential* (b-WD) that represented the percentage of loss of SRF or ERPF, considering the baseline value. This variable was used in statistical analysis to eliminate the possible confounder of a different patient's scintigraphic baseline value in the preoperative setting, with 1) b-WD of SRF = (n POM SRF − baseline SRF)/baseline SRF, where n = 3, 12, 24, 36, and 48, respectively, and 2) b-WD of ERPF = (n POM ERPF − baseline ERPF)/baseline ERPF, where n = 3, 12, 24, 36, and 48, respectively.

2.6. Pathology assessment

A dedicated uropathologist analyzed fresh-tissue specimens from the operative room and assigned extension of the primary tumor according to the 2009 version of TNM classification [18]. After fixation in a 10% formalin solution, all specimens were step-sectioned at 5-mm intervals and the entire specimen was analyzed, including the distance between the inked margin and the tumor, with the aim of assigning the mean value of the thickness of the peritumoral healthy tissue [19]. Histologic subtypes and nuclear grade were defined according to the World Health Organization classification [20] and to the Fuhrman classification [21], respectively. PSM was defined as cancer cells at the level of inked parenchymal excision surface [19].

2.7. Statistical analysis

Means and standard deviations were used to report continuous variables. Frequencies and proportions were used for categoric variables. The means of continuous variables were compared using the student t test after verifying that variables to be analyzed were approximately normally distributed. Analysis of variance (ANOVA) was used to compare the means of more than two groups. Multivariable linear regression analysis was used to identify independent predictors of SRF and ERPF b-WD changes. All variables potentially influencing postoperative renal function were included in the models.

All tests were two sided, and p values <0.05 were considered significant. All statistical analyses were performed using Statistic 6 (Statsoft Inc.; Tulsa, OK, USA).

3. Results

Seventy-five patients were enrolled during the specified period. Three patients were excluded: One patient was not analyzed due to horseshoe-shaped kidney, and two patients had early postoperative complications (one had acute bleeding causing severe hypotension and one had a urinary fistula) and were excluded from undergoing following scintigraphic controls. Of 72 analyzable patients, 54 reached the minimum follow-up of 4 yr and were considered the population of the study. Table 1 shows the demographic, perioperative, and pathologic findings of these patients.

Observed postoperative complications (n = 4; 7.4%) were grade 1–2, according to Clavien classification. Specifically, two patients required transfusion for postoperative bleeding, one patient was medically treated for pneumonia, and one patient was treated for pleural effusion. During oncologic follow-up, no patient showed local recurrence or distant progression. No patient died during the follow-up period.

Neither SCr nor eGFR changed significantly during follow-up (Table 2). Conversely, either the mean value or the value at 3 mo after LPN, both for SFR (48.05 ± 4.33 vs 44.76 ± 2.40; p = 0.0030) (Fig. 1a) and ERPF (182.70 ± 34.01 vs 153.54 ± 42.34; p = 0.0001) (Fig. 1b) of the operated kidney decreased significantly in comparison with their baseline values. This decrease remained stable for follow-up measurements. Accordingly, no differences were found among the five postoperative functional measurements (Table 2). Moreover, SRF b-WD (Fig. 1c) and ERPF b-WD (Fig. 1d) were comparable at every time point.

At multivariable analysis (Table 3), age (p = 0.03) and WIT (p = 0.03) turned out to be independent predictors of SRF b-WD increasing 3 mo after LPN. Only WIT was a predictor of ERPF b-WD increasing (p = 0.0210) 3 mo after LPN, while 4 yr after PN, only WIT predicted ERPF b-WD increasing. Conversely, no risk factor for worsening of SRF b-WD was detected.

BMI and CCI did not change statistically at the measured time points. No new onset of CVDs was registered.

4. Discussion

Many studies evaluating functional outcomes after LPN have been performed in patients either with a solitary kidney or with a normal contralateral kidney. These studies used different markers of kidney function, mainly aiming to identify a *safe* WIT cut-off. Results have varied based on the individual experience of the surgeons involved, the patient population size, and the markers used. Although some authors suggested that every minute counts when the renal hilum is clamped [5], the majority of these studies indicate a safe WIT cut-off range between 20 and 25 min [5], [6] and [7]. In previous studies, the 25-min WIT cut-off appeared to be the most clinically helpful [5], [22] and [23].

It is well known that warm ischemia (WI) causes a direct hypoxic injury to the kidney [24], but the natural history of this recorded damage is not well understood. The aim of the present prospective study was to better elucidate this natural history.

We analyzed 54 patients who underwent LPN performed with WI and we evaluated renal function by using SCr, eGFR and, specifically, RS. This nuclear-medicine technique has been used in various studies in the urologic literature [12], [13] and [22] to estimate renal damage of operated kidney after intervention by using SRF and ERPF.

All analyzed patients reached a minimum follow-up time of 4 yr and we considered this length of follow-up sufficient to study the history of renal function following LPN.

Our results confirmed that SCr and derived measures have low sensitivity for evaluating kidney damage in cases presenting normal or moderately reduced kidney function (CKD stage I/II) at follow-up. In contrast, by using SRF and ERPF estimated by RS, we recorded loss of renal function at the third POM with respect to baseline. This loss remained stable over time as confirmed by follow-up measurements of SRF and ERPF and b-WD variables. Thus we can state that major loss of kidney function is recorded by the third POM, whereas kidney function remains stable over further follow-up. These findings may suggest that future studies of early kidney damage should focus on the results of RS and should accurately record SRF and ERPF data.

Confirming literature findings, the multivariable linear regression analysis evaluating our data at postoperative months 3 and 48 indicated that WIT plays a crucial role in predicting worsening of scintigraphic parameters after LPN. Moreover, age was statistically significant on third-POM analysis based on SRF b-WD, confirming that unmodifiable parameters also have an important impact on renal function [25]. In the present study, all other parameters demonstrated no statistical significance in predicting kidney function impairment over the course of a series of long-term follow-ups.

One of the concerns with long-term kidney damage is that pathogenic insult (eg, WIT) may trigger a mechanism of renal damage maintained by cytokines produced by cells of the distal tubuli that are able to exacerbate the inflammatory response, stimulating further injury [24] and [26]. This is not supported by our findings. On the contrary, our results support the hypothesis of limited damage, remaining stable over time.

With regard to comorbidities, we recorded neither an increase in CCI nor a new onset of CVDs with respect to the baseline conditions. According to our data at the fourth postoperative year, we can state that the limited injury to kidney parenchyma following LPN is not sufficient to trigger mechanisms involved in hypertension development and following CVDs or comorbidities related to postischemic renal failure.

We did not record any local recurrence or evidence of new-onset parenchymal scars among patients who had a histologic diagnosis of malignant tumor and underwent CT scan during follow-up. The absence of any parenchymal scar indirectly confirmed that there is not a fibrogenic response to ischemia and may suggest that there is not progressive involvement of the whole parenchyma.

5. Conclusions

In patients who undergo LPN performed with WI, the majority of renal damage detected by RS is recorded within the third POM without further worsening over time. WI seems to be the most important independent variable for predicting renal damage and surgeons should make every effort to minimize WI intervals. Moreover, it seems that renal ischemia does not trigger any mechanism leading to new onset of morbidities after LPN.

manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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Table 1.

Demographic, perioperative, and pathologic data and complications

	Patients ($n = 54$)
Age, yr, mean (SD)	57.61 (13.92)
Males, no. (%)	38 (70.4)
BMI, kg/m^2, mean (SD)	26.61 (3.40)
CCI, mean (SD)	0.90 (1.40)
SCr, mg/dl, mean (SD)	0.97 (0.23)
EGFR, ml/min, mean (SD)	85.76 (25.71)
SRF, %, mean (SD)	48.05 (4.33)
ERPF, ml/min × 1.73 m^2, mean (SD)	182.70 (34.01)
ASA score ≥3 (SD)	27 (50.0)
Right-sided LPN, no. (%)	23 (42.6)
Transperitoneal approach, no. (%)	39 (72.2)
CT scan size, cm, mean (SD)	3.69 (1.39)
RENAL nephrometry score, mean (SD)	5.00 (1.39)
Operative time, min, mean (SD)	121.02 (34.52)
WIT, min, mean (SD)	27.98 (11.12)
WIT, min, range	9–60
EBL, ml, mean (SD)	127.89 (82.73)
Intraoperative complications, no. (%)	0 (0)
Postoperative complications, no. (%)	4 (7.4)
Thickness of peritumoral healthy tissue rim, mm, mean (SD)	4.40 (3.12)
Malignant lesions, no. (%)	41 (76.0)
Positive surgical margins, no. (%)	0 (0)

BMI = body mass index; CCI = Charlson comorbidity index; SCr = serum creatinine; eGFR = estimated glomerular filtration rate; SRF = split renal function; ERPF = effective renal plasmatic flow; ASA = American Society of Anesthesiology; LPN = laparoscopic partial nephrectomy; CT = computed tomography; WIT = warm ischemia time; EBL = estimated blood loss; SD = standard deviation.

Table 2.

Functional results at timed controls

	Baseline (0)	3rd POM (1)	12th POM (2)	24th POM (3)	36th POM (4)	48th POM (5)	ANOVA test		*t* test
							Overall (baseline and postoperative controls; 0 vs 1 vs 2 vs 3 vs 4 vs 5)	Only postoperative controls (1 vs 2 vs 3 vs 4 vs 5)	Baseline vs mean postoperative value
SCr, mg/dl, mean (SD)	0.97 (0.23)	0.96 (0.14)	0.99 (0.23)	0.99 (0.22)	0.98 (0.34)	0.97 (0.18)	0.1912	0.1611	0.8292
EGFR, ml/min, mean (SD)	85.76 (25.71)	88.22 (24.01)	84.50 (26.03)	84.46 (25.85)	84.04 (24.20)	85.15 (24.76)	0.1407	0.1046	0.9205
SRF, %, mean (SD)	48.05 (4.33)	44.76 (6.71)	44.52 (6.20)	44.91 (5.89)	45.26 (5.80)	45.78 (5.02)	<0.0001	0.2851	0.0048
ERPF, ml/min × 1.73 m^2, mean (SD)	182.70 (34.01)	153.54 (42.34)	150.59 (41.87)	152.87 (40.41)	155.57 (41.12)	157.31 (38.90)	<0.0001	0.3263	0.0001

POM = postoperative month; ANOVA = analysis of variance; SCr = serum creatinine; eGFR = estimated glomerular filtration rate; SRF = split renal function; ERPF = effective renal plasmatic flow; SD = standard deviation.
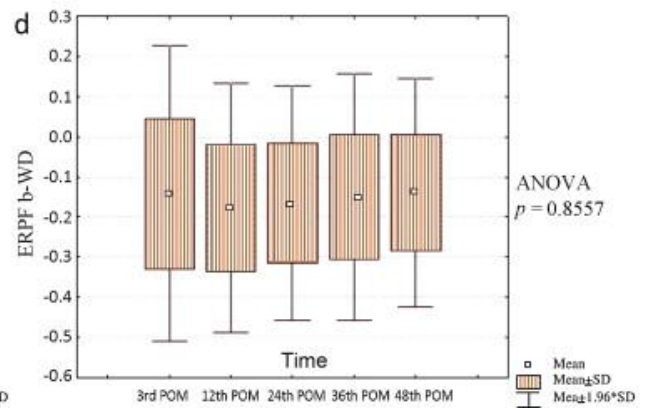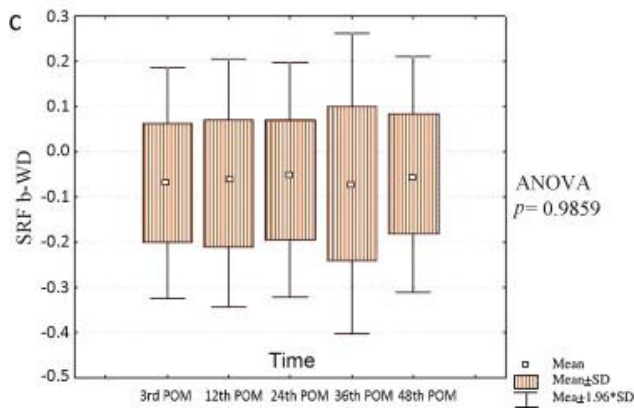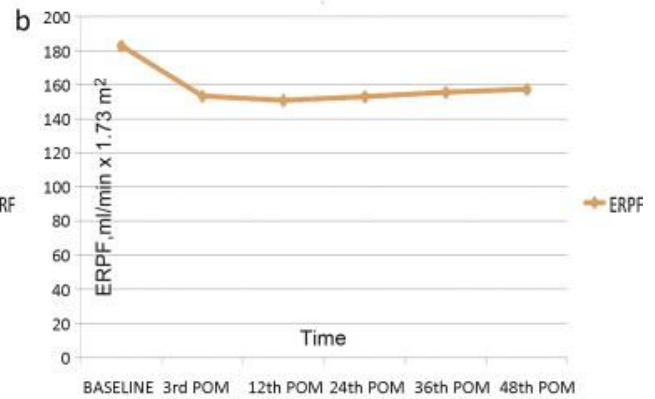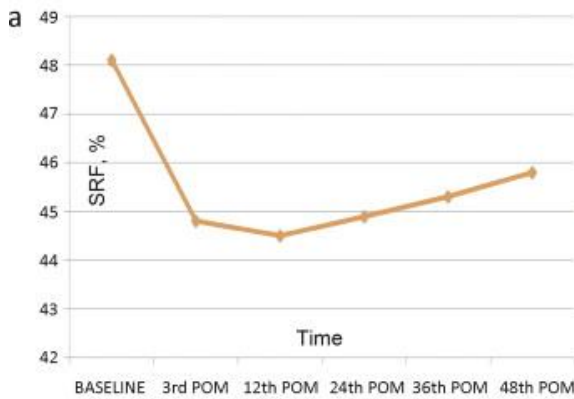
Table 3.

Multivariable linear regression model

	SRF b-WD		ERPF b-WD	
	3rd POM	48th POM	3rd POM	48th POM
	p value		*p* value	
Intercept	0.1763	0.4589	0.3460	0.3709
CCI	0.6188	0.5149	0.8158	0.8792
Age, yr	0.0310	0.0792	0.6106	0.3466
Baseline BMI	0.7304	0.9413	0.2278	0.3786
CT scan size, cm	0.2079	0.7326	0.2442	0.1536
RENAL score	0.9972	0.7248	0.898613	0.5908
Peritumoral healthy tissue rim thickness, mm	0.4865	0.2845	0.7518	0.8570
WIT, min	0.0241	0.1314	0.0210	0.0157

SRF = split renal function; ERPF = effective renal plasmatic flow; b-WD = baseline-weighted differential; POM = postoperative month; CCI = Charlson comorbidity index; BMI = body mass index; CT = computed tomography; WIT = warm ischemia time.