Renal functional outcome after laparoscopic partial nephrectomy using dynamic renal scintigraphy

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Introduction: *To explore postoperative operation-side renal functional outcome after laparoscopic partial nephrectomy (LPN) using dynamic renal scintigraphy.*
Materials and methods: *Between July 2006 and December 2014, 62 patients with localized renal tumor received ischemic LPN at our institution. Preoperative, 6 months postoperative, and 12 months postoperative split renal functions were evaluated by dynamic renal scintigraphy using radionuclide technetium-99m-mercaptoacetyltriglycine. Postoperative operation-side renal function was calculated. To assess the significant factors affecting postoperative operation-side renal functional decrease, simple regression and multiple regression analyses were carried out.*
Results: *Postoperative operation-side renal functions were significantly decreased to 86.6% at 6 months and 86.9% at 12 months postoperatively ($p < 0.0001$). Simple regression analyses revealed that postoperative operation-side renal functions were significantly decreased with prolonged warm ischemia time at 6 months and 12 months postoperatively ($p = 0.0058$ and 0.0032, respectively). Multiple regression analysis identified warm ischemia time as an independent predictive factor for operation-side renal functional decreases at 6 months and 12 months postoperatively ($p = 0.0158$ and 0.0109, respectively).*
Conclusions: *Irreversible renal damage using dynamic renal scintigraphy after LPN was observed. With prolongation of warm ischemia time during LPN, postoperative operation-side renal function was significantly decreased.*

Key Words: laparoscopic partial nephrectomy, dynamic renal scintigraphy, split renal function, warm ischemia time

Introduction

Nephron-sparing surgery has emerged as a standard treatment for small renal tumors, providing a similar cancer control outcome to radical nephrectomy with the benefit of renal functional preservation.[1,2] Laparoscopic partial nephrectomy (LPN) is a feasible surgical procedure for selected patients with small, localized renal tumors. Although it is a minimally invasive nephron-sparing surgery, it has several technical difficulties, such as intracorporeal tumor resection and parenchymal suturing. Vascular clamping allows better visualization, helping facilitate complete and accurate tumor resection, and precise surgical closure of the collecting system and parenchymal defect.[3] The most common method used to perform warm ischemia is clamping of the renal artery with or without the renal vein, but it entails renal ischemia and sometimes leads to ischemic damage when prolonged. Warm ischemia time was identified as the most important factor affecting renal functional outcome after LPN.[4]

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Renal scintigraphy is the only method to quantify real changes in the amount of renal functional loss for an affected kidney.[5,6] Nuclear scans can indicate damage to the affected kidney that is not reflected in serum creatinine measurements and estimated glomerular filtration rate calculations.[7] The present study explored the postoperative operation-side renal functional outcome evaluation using dynamic renal scintigraphy after LPN.

Materials and methods

The present study was performed with the approval of the Kitasato University Medical Ethics Organization (approval no. KMEO B16-155). The requirement for informed consent was waived due to the retrospective nature of the analyses. Between July 2006 and December 2014, 62 patients with localized renal tumor who received ischemic LPN and were examined preoperatively and postoperatively with dynamic renal scintigraphy at our institution were enrolled. The sample group contained 42 men and 20 women, with a median age of 64 years (range 36-81 years) at the time of operation. Demographic data included clinical tumor size, tumor sites, and location according to the R.E.N.A.L. nephrometry score.[8] Perioperative data included operative time, warm ischemia time, estimated blood loss, and specimen weight.

LPN was performed by two surgeons in a similar manner, and approach (transperitoneal or retroperitoneal) was based on tumor location. The renal hilum and renal artery were identified. Gerota's fascia was dissected off the renal surface, preserving the perirenal fatty tissue in contact with the tumor. Using intraoperative ultrasound, the incision line was determined and circumferentially scored by electrocautery. About 5 mm normal parenchymal margin was taken along with the tumor. A vascular bulldog clamp was used for complete vascular occlusion of the renal artery(s) to provide a bloodless operative field. The tumor was excised using cold scissors along the marking. Any intraoperative pelvicalyceal injury was reconstructed with absorbable sutures. The renal parenchymal defect was sutured with polyglactin or polyglyconate. At the end of renal parenchymal reconstruction, renal artery(s) was declamped. Before and after arterial clamping, 100 mL each of 20% mannitol was injected intravenously.

Preoperative, 6 months postoperative, and 12 months postoperative split renal functions were evaluated by dynamic renal scintigraphy using radionuclide technetium-99m-mercaptoacetyltriglycine (^{99m}Tc-MAG3). Postoperative operation-side renal function was calculated: postoperative/preoperative split renal function (%).

The Wilcoxon signed-rank test was used to evaluate for a statistically significant difference in the reduction of renal function. To assess the significant factors affecting postoperative operation-side renal functional decrease, simple regression and multiple regression analyses were carried out. All analyses were performed using StatView software, version 5.0 (SAS Institute, Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

Results

The characteristics of the patients are summarized in Table 1. The median tumor size was 2.2 cm (range 1.1-

TABLE 1. **Patient characteristics**

Gender, n (%)	
Male	42 (67.7)
Female	20 (32.3)
Age (years)	
Median	64
Range	36-81
Mean ± SD	61.5 ± 11.6
Body mass index (kg/m^2)	
Median	23.6
Range	14.5-30.4
Mean ± SD	23.5 ± 3.0
Tumor size (cm)	
Median	2.2
Range	1.1-4.8
Mean ± SD	2.3 ± 0.8
Tumor sites, n (%)	
Right	36 (58.1)
Left	26 (41.9)
R.E.N.A.L. nephrometry score	
Median	5
Range	4-8
Mean ± SD	5.6 ± 1.4
Complexity, n (%)	
Low (4-6)	46 (74.2)
Moderate (7-9)	16 (25.8)
Suffix, n (%)	
"A"nterior	24 (38.7)
"P"osterior	18 (29.0)
"X"	20 (32.3)

SD = standard deviation

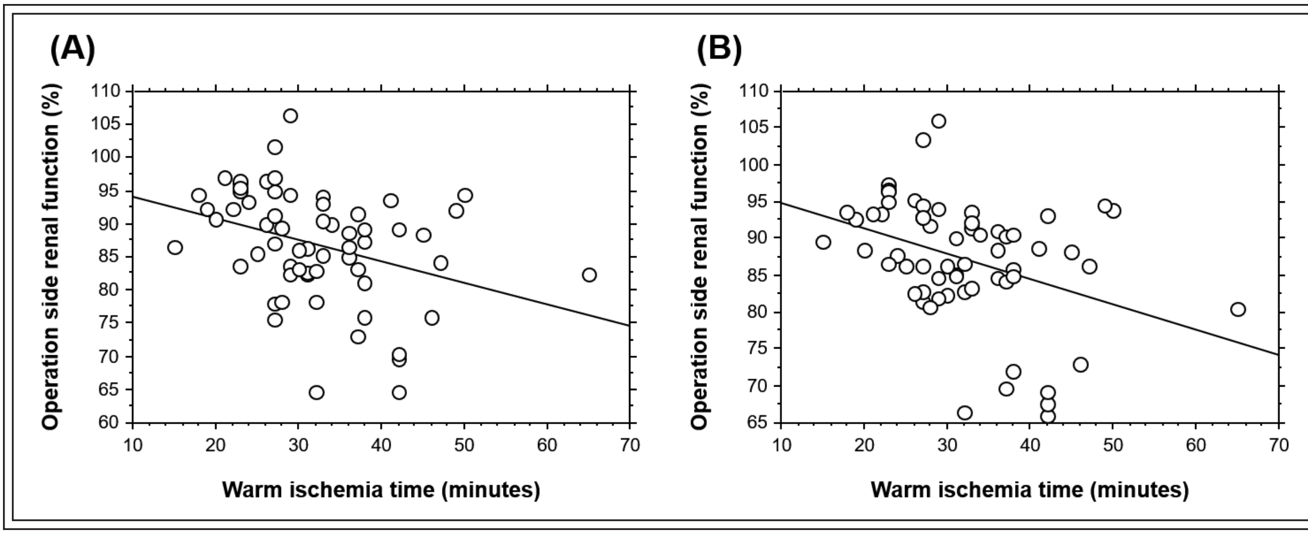

Figure 1. Postoperative operation-side renal functions were significantly decreased with prolonged warm ischemia time at **(A)** 6 months (p = 0.0058) and **(B)** 12 months (p = 0.0032) postoperatively.

4.8 cm), and the median R.E.N.A.L. nephrometry score was 5 (range 4-8). There were no hilar tumors (suffix "h"). LPN was performed via transperitoneal approach in 39 patients and via retroperitoneal approach in 23 patients. The mean and median operative time was 200.8 ± 40.7 and 195 minutes (range 120-325 minutes), the mean and median warm ischemia time was 32.1 ± 9.0 and 31 minutes (range 15-65 minutes), and the mean and median estimated blood loss was 53.8 ± 84.0 and 20 mL (range 10-450 mL). Histopathological examination revealed renal cell carcinoma in 54 patients (87.1%), angiomyolipoma in 5 patients (8.1%), oncocytoma in 1 patient (1.6%), and adenoma in 2 patients (3.2%).

Postoperative operation-side renal functions were significantly decreased to 86.6% at 6 months and 86.9% at 12 months postoperatively (p < 0.0001).

Simple regression analyses revealed that postoperative operation-side renal functions were significantly decreased with prolonged warm ischemia time at 6 months and 12 months postoperatively (p = 0.0058 and 0.0032, respectively), Figure 1. R.E.N.A.L. nephrometry score, operative time, estimated blood loss, and specimen weight did not appear to have statistically significant correlation at each time point. Multiple regression analysis included age, body mass index, tumor size, R.E.N.A.L. nephrometry score, operative

TABLE 2. **Multiple regression analysis**

	6 months postoperatively		**12 months postoperatively**	
	Coefficient	**p value**	**Coefficient**	**p value**
Age	0.038 (−0.152-0.229)	0.6877	0.079 (−0.110-0.269)	0.4060
BMI	0.438 (−0.341-1.216)	0.2645	0.363 (−0.410-1.137)	0.3506
Tumor size	0.125 (−0.328-0.578)	0.5818	0.170 (−0.280-0.620)	0.4529
R.E.N.A.L. nephrometry score	−0.329 (−2.098-1.441)	0.7109	−0.207 (−1.966-1.553)	0.8148
Operative time	−0.038 (−0.102-0.026)	0.2343	−0.038 (−0.101-0.026)	0.2404
EBL	0.022 (−0.005-0.050)	0.1027	0.016 (−0.011-0.043)	0.2308
Warm ischemia time*	−0.339 (−0.612-−0.066)	0.0158	−0.357 (−0.628-−0.086)	0.0109
Specimen weight	−0.130 (−0.468-0.208)	0.4447	−0.138 (−0.474-0.197)	0.4120

*statistically significant
BMI = body mass index; EBL = estimated blood loss

time, warm ischemia time, estimated blood loss, and specimen weight. Warm ischemia time was identified as an independent predictive factor for operation-side renal functional decrease at 6 months and 12 months postoperatively ($p = 0.0158$ and 0.0109, respectively), Table 2.

Discussion

Several studies revealed that the length of warm ischemia time is the most important predictor of postoperative renal function after LPN.[7,9-14] Warm ischemic renal damage has been considered as an important factor of remnant renal function of the affected kidney.[7] Nuclear renal scintigraphy is a useful method to quantify split renal function of the damaged kidney.[7,9,12-14] Kobayashi et al[9] evaluated the functions of an affected kidney after LPN using renal scintigraphy with ^{99m}Tc-MAG3. The median contribution of the affected kidney to total renal function in 10 patients was 50.0%, 41.7% and 36.1% before surgery, 1 week, and 3 months after LPN, respectively.[9] Porpiglia et al[12] also evaluated the long term effect of warm ischemia time on renal function using split renal function estimated by ^{99m}Tc-MAG3. A total of 54 patients who underwent LPN were prospectively examined. Split renal function of the treated kidney significantly decreased to 93.2% at 3 months after LPN and subsequently remained stable through the 48 month follow up duration. The regression model demonstrated that warm ischemia time contributes to irreversible kidney damage. Warm ischemia time plays a crucial role in predicting worsening of scintigraphic parameters after LPN.[12]

In the present study, split renal function was evaluated by dynamic renal scintigraphy using ^{99m}Tc-MAG3 at 3 time points, preoperatively, 6 months postoperatively, and 12 months postoperatively. Postoperative operation-side renal functions were significantly decreased to 86.6% at 6 months and 86.9% at 12 months postoperatively ($p < 0.0001$). Multiple regression analysis identified warm ischemia time as an independent predictive factor for operation-side renal functional decrease at 6 months and 12 months postoperatively ($p = 0.0158$ and 0.0109, respectively). It is an important finding to determine irreversible renal damage using dynamic renal scintigraphy after LPN. Although warm ischemia times of the present study were relatively long, yet still there was a fairly small loss in operation-side renal function. Even with warm ischemia time ≥ 45 minutes (6 patients) there was relatively still good residual renal function. This is valuable information suggesting that if LPN is difficult and warm ischemia time is long, it should not give up and should not perform radical nephrectomy since reasonable renal function may still be present even after ≥ 45 minutes.

Warm ischemia causes a direct hypoxic injury to the treated kidney.[15] Postischemic renal damage have been attributed to persistent vasoconstriction, in part a result of ensuring activation of tubuloglomerular feedback due to enhanced delivery of solute to the macula densa. Increased solute delivery to the distal nephron is caused by impairment of both tight junctions and cell-cell adhesion along the lateral membrane of the proximal tubule cells, resulting in decreased sodium reabsorption through the loss of proximal tubule cell polarity for Na^+/K^+-ATPase distribution.[16,17] Long term kidney damage by warm ischemia may trigger a mechanism of renal damage maintained by cytokines produced by cells of the distal tubule that are able to exacerbate the inflammatory response, stimulating further injury.[15,18]

Mercaptoacetyltriglycine (MAG3) clearance has been reported to parallel creatinine clearance or to be superior to the conventional creatinine clearance for monitoring changes in renal function.[19,20] MAG3 is extracted by the renal tubules similar to para-aminohippuric acid and iodine-131-orthoiodohippurate; consequently, MAG3 clearance provides a measurement of effective renal plasma flow.[21] The normal MAG3 clearance rate is approximately 300 to 320 mL/min/1.73 m^2.[22,23] MAG3 clearance is much more reproducible and shows a greater sensitivity to changes in renal function.[20]

Mannitol was used in the present study to prevent warm ischemic damage. All patients received 100 mL each of 20% mannitol injection before and after arterial clamping, so the real effect of prevention was hard to investigate. Mannitol has traditionally been given intravenously before arterial occlusion to prevent ischemic renal damage with decrease of intracellular swelling.[18] However, a recent study revealed that mannitol made no significant difference in both the postoperative estimated glomerular filtration rate and its decrease rate at any point during the postoperative period. There might be no advantage from the administration of mannitol to reduce ischemic renal damage.[24]

The possibility of renal functional loss due to removal of functioning renal tissue or devascularization of areas of the kidney during dissection should be mentioned. However, accurate quantifications of these renal volumes are difficult. Instead of these, removal specimen weight was used on simple regression analysis and multiple regression analysis in the present study. Specimen weight did not affect postoperative operation-side renal functional decrease. Other tumor characteristics (tumor size and R.E.N.A.L. nephrometry score) also did not affect postoperative operation-side renal function.

The present study had several limitations. First, this was a single-institutional study, and, second, the sample size was small. However, significant results were obtained and we do not consider that these limitations affected the validity of our results.

In many centers, LPN is currently being switched to robot-assisted partial nephrectomy (RAPN). Our institution has also used RAPN in place of LPN since 2015. However, the present study is meaningful to understand the effect of warm ischemia on renal functional outcome after LPN.

In conclusion, irreversible renal damage using dynamic renal scintigraphy after LPN was observed. With prolongation of warm ischemia time during LPN, postoperative operation-side renal function was significantly decreased. Warm ischemia time is an independent predictive factor for operation-side renal functional decrease after LPN. □

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