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Predictive factors of prolonged warm ischemic time (≥30 minutes) during partial nephrectomy under pneumoperitoneum

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Purpose: Current clinical data support a safe warm ischemia time (WIT) limit of 30 minutes during laparoscopic partial nephrectomy (LPN) or robot-assisted partial nephrectomy (RPN). We evaluated independent factors predicting prolonged WIT (more than 30 minutes) after LPN or RPN.

Materials and Methods: A retrospective data review was performed for 317 consecutive patients who underwent LPN or RPN performed by the same surgeon from October 2007 to May 2013. Patients were divided into two groups: group A was defined as prolonged WIT (≥30 minutes) and group B as short WIT (<30 minutes). We compared clinical factors between the two groups to evaluate predictors of prolonged WIT.

Results: Among 317 consecutive patients, 80 were in the prolonged WIT group. Baseline characteristics were not significantly different between the groups. In the univariable analysis, PADUA (preoperative aspects and dimensions used for an anatomical) score (p=0.001), approach method (transperitoneal or retroperitoneal approach; p<0.001), and surgeon experience (p<0.001) were significantly associated with prolonged WIT. In the multivariable analysis, PADUA score (p=0.032), tumor size (≥25 mm; odds ratio, 2.98; 95% confidence interval, 1.48–5.96; p=0.002), and surgeon experience (p<0.001) were independent predictors of prolonged WIT.

Conclusions: Surgeon experience, tumor size, and PADUA score predicted prolonged WIT after RPN or LPN. Among these factors, increasing surgical experience with LPN or RPN is the most important factor for preventing prolonged WIT.

Keywords: Laparoscopy; Nephrectomy; Robotic surgical procedures; Warm ischemia

INTRODUCTION

The incidence of renal cell carcinoma is consistently increasing, and the increase in use of imaging technologies has resulted in an increase in the incidental detection of renal cell carcinoma, especially of small renal masses [1]. Nephron-sparing surgery has become the standard treatment for small renal masses, demonstrating improved overall survival and superior preservation of renal function compared with traditional radical nephrectomy [2]. In

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addition, laparoscopic partial nephrectomy (LPN) and robot-assisted partial nephrectomy (RPN) have been accepted as treatment options for small renal masses with adequate oncologic outcomes [3].

Several factors predict renal functional outcome after partial nephrectomy, including older age, sex, lower preoperative glomerular filtration rate (GFR), single kidney, tumor size, and longer ischemic interval [4]. The warm ischemia inevitable in LPN or RPN can produce ischemic renal damage. The limit of 30 minutes in patients with normal preoperative kidney function is currently accepted as a safe warm ischemia time (WIT) [5,6]. Our previous study demonstrated that patients with a WIT>28 minutes had a significantly greater decrease in the GFR of the affected kidney; in multivariate analysis, WIT was an independent predictive factor of functional reduction of the affected kidney [7]. Although a WIT ranging from 20 to 30 minutes was thought to be safe, some authors have suggested that every minute counts when the renal hilum is clamped. To minimize ischemic renal injury, many surgeons make an effort to decrease the WIT to less than 30 minutes during partial nephrectomy under pneumoperitoneum. However, there are few studies on preoperative predictors of prolonged WIT during LPN or RPN performed by a single surgeon. In this study, we evaluated patients who underwent LPN or RPN and tumor characteristics predictive of prolonged WIT.

MATERIALS AND METHODS

With the approval of our Institutional Review Board, we retrospectively analyzed the medical records of 317 patients who underwent partial nephrectomy. Partial nephrectomy was conducted by laparoscopic or robot-assisted surgeries and was performed by the same surgeon between October 2007 and May 2013. According to the tumor location, we performed transperitoneal approaches for anteriorly or laterally located tumors and retroperitoneal approaches for posteriorly located tumors. For arterial clamping during surgery, we used Bulldog clamps (Aesculap, Center Valley, PA, USA) (Fig. 1A). Color Doppler laparoscopic ultrasound was used to confirm whether hilar clamping was proper or not. Resection of the tumor was completed with scissors, without application of electrosurgical coagulation devices (Fig. 1B). After tumor excision, surgical bed hemostasis was achieved by oversewing vessels by using 3-0 PDS or 3-0 V-Loc sutures with a Lapra-Ty clip (Ethicon, Cincinnati, OH, USA) at the terminal end (Fig. 1C). The renal parenchyma was repaired with 1-0 Vicryl sutures placed in an contiuous fashion across the defect, and the sliding technique with Hem-o-lok clip was used to tighten and secure the sutures (Fig. 1D). Our surgical technique is demonstrated in a Supplementary material (video clip). Ischemia time was defined as the interval between placement of the first

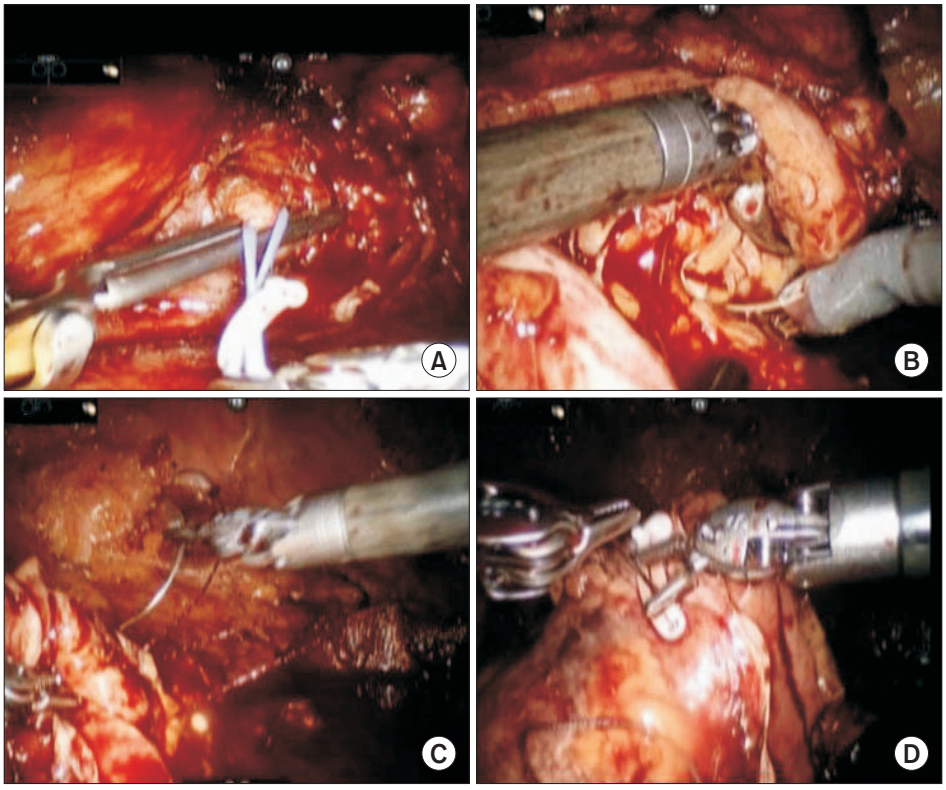

Fig. 1. Images from robot-assisted laparoscopic partial nephrectomy. (A) Arterial clamping with Bulldog clamps, (B) Resection of the tumor, (C) Surgical bed hemostasis, and (D) Sliding clip technique renorrhaphy with 1-0 Vicryl. Scan this QR code to see the accompanying video, or visit www.kjurology.org or https://youtu.be/FcFHDcIB1UE.

Table 1. Comparison of baseline characteristics and perioperative parameters between the short warm ischemia time group (WIT<30 minutes) and the prolonged warm ischemia time group (WIT≥30 minutes)

Characteristic	WIT<30 min (n=237)	WIT≥30 min (n=80)	p-value
Sex			
Male	152 (64.1)	57 (71.3)	0.246
Female	85 (35.9)	23 (28.7)	
Age (y)	51.8±11.9	51.6±11.1	0.857
Body mass index (kg/m^2)	24.8±3.1	25.5±4.0	0.104
Preoperative GFR (mL/min/1.73 m^2)	86.5±16.6	87.6±18.4	0.648
Clinical tumor size (mm)	27.0±12.3	30.1±14.6	0.065
ASA score			0.332
1	106 (44.7)	40 (50.0)	
2	129 (54.4)	38 (47.5)	
3	2 (0.8)	2 (2.5)	
C-index	3.03±1.86	2.74±1.66	0.216
R.E.N.A.L. score	6.26±1.49	6.83±1.44	0.003
Low (4–6)	133 (56.1)	33 (41.9)	0.063
Moderate (7–9)	101 (42.6)	45 (56.3)	
High (10–12)	3 (1.3)	2 (2.5)	
PADUA score	7.47±0.98	7.88±1.14	0.003
Low (6–7)	130 (54.9)	30 (37.5)	0.013
Moderate (8–9)	97 (40.9)	42 (52.5)	
High (≥10)	10 (4.2)	8 (10.0)	
Warm ischemia time	19.8±5.8	38.6±8.9	0.003
Pathologic tumor size (mm)	24.9±11.6	27.3±12.4	0.130
pT stage[a]			0.062
pT1a	196 (90.3)	73 (98.6)	
pT1b	18 (8.3)	1 (1.4)	
pT3a	3 (1.4)	0 (0)	
Operation time (min)	185.8±63.0	253.6±94.4	<0.001
EBL (mL)	179.7±146.5	288.9±232.7	<0.001
Negative margin (mm)	4.8±3.2	4.4±4.1	0.325
Approach methods			<0.001
Transperitoneal	128 (54.0)	65 (81.3)	
Retroperitoneal	109 (46.0)	15 (18.8)	
Surgical type			0.193
LPN	100 (42.2)	41 (51.2)	
RPN	137 (57.8)	39 (48.8)	

Values are presented as number (%) or mean±standard deviation.
WIT, warm ischemia time; GRF, glomerular filtration rate; ASA, American Society of Anesthesiologists; R.E.N.A.L., radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior and location relative to polar lines; PADUA, preoperative aspects and dimensions used for an anatomical; EBL, estimated blood loss; LPN, laparoscopic partial nephrectomy; RPN, robot-assisted laparoscopic partial nephrectomy.
[a]:Pathologically benign tumors were excepted from pathologic T stage.

arterial clamp and removal of the last clamp.

Demographic and patient characteristics were recorded, including age, sex, body mass index, American Society of Anesthesiologists classification, preoperative estimated GFR, clinical tumor size, and pathologic outcome. Clinical tumor size was recorded as the largest diameter seen on radiological images. The nephrometry score (nephrometry score; R.E.N.A.L. [radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior and location relative to polar lines] score, PADUA [preoperative aspects and dimensions used for an anatomical] score, and C-index) was determined by a retrospective review of images. Patients were divided into two groups: group A was defined as prolonged WIT (≥30 minutes) and group B as short WIT (<30 minutes). Patient characteristics were compared between the two groups.

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Perioperative outcomes including operative time, estimated blood loss (EBL), pathologic tumor size, method of surgery (LPN or RPN), and approach method (transperitoneal or retroperitoneal) were compared between groups. We evaluated multiple factors as predictors of prolonged ischemic time. To assess the impact of surgeon experience on WIT, we categorized the patients in groups of 50 consecutive cases.

All data analyses were performed by using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Student t-tests and Pearson chi-square tests were used for comparisons of means and proportions, respectively. Univariable and multivariable regression models were used to assess predictors of intraoperative prolonged WIT. All tests were two-sided, and statistical significance was set at $p<0.05$.

RESULTS

Among the 317 consecutive patients, there were 209 males (65.8%) and 108 females (34.2%) with a median age of 53.5 years (range, 29–78 years). A total of 80 patients were included in group A and 237 patients in group B. Mean WIT was 38.6±8.9 minutes in group A and 19.8±5.8 minutes in group B, respectively (Table 1).

Demographic characteristics were not significantly different between the two groups. However, the PADUA score (p=0.006), R.E.N.A.L. score (p=0.003), operative time (p<0.001), EBL (p<0.001), and approach method (p<0.001) did differ significantly between the two groups (Table 1).

Concerning surgeon experience, the group proportions changed over time. Cases 1–50 (group A: 68% vs. group B: 32%) and 51–100 (group A: 54% vs. group B: 46%) had higher proportions of group A than group B. After these 100 cases, WIT significantly decreased, ultimately demonstrating an absolute majority of patients in group B after the surgeon had accumulated more than 150 cases (p<0.001) (Fig. 2).

Univariable analysis identified PADUA score (p=0.008), approach method (<0.001), and surgeon experience (p<0.001) to be significantly associated with prolonged WIT. In the multivariable analysis, PADUA score (p=0.032), tumor size (odds ratio [OR], 2.98; 95% confidence interval [CI], 1.48–5.96; p=0.002), and surgeon experience (p<0.001) were independent predictors of prolonged WIT. Among these, surgeon experience was the strongest independent predictor. According to cumulative surgery cases, compared with the experience of 50 cases of surgery, although the risk of prolonged WIT was not reduced from cases 51–100 (p=0.202), as subsequent surgery experience accumulated, a significant reduction in prolonged WIT was shown (Table 2).

In a subanalysis according to type of surgery (RPN or LPN), tumor size (OR, 3.21; 95% CI, 1.24–8.28; p=0.016) and surgeon experience (p<0.001) were independent predictors of prolonged WIT in the RPN group, whereas surgeon experience (p<0.001) was the only independent predictor of prolonged WIT in the LPN group (Table 3). Among the variables making up the nephrometry score, the R.E.N.A.L. score in patients who underwent RPN (6.75±1.42) was higher than that of those who underwent LPN (5.96±1.48, p<0.001).

DISCUSSION

Current guidelines show that patients with clinically staged T1 renal tumors should undergo partial nephrectomy whenever technically feasible [8]. Several retrospective studies have shown acceptable oncologic outcomes of partial nephrectomy for not only small renal tumors, but also large localized renal tumors [9,10]. Postoperative renal function is better preserved with partial nephrectomy than with radical nephrectomy; however, several clinical factors impact renal function after surgery, and profound renal functional loss can occur even after partial nephrectomy. Since Lane et al. [4] showed that ischemia time during partial nephrectomy is the greatest modifiable predictive risk factor of postoperative functional loss, WIT has been found to be associated with a significant loss of renal function of the affected kidney, mainly in patients who experienced prolonged WIT. To date, however, there are few studies on factors that affect WIT prolongation.

In the comparison of perioperative factors between groups A and B, the ratios of the surgical approach method

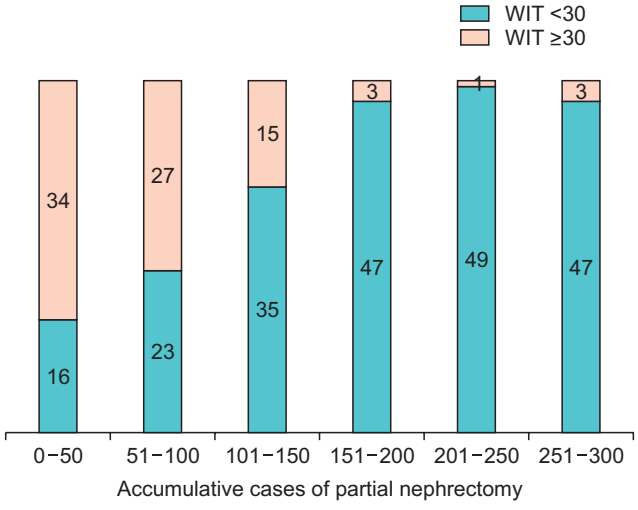

Fig. 2. Changes in proportions of prolonged warm ischemia time (WIT) and short WIT by accumulated cases of partial nephrectomy.

Table 2. Univariable and multivariable analyses of prolonged warm ischemia time

Variable	Univariable analysis	Multivariable analysis		
	p-value	OR	95% CI	p-value
PADUA score	0.008			0.020
Low (6–7)	-	-	-	-
Moderate (8–9)	0.032	1.76	0.89–3.46	0.104
High (≥10)	0.006	6.94	1.63–29.51	0.001
R.E.N.A.L. score	0.115			-
Low (4–6)	-	-	-	-
Moderate (7–9)	0.049	-	-	-
High (10–12)	0.334	-	-	-
Tumor size (≥25 mm)	0.166	3.06	1.56–6.02	0.001
Surgeon experience (case)	<0.001	-	-	<0.001
1– 50	-	-	-	-
51–100	0.159	0.60	0.26–1.42	0.246
101–150	0.001	0.24	0.10–0.59	0.002
151–200	<0.001	0.03	0.01–0.10	<0.001
201–250	<0.001	0.01	<0.01–0.06	<0.001
251–300	<0.001	0.02	0.01–0.11	<0.001
Approach method				
Retroperitoneal	-	-	-	-
Transperitoneal	<0.001	-	-	-
Surgical type				
LPN	-	-	-	-
RPN	0.133	-	-	-

OR, odds ratio; CI, confidence interval; PADUA, preoperative aspects and dimensions used for an anatomical; R.E.N.A.L., radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior and location relative to polar lines; LPN, laparoscopic partial nephrectomy; RPN, robot-assisted laparoscopic partial nephrectomy.

Table 3. Multivariable analysis of prolonged warm ischemia time according to surgical type

Variable	RPN			LPN		
	HR	95% CI	p-value	HR	95% CI	p-value
Tumor size (≥25 mm)	3.21	1.24–8.28	0.016	-	-	-
Surgeon experience (case)			<0.001			<0.001
1–50	-	-	-	-	-	-
51–100	0.10	0.03–0.37	0.001	0.097	0.03–0.34	<0.001
101–150	0.02	0.004–0.150	<0.001	0.00	-	0.997

RPN, robot-assisted laparoscopic partial nephrectomy; LPN, laparoscopic partial nephrectomy; HR, hazard ratio; CI, confidence interval.

differed. This finding is attributed to the fact that the transperitoneal approach was used in a large proportion of the initial cases in our series. As surgical experience accumulated, the surgeon's preference changed to a retroperitoneal approach for posterior or laterally located renal tumors. Actually, surgical approach was not a predictor of WIT, as shown by the multivariable analysis.

There are several reports of a higher nephrometry score being significantly associated with increased WIT [11-13]. Ficarra et al. [12] found that surgeon experience, clinical tumor size, anatomic characteristics determined by the PADUA classification score, and upper collecting system repair were independent predictors of WIT>20 minutes. Recently, Wang et al. [13] showed a much stronger correlation between nephrometry score and WIT, with the C-index system (coefficient, –0.609) and the PADUA score system (coefficient, 0.735) showing the strongest correlation in the overall analysis, whereas the R.E.N.A.L. nephrometry score showed a relatively weaker correlation. In concordance with previous studies, our results indicate that each component of the nephrometry score is correlated with WIT. Among the variables making up the nephrometry score, our study demonstrated that only the PADUA score (p=0.032) could predict WIT>30 minutes. These findings suggest

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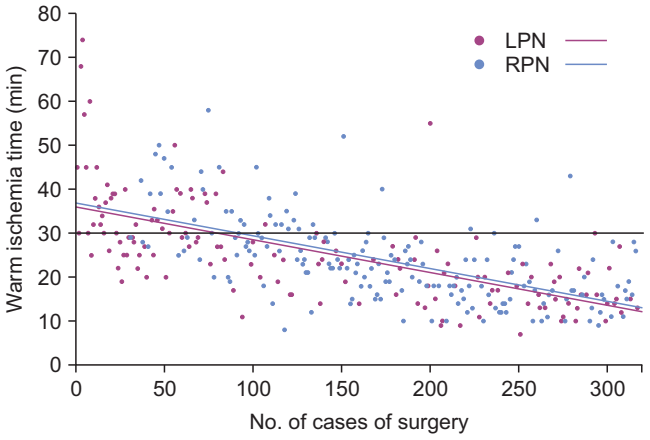

Fig. 3. Warm ischemia time according to surgeon experience for each type of surgery. LPN, laparoscopic partial nephrectomy; RPN, robot-assisted laparoscopic partial nephrectomy.

that risk group stratification using the PADUA score may improve patient selection for partial nephrectomy, especially for novice surgeons.

However, the results of our subgroup analysis showed that using the nephrometry score to predict prolonged WIT in the groups divided by surgical type (RPN or LPN) was not effective. We hypothesize that this discrepancy in results depends on the WIT cutoff value. Previous studies have set the WIT cutoff value to 20 minutes, whereas we evaluated the predictors of prolonged WIT defined as longer than 30 minutes.

Regarding surgeon experience, Mottrie et al. [14] demonstrated that surgeon experience significantly correlated with robotic console time ($p<0.001$) and WIT ($p<0.0001$). We also found that surgeon experience was associated with reduced risk of prolonged WIT. We stratified the cases into six chronologic periods of 50 accumulative cases. When we compared each period, the ratios of group A were 68%, 54%, 30%, 6%, 4%, and 4%, respectively. Our data showed that prolonged WIT was very rare when surgeon experience was greater than 150 cases of partial nephrectomy under pneumoperitoneum. In further subgroup analysis, surgeon experience was the most important predictor of WIT in both the RPN and LPN groups. After 50 cases of each type of surgery were accumulated, the risk of prolonged WIT was reduced dramatically compared with that in the first 50 cases (Fig. 3).

Several current studies have shown shorter learning curves for RPN than for LPN. Two systematic reviews and meta-analyses of RPN versus LPN reported no significant differences in perioperative outcomes between the two groups, except for a significantly shorter WIT [15,16]. However, type of surgery was not predictive of prolonged WIT in the present study. Several possible confounding factors could have impacted this result. More complex cases were treated with RPN because of its likelihood to greatly mitigate the difficulty of complex partial nephrectomy.

CONCLUSIONS

Surgeon experience, PADUA score, and tumor size are significant predictors of prolonged WIT during partial nephrectomy under pneumoperitoneum. Among these predictive factors, accumulating surgical experience is the most important and the only modifiable factor for reducing the risk of prolonged WIT.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

SUPPLEMENTARY MATERIAL

An accompanying video can be found in the 'urology in motion' section of the journal homepage (www.kjurology.org). The supplementary video clips can also be accessed by scanning a QR code located on the Fig. 1 of this article, or be available on YouTube (https://youtu.be/FcFHDcIB1UE).

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Patard JJ, Shvarts O, Lam JS, Pantuck AJ, Kim HL, Ficarra V, et al. Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. J Urol 2004;171(6 Pt 1):2181-5.
3. Benway BM, Bhayani SB, Rogers CG, Dulabon LM, Patel MN, Lipkin M, et al. Robot assisted partial nephrectomy versus laparoscopic partial nephrectomy for renal tumors: a multi-institutional analysis of perioperative outcomes. J Urol 2009;182:866-72.
4. Lane BR, Babineau DC, Poggio ED, Weight CJ, Larson BT, Gill IS, et al. Factors predicting renal functional outcome after partial nephrectomy. J Urol 2008;180:2363-8.
5. Becker F, Van Poppel H, Hakenberg OW, Stief C, Gill I, Guazzoni G, et al. Assessing the impact of ischaemia time during partial nephrectomy. Eur Urol 2009;56:625-34.
6. Godoy G, Ramanathan V, Kanofsky JA, O'Malley RL, Tareen BU, Taneja SS, et al. Effect of warm ischemia time during laparoscopic partial nephrectomy on early postoperative glomerular filtration rate. J Urol 2009;181:2438-43.

7. Choi JD, Park JW, Choi JY, Kim HS, Jeong BC, Jeon SS, et al. Renal damage caused by warm ischaemia during laparoscopic and robot-assisted partial nephrectomy: an assessment using Tc 99m-DTPA glomerular filtration rate. Eur Urol 2010;58:900-5.
8. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1271-9.
9. Roos FC, Brenner W, Muller M, Schubert C, Jager WJ, Thuroff JW, et al. Oncologic long-term outcome of elective nephron-sparing surgery versus radical nephrectomy in patients with renal cell carcinoma stage pT1b or greater in a matched-pair cohort. Urology 2011;77:803-8.
10. Sprenkle PC, Power N, Ghoneim T, Touijer KA, Dalbagni G, Russo P, et al. Comparison of open and minimally invasive partial nephrectomy for renal tumors 4-7 centimeters. Eur Urol 2012;61:593-9.
11. Hayn MH, Schwaab T, Underwood W, Kim HL. RENAL nephrometry score predicts surgical outcomes of laparoscopic partial nephrectomy. BJU Int 2011;108:876-81.
12. Ficarra V, Bhayani S, Porter J, Buffi N, Lee R, Cestari A, et al. Predictors of warm ischemia time and perioperative complications in a multicenter, international series of robot-assisted partial nephrectomy. Eur Urol 2012;61:395-402.
13. Wang L, Wu Z, Ye H, Li M, Sheng J, Liu B, et al. Correlations of tumor size, RENAL, centrality index, preoperative aspects and dimensions used for anatomical, and diameter-axial-polar scoring with warm ischemia time in a single surgeon's series of robotic partial nephrectomy. Urology 2014;83:1075-9.
14. Mottrie A, De Naeyer G, Schatteman P, Carpentier P, Sangalli M, Ficarra V. Impact of the learning curve on perioperative outcomes in patients who underwent robotic partial nephrectomy for parenchymal renal tumours. Eur Urol 2010;58:127-32.
15. Aboumarzouk OM, Stein RJ, Eyraud R, Haber GP, Chlosta PL, Somani BK, et al. Robotic versus laparoscopic partial nephrectomy: a systematic review and meta-analysis. Eur Urol 2012;62:1023-33.
16. Zargar H, Bhayani S, Allaf ME, Stifelman M, Rogers C, Larson J, et al. Comparison of perioperative outcomes of robot-assisted partial nephrectomy and open partial nephrectomy in patients with a solitary kidney. J Endourol 2014;28:1224-30.

http://dx.doi.org/10.4111/kju.2015.56.11.742