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Role Of Robot-Assisted Partial Nephrectomy For Renal Cell Carcinomas In The Purpose Of Nephron Sparing

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Introduction: Surgery remains the standard treatment for localized renal cell carcinomas, and partial nephrectomy is considered before radical nephrectomy with the aim of preserving renal function. This study aimed to compare robot-assisted and open partial nephrectomy for the purpose of nephron sparing.

Materials and methods: We retrospectively enrolled consecutive patients who received partial nephrectomy at a single tertiary medical center from January 2008 to January 2015. Medical records and radiographic images were reviewed. We analyzed the patients' general characteristics, underlying disease, complications, length of hospital stay, renal tumor complexity, surgery type, renal function, and specimen and tumor size. A comparison between open and robot-assisted nephrectomy groups was performed.

Results: A total of 136 patients were enrolled, with a male to female ratio of 2:3 and a mean age of 57.8 years. Of these, 71 and 65 patients received open and robot-assisted surgery, respectively. Compared with the open group, patients who underwent robot-assisted surgery were significantly younger (56.0 versus 60.1 years old), had a longer operative time (303 versus 224 min), and a lower kidney ischemic time (33.4 versus 46.9 min). Given similar tumor sizes, the tumor-to-excision ratio was significantly higher in the robot-assisted group (51.7% versus 39.8%), and the excisional volume loss (EVL) was smaller (12.7 versus 19.6 mL). Preoperative glomerular filtration rate and EVL were significant predictors of long-term renal function preservation in the multivariate analysis.

Conclusion: When performing partial nephrectomy, a robot-assisted procedure could increase the accuracy of excision without increasing the risk of positive surgical margin. Lower EVL could assist in better long-term postoperative renal function preservation.

Keywords: renal cell carcinoma, robotic-assisted system, partial nephrectomy, excisional volume loss, nephron sparing, renal function preservation

Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all adult malignancies and is one of the most lethal urological cancers. Since the 1970s, radiographic imaging, including ultrasonography and computed tomography, has not only increased the RCC detection frequency[1,2] but also aided early detection of asymptomatic or incidental localized RCCs.[3,4]

Surgery, the standard curative treatment for localized RCCs, involves the excision of the entire tumor with an adequate surgical margin. Radical nephrectomy (RN) was once widely performed in patients with localized renal tumors suspected

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or confirmed to be malignancy, even including T1-stage tumors. However, multiple management strategies in addition to RN are currently available; these include partial nephrectomy (PN), thermal ablation, and active surveillance. PN currently considered a standard treatment for localized renal tumors.[5–8]

PN is preferred over RN for small tumors or other feasible cases[9–11] because the post-RN chronic kidney disease (CKD) risk is high, as reported in several longitudinal follow-up studies. These include a landmark study by the Memorial Sloan Kettering Cancer Center,[12] in which Huang et al. studied 662 patients with small solitary renal tumors whose serum creatinine level and opposite kidney were normal. Nearly one-quarter of these patients had preexisting grade 3 CKD, with a 3-year probability of no new onset of grade 3 or higher CKD of 80% after PN and 35% after RN.

CKD is associated with cardiovascular events and death, with their relative risk increasing with upstaging of CKD.[13] The favorable outcomes of PN, such as reduced risk of CKD and overall mortality, in the treatment of T1-stage renal tumors have been confirmed.[14] Moreover, in some patients, the oncological outcomes of PN can be equivalent to those of RN.[5]

Minimally invasive approaches to perform PN have provided encouraging results.[15,16] Laparoscopic and robot-assisted PN (RPN) appear to have an equivalent margin status and oncological outcomes compared with open PN (OPN), provided the surgeon is experienced and patient selection is sensible.[16–18]

Main goal of this study is to compare renal function preservation between OPN and RPN, and to further find the possible predictors. We also compared the surgical and oncological outcome in these two groups. compared surgical and oncological outcomes and renal function changes after open and robot-assisted PN and identified factors that can predict consequent renal function preservation.

Materials And Methods

Patients

We conducted this retrospective study of consecutive patients who received PN at a single tertiary medical center from January 2008 to January 2015. We reviewed the medical charts and radiographic images of patients diagnosed as having RCC and were eligible for PN according to evaluation by our uro-oncology team. Patients who decided to receive PN (either OPN or RPN) after discussion with the surgeons were enrolled. The benefits and risks of OPN and RPN were both explained and discussed with the patients in the outpatient department. The choice between OPN and RPN depended on the patients' preference. In OPN, we routinely used cold ischemia during tumor resection. Before standard renorrhaphy with renal parenchyma primary closure, we use small-size suture (for example, dexon 4-0) to perform collecting system repair in possible defect and all visible cut surface of vessels in the parenchymal incisional plane. In RPN group, collecting system repair is only performed in obvious defect, and then primary closure of renal parenchyma was done.

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. The patient consent to review their medical records was waived by the Institutional Review Board of Chang Gung Memorial Hospital due to retrospective study. The patient data confidentiality and compliance fulfilled the Declaration of Helsinki, which is approved by the board.

Data Collection

General preoperative characteristics, including sex, age, PADUA score, RENAL score, tumor side and stage, diabetes mellitus, hypertension, serum creatinine concentration, and estimated glomerular filtration rate (eGFR), were recorded. Surgical characteristics, including surgical methods, operation time, blood loss, kidney ischemic time, major perioperative complications (defined as Clavien-Dindo Classification ≥ grade III), hospital stay, and surgical margin status, were also collected. We calculated the whole excisional specimen size and actual tumor volume based on the measurements reported by pathologists. The estimated volume was calculated by the formula for an ellipsoid $4\pi XYZ/3$ (actual tumor volume) and $4\pi X'Y'Z'/3$ (excisional volume), respectively (Figures 1 and 2). We then defined the tumor-to-excision ratio as (actual tumor volume/excisional volume) and excisional volume loss (EVL) as (excisional volume − actual tumor volume).

Renal function was measured as the serum creatinine levels immediately post-operation (within 1 week of surgery) and 3 and 12 postoperative months. Renal function change was presented as the glomerular filtration rate (GFR) preservation (GFR-P), given by (eGFR at third postoperative month) or (eGFR at 12th postoperative month/preoperative eGFR).

Statistical Analyses

We compared general and surgical characteristics between open and robot-assisted PN groups and analyzed factors

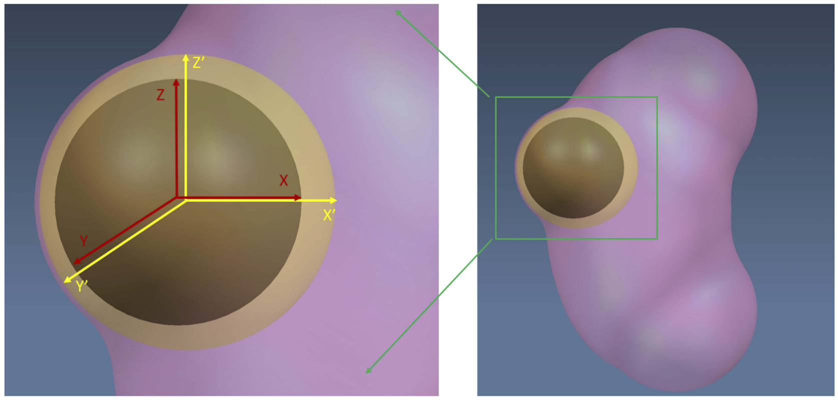

Figure 1 Illustration of actual tumor volume, excisional volume, and resection ratio.

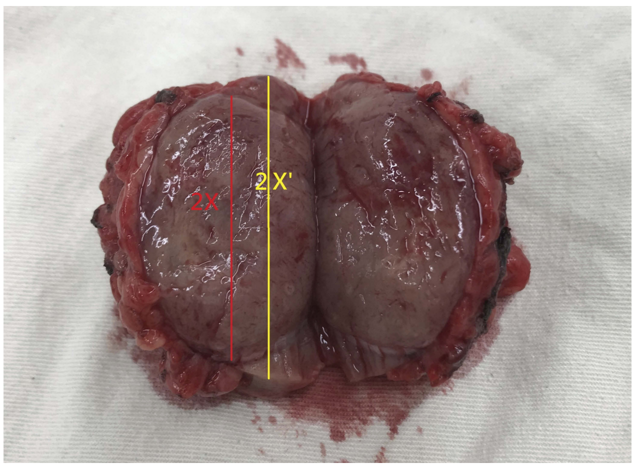

Figure 2 Photograph of specimen to illustrate the measurement of length.

possibly affecting short- and long-term renal function deterioration. The chi-square and independent *t*-tests were used to examine associations between nominal and continuous variables, respectively. We regarded *p* values of less than 0.05 as significant. All statistical analyses were performed using IBM SPSS Statistics (version 22).

Results

A total of 136 patients were included, all of whom were diagnosed as having RCC and received PN for tumor excision. The mean age was 57.8 years, with a male-to-female ratio of 2:3. The average PADUA and RENAL scores were 8.38 and 6.93, respectively. T1a- and T1b-stage tumors accounted for 78% and 19% of the cases, respectively, whereas T2a or higher–stage tumors accounted for only 3% of the cases.

Open and robot-assisted PN was administered to 71 (52.2%) and 65 (47.8%) patients, respectively. The average surgical time was 261 mins, with an average ischemic time of 39.1 mins. The average excisional volume and actual-tumor volumes were 34.4 and 18.6 mL, respectively; thus, the average tumor-to-excisional ratio was 45.5%. Detailed general and surgery-related characteristics are listed in Table 1.

Patients in the open group were significantly older than those in the robot-assisted group (60.1 versus 56.0 years) and had a shorter surgical time (224.3 versus 302.5 mins) and longer kidney ischemic time (46.9 versus 33.4 mins). The actual tumor volume was similar in both the open and robotic-assisted groups (18.8 ± 36.4 and 18.3 ± 31.9 mL, respectively; $p = 0.943$); however, the tumor-to-excision ratio was significantly lower in the open group (39.8% versus 51.7%; $p = 0.001$), thus resulting in a significantly smaller EVL in the robot-assisted group. A detailed comparison of parameters between the open and robot-assisted groups is listed in Table 2.

Table 3 lists parameters possibly correlated with the tumor-to-excision ratio. In the univariate analysis, robot-assisted PN, higher PADUA score, higher preoperative GFR, and larger actual tumor volume were significantly correlated with a higher tumor-to-excision ratio, whereas in the multivariate analysis, only robot-assisted PN and larger actual tumor volume were significant predictors of a higher ratio. Tumor-to- excision ratio was not significantly correlated with positive surgical margin (PSM).

Renal function change was defined using GFR-P. Predictors for GFR-P 3 and 12 months after PN are listed in Table 4. In the univariate analysis, robot-assisted surgery, PADUA score, RENAL score, preoperative GFR, and EVL were significant predictors for GFR-P 3 months after PN, whereas only robot-assisted surgery and preoperative GFR remained significant predictors in the multivariate analysis. At 12 months after PN, PADUA score, RENAL score, preoperative GFR, excisional volume, and

Table 1 Patients' General Characteristics

Variables		**Mean**	**SD**	**Range/Percentage**	
Total Number		136			
Gender	Male Female	95 41		69.9% 30.1%	
Age		57.8	12.4	25–80	Year-old
PADUA		8.38	1.52	6–12	
RENAL		6.93	1.67	4–10	
Side	Right Left	67 69		49.3% 50.7%	
Stage	T1a T1b T2a >T2a	106 26 2 2		77.9% 19.1% 1.5% 1.5%	
DM	Yes No	40 96		29.4% 70.6%	
HTN	Yes No	69 67		50.7% 49.3%	
Preoperative Cr		0.93	0.34	0.48–3.0	mg/dL
Preoperative GFR		85.4	26.0	20.3–183.1	mL/min/1.73m2
Surgery related Characteristics					
Surgical Method	Open	71		52.20%	
	Robotic-assisted	65		47.80%	
Operation Time		261.7	85.0	117–664	mins
Blood Loss		193.6	344.7	5–2700	mL
Ischemic Time		39.1	15.7	12–87	mins
Complication	Yes No	7 129		5.1% 94.9%	
Hospital Stay Excisional Volume Actual Tumor Volume Tumor-to-Excision Ratio		8.01 34.4 18.6 45.5	4.4 43.2 34.2 21.5	4–46 2.4–314.2 0.2–293.2 3–95	days mL mL %
Pathology	Clear cell Chromophobe Papillary Others	103 20 10 3		75.7% 14.7% 7.4% 2.2%	
Positive Surgical Margin	Yes No	7 129		5.1% 94.9%	
Recurrence	Yes No	6 130		4.4% 95.6%	

Abbreviations: DM, diabetes mellitus; HTN, hypertension; GFR, glomerular filtration rate; Cr, creatinine.

Table 2 Comparison Of Patients Receiving Robotic-Assisted Or Open Partial Nephrectomy

Variables		Open PN			Robotic-Assisted PN			
Number		71			65			
								p value
Gender	Male Female	53 18			42 23			0.203
Age		60.1	12.6	Year-old	56.0	12.1	Year-old	0.042*
Stage	T1a T1b T2a T3a	57 12 1 1			49 14 1 1			0.920
PADUA score RENAL score Operation Time Blood Loss		8.48 7.00 224.3 141.7	1.44 1.62 55.4 163.3	 Mins mL	8.28 6.86 302.5 250.3	1.60 1.74 93.0 463.9	 Mins mL	0.442 0.632 0.000** 0.077
Blood transfusion	Yes No	5 66			5 60			0.885
Ischemic Time Hospital Stay		46.9 8.75	15.4 5.6	Mins Days	33.4 7.20	13.5 2.1	Mins Days	0.000** 0.034*
Complication	Yes No	3 68			4 61			0.611
Recurrence	Yes No	3 68			3 62			0.912
Positive Surgical Margin	Yes No	2 69			5 60			0.199
Excisional Volume Actual Tumor Volume Tumor-to-Excision Ratio Excisional Volume Loss		37.7 18.8 39.8 19.6	45.1 36.4 18.3 17.5	mL mL % mL	30.9 18.3 51.7 12.7	41.1 31.9 23.1 14.5	mL mL % mL	0.360 0.943 0.001** 0.013*

Notes: *Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed).

Table 3 Factors Correlated To Tumor-To-Excision Ratio

Variables		Pearson Correlation		*Univariate p Value*	*Multi-Variate p Value*
Age		−0.082		0.345	
Robotic-assisted		0.276	**	0.001	0.002
PADUA		0.184	*	0.033	0.213
RENAL		0.160		0.064	0.512
Preoperative GFR	mL/min/1.73m2	0.175	*	0.043	0.221
Actual Tumor Volume	mL	0.426	**	<0.001	<0.001
Positive surgical margin		0.132		0.127	–

Notes: *Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed).

EVL were significant predictors of GFR-P, whereas they were only preoperative GFR and EVL in the multivariate analysis.

Figure 3 illustrates the trend of GFR and GFR-P preoperatively, immediately postoperatively, and at 3 and 12 months postoperatively in all patients (Figure 3A and B).

Table 4 Predictors For GFR-P

		POM3				POM12			
		Pearson Correlation		*Univariate p Value*	*Multi-Variate p Value*	Pearson Correlation		*Univariate p Value*	*Multi-Variate p Value*
Age		−0.042		0.627		0.040		0.647	
Robotic-assisted		0.183	*	0.033	0.008	0.023		0.787	0.589
PADUA		−0.192	*	0.025	0.812	−0.300	**	0.000	0.077
RENAL		−0.217	*	0.011	0.224	−0.252	**	0.003	0.600
Tumor-to-excision Ratio		0.105		0.385		−0.060		0.488	
Operation Time	mins	0.143		0.097		−0.030		0.725	
Blood Loss	mL	−0.072		0.406		−0.077		0.373	
Ischemia Time	mins	−0.036		0.727		−0.053		0.605	
Preoperative GFR	mL/min/1.73m2	−0.207	*	0.016	0.000	−0.259	**	0.002	0.000
Excisional Volume	mL	−0.125		0.148	–	−0.218		0.011	–
Actual Tumor Volume	mL	−0.074		0.394	0.874	−0.147		0.088	0.787
Excisional Volume Loss	mL	−0.190	*	0.027	0.219	−0.275	**	0.001	0.037

Notes: *Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed).

The trend of GFR and GFR-P in subgroups with an EVL of ≥16 mL or <16 mL is illustrated in Figure 3C and D.

Discussion

PN is currently the gold standard for surgical treatment of patients with small renal tumors. With equivalent oncological outcomes, the key benefits of PN are preserving renal function and limiting the risks of CKD, cardiovascular morbidity, and death.[13,19] A large proportion of PN is performed using a minimally invasive approach,[20] even in patients with complex renal masses,[21] and this trend is increasing.[8]

During PN, nephron injury can result from a prolonged warm ischemia time, sacrificed benign parenchyma during surgical excision, or iatrogenic injury during reconstruction.[22] Lower accuracy of surgical excision during PN may contribute to long-term renal dysfunction. Srinath et al demonstrated that non-neoplastic parenchyma volume removed in PN (i.e., EVL) was associated with the upstaging of CKD.[23] In our study, higher EVL was a significant predictor for lower long-term renal function preservation in multivariate analysis; however, it was not associated with the short-term outcome significantly. Similarly, ischemic time was not associated with renal function preservation—consistent with findings that EVL is the predominant factor affecting ultimate renal function.[24,25]

In theory, minimizing the gap between the surgical and actual-tumor margins can considerably reduce as much EVL as possible and thus preserve renal function. Thompson reported that a 5% increase in preserved renal volume could reduce the risk of stage-4 CKD by 17%.[26] This result supports the currently prevalent use of a closer surgical resection margin, but increase PSM risk.

The accuracy of tumor excision during PN can be presented as the tumor-to-excision ratio. This study demonstrated that factors associated with excision accuracy were robot-assisted surgery, excisional and tumor volume, and tumor complexity. With a similar tumor size and tumor complexity, excision accuracy was higher in the robot-assisted group than in the open group, resulting in significantly lower EVL. Neither robot-assisted surgery nor tumor-to- excision ratio increased PSM risk.

Higher excision accuracy could be explained by the advantages of the robot-assisted system (da Vinci Surgical System, Intuitive Surgical). In addition to the general benefits of minimally invasive surgery, a robot-assisted system can provide increased magnification, precise camera control, seven degrees of freedom, tremor filtration, and three-dimensional vision. These advantages can be

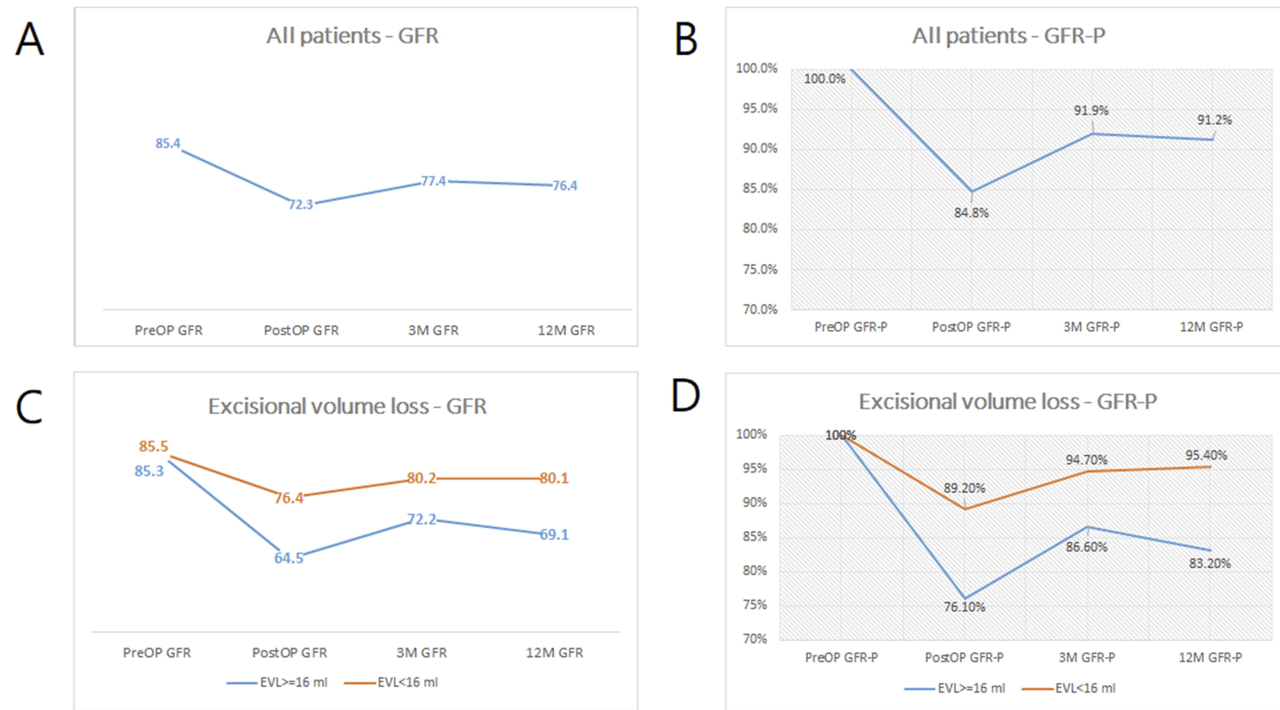

Figure 3 (A-B) The trend of GFR and GFR-P before and after partial nephrectomy in all patients. **(C-D)** The trend of GFR and GFR-P in patients with an EVL of ≥16 mL or <16 mL.

particularly useful when the tumor location is difficult to access or when performing resection and renorrhaphy. Intraoperative ultrasonography is more frequently used to identify the depth and location of tumors, particularly in endophytic or small tumors. The benefits of a robot-assisted system can help clinicians perform more precise resection and preserve as much healthy renal parenchyma as possible.

Parenchyma quality may be an essential factor affecting renal function, although there may be a difference between CKD resulting from medical causes (CKD-M) or from surgery (CKD-S). In a large population study, the mean annual decline in the renal function was 4.7% in patients with CKD-M compared with that of only 0.7% in patients with CKD-S. However, because parenchyma quality is a nonmodifiable factor, clinicians have focused more on the leading potentially modifiable factor, namely EVL.[24]

Toshio reported that a solitary kidney significantly affects excision accuracy when performing PN but without increasing PSM risk.[27] This finding indicates that EVL can be minimized through the surgeon's caution and the use of instruments, regardless of tumor size or complexity.

A limitation of this study is its retrospective design and relatively small sample size. Although we demonstrated the possible benefits of a robot-assisted system for surgical precision during PN, the results still require confirmation in a prospective large-scale study. Examination of longer-term renal function trends also requires a longer follow-up period.

Conclusion

PN has become the mainstay for treatment of small renal tumors. Its main advantage is nephron preservation, thus decreasing the risk of CKD development or upstaging. Clinicians should make every effort to minimize nephron injury during surgery, including lower EVL and shorter ischemic time. A robot-assisted PN system not only can ensure minimal postoperative discomfort, shorter hospital stays, and more rapid recovery compared with open surgery but also may improve excision accuracy during PN and thus preserve more healthy parenchyma without affecting the surgical margin. Lower EVL represents the only major modifiable predictor for better renal function preservation after PN.

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Disclosure

The authors report no conflicts of interest in this work.

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