Oncologic Outcomes Following Positive Surgical Margins in Patients who Underwent Open Versus Laparoscopic Partial Nephrectomy

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Purpose: To evaluate oncological outcomes in patient with positive surgical margin (PSM) following partial nephrectomy (PN).

Material and methods: In this retrospective study, we enrolled the data of patients who underwent PN between 2008 and 2017. The inclusion criteria were a definite diagnosis of kidney tumor who underwent PN with at least one year follow up.

Results: From the 450 patients who underwent PN, The PSM was found in 35 (22 male/13 female) patients. 18/237 (7.6%) and 17/213 (7.9%) of them were in open and laparoscopic group, respectively. Clear cell RCC was the most prevalent pathology (18 patients) in the PSM patients. The mean time of follow up was 46 ± 2.02 months. Recurrence was developed in 5 (14.2%) patients. There was no correlation between recurrence and sex (p=1.00), surgery type (p = 0.658), age (p = 0.869), tumor size (p = 0.069), pathology (p = 0.258) and stage (p = 0.744) in PSM patients. Recurrence free survival was similar between the open and laparoscopy groups in PSM patients (p = 0.619).

Conclusion: Beside numerous advantages of minimally invasive techniques, laparoscopic approach would be comparable to conventional open partial nephrectomy in terms of oncologic outcomes. The rate of recurrence following partial nephrectomy in PSM patients is considerable and closely monitoring is mandatory.

Keywords: partial nephrectomy; positive surgical margins; local recurrence; laparoscopy

INTRODUCTION

Over the last couple of decades, the incidence of renal cell carcinoma (RCC) has increased by about 2% annually because of new diagnosis techniques and incidental detection of asymptomatic small renal masses[(1)]. Today, by improving surgical techniques in nephron sparing surgery, physicians are interested to manage small renal tumors by partial nephrectomy (PN) to preserve normal renal parenchyma and kidney function, reduce risk of chronic kidney disease and renal replacement therapy [(2,3)]. However, finding positive surgical margin (PSM) on final pathology examination would be a concern and ranges from 0–10% in different published studies[(4,5)]. Although new studies suggest that the presence of PSM does not adversely affect outcomes; but these patients should be managed expectantly with close follow-up. However, some specialists prefer to perform an immediate or delayed complete (radical) nephrectomy in patients with a PSM[(6-8)].
Traditionally, open partial nephrectomy was the selected method to treat patients with small renal tumors. Nowadays laparoscopic partial nephrectomy beside robotic approach, provides the advantages of a minimally invasive technique while showing comparable to the traditional open approach in terms of oncological and functional outcomes[(9-11)].
In this study we purpose to determinate the incidence of positive surgical margin and evaluate oncological outcomes and the risk factors of recurrence in PSM patients. We also aimed to evaluate the role of laparoscopic surgery in partial nephrectomy and investigate its impact on oncological outcomes in our referral center as an Endourology-Laparoscopy Fellowship training center.

MATERIALS AND METHODS

In this retrospective study, we enrolled the data of patients who underwent partial nephrectomy in our referral center between 2008 and 2017. The inclusion criteria were a definite diagnosis of kidney tumor who underwent partial nephrectomy with at least one year

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Table 1. The characteristics and pathologic data of patients who underwent partial nephrectomy

	Laparoscopic PN	Open PN	*p*-value
Male/female	113/100	134/103	0.458
Mean age±SD	49.9 ± 13.5	51.3 ± 13.4	0.274
Tumor side (R/L)	8/9	11/7	0.505
Positive surgical margin	17	18	0.247
Mean specimen size±SD	5.60 ± 2.35	6.65 ± 3.34	< 0.001
Mean Tumor size±SD	3.91 ± 1.82	4.87 ± 2.70	< 0.001
Tumor size (%)			< 0.001
<4cm	141 (66.9)	114 (48.7)	
>4 <7 cm	62 (29.4)	87 (37.1)	
>7 <10cm	6 (2.8)	21 (8.9)	
>10cm	2 (0.9)	12 (0.05)	
Normal renal tissue (cm)	1.71 ± 1.56	1.78 ± 2.19	0.699
Surgical Pathology (%)			0.722
RCC clear cell	95 (44.6)	116 (49)	
RCC papillary	33 (15.5)	32 (13.5)	
RCC chromophobe	24 (11.3)	22 (9.3)	
Angiomyolipoma	37 (17.4)	33 (13.9)	
Oncocytoma	14 (6.6)	11 (4.6)	
Cystic nephroma	2 (0.9)	16 (6.7)	
Metanephric adenoma	4 (1.8)	2 (0.8)	
other	4 (1.8)	5 (2.1)	

follow up in alive patients. Follow up included history, physical examination, blood tests, chest X ray, abdomino-pelvic computed tomography scan every 6 to 12 months in first 5 years and then annually[12]. The exclusion criteria included: patients with incomplete follow up information and whose surgery converted to radical nephrectomy for any reasons or underwent further surgery to achieve negative surgical margin. This study was conducted in accordance with the Declaration of Helsinki.

The demographic and clinical data of the patients were retrieved from the hospital's databank. These data included age, sex, date of diagnosis, pathologic report, specimen and tumor size and the state of surgical margin. All the specimens were evaluated by an expert uro-pathologist in our center. The pathologist examined the outer layer of the specimen and if cancer cells are present to the edge of the removed tissue, he would report a positive surgical margin. Any new detection of the tumor mass in the same surgery side in follow up imaging considered as local recurrence.

Quantitative data are shown as mean ± SD for data with normal distribution or median [interquartile range] for non-normally distributed data. Quantitative data were compared between the groups by Student's t-test, Fisher's exact or Mann-Whitney test probability test, where applicable. Recurrence free survival rates were calculated using the Kaplan–Meier survival method including a log-rank test. We utilized SPSS version 21.0 software (IBM Corporation, Armonk, NY, USA) for statistical analysis. Two-tailed *P*-values < 0.05 were considered for the statistical level of significance.

RESULTS

In this study, the total number of 450 patients underwent partial nephrectomy due to renal tumor. The mean±SD age was 50.64±13.50 years. the median time of follow up was 36 months (IQR, 30-48). The mean ± SD specimen size and tumor size were 6.15±3.02 and 4.41 ± 2.37 cm, respectively. From these data, we calculated the mean normal renal parenchyma size was 1.75 ± 1.91 cm. The tumor was placed in the right side in 19 (54.3%) and in the left side in 16 (45.7%) patients. endophytic mass was found only in one patient. The pathologic reports showed that clear cell renal cell carcinoma was the most prevalent pathology (211 patients) among all participants. After clear cell RCC, angiomyolipoma (70), papillary RCC (65), chromophobe RCC (46), oncocytoma (25), cystic nephroma (18) and metanephric adenoma[6] were ranked next. The total number of 237 and 213 patients underwent open and laparoscopic partial nephrectomy, respectively. All these data are shown in **Table 1** separately between the open and laparoscopic partial nephrectomy groups.

The Positive surgical margin was found in 35 (22 male/13 female) patients' pathologic report. 18 (51.4%) and 17 (48.6%) of them were in open and laparoscopic group, respectively. Again, clear cell RCC was the most prevalent pathology (18 patients) in the PSM patients' pathology reports and papillary RCC and chromophobe RCC was reported in 9 and 8 patients, respectively. In the evaluation of the correlation between positive surgical margin and other findings, it was interesting to notice that positive surgical margin was occurred more in the smaller tumors. The mean±SD tumor size was 3.98 ± 2.26 and 4.21 ± 2 cm in positive and negative surgical margin patients, respectively ($p = 0.022$).

Recurrence was developed in 5 (14.2%) patients. The median time to recurrence was 36 months (IQR, 18-42 months). Fisher exact test and Mann-Whitney Test showed that there is no correlation between recurrence and sex (2 female vs 3 male, $p = 1.00$), surgery type (2 open, 3 laparoscopies, $p = 0.658$), age (mean age 54.00 ± 10.65 vs 59.53 ± 9.49 in recurrence (+) and (-), $p = 0.869$), tumor size (4.08 ± 1.67 vs 3.82 ± 1.23 cm in recurrence (+) and (-), $p = 0.069$), pathology (3 clear cell RCC, 1 papillary RCC and 1 chromophobe RCC, $p = 0.258$) and stage (4 T1a and 1 T3a, $p = 0.744$) in PSM patients.

Kaplan–Meier survival method including a log-rank test showed that recurrence free survival was similar between the open and laparoscopy groups in PSM patients ($p = 0.619$).

DISCUSSION

Laparoscopic technique has been used to treat renal tumors for more than 30 years. However, there is an

expressed concern about the oncological efficacy when minimally invasive approach is applied to treat malignancies[13,14]. Some physicians believe that obtaining negative surgical margins, achieving adequate hemostasis, and accurately repairing any injury to the collecting system is more convenient in conventional open approach; while several studies comparing laparoscopic nephrectomy with conventional open approach have shown no differences in feasibility and cancer control rates[15-18].

As it shown in **Table 1**, in this study, laparoscopic PN was performed more prevalent in smaller tumors but the incidence of positive surgical margins didn't differ between open and partial groups. Further analysis also showed that, there was no correlation between surgical approach (laparoscopy vs open) and recurrence in positive surgical margins and recurrence free survival is similar between positive surgical margins patients who underwent open or laparoscopic partial nephrectomy. Similar to our study, in the evaluation of 1541 patients who underwent partial nephrectomy by either laparoscopy or open approach, Lane et al[19] showed that surgical approach was not a predictor for positive surgical margin and recurrence. They also found that median glomerular filtration rate decrease was similar between two groups. Beside tumor size, nuclear grading and pT3a stage were the most important predictors of positive surgical margin in a large systematic review of 36 retrospective study[20].

In a recent systematic review and meta-analysis, You C et al[21] in the evaluation of 26 studies with 8095 patients, analyzed the current evidence on oncological, surgical, and functional outcomes between laparoscopic partial nephrectomy and open partial nephrectomy. Operation time (p = 0.13), recurrence (p = 0.56), cancer-specific survival (p = 0.72), disease-free survival (p = 0.72), intraoperative complications (p = 0.94), and variations of estimated glomerular filtration rate were similar between two groups. Less estimated blood loss (P < 0.00001), lower blood transfusion (p = 0.04), lower total (p = 0.03) and postoperative complications (p = 0.02), higher positive surgical margin (p = 0.005), shorter length of hospital stay (p < 0.00001), higher overall survival (p < 0.00001), and less increased serum creatinine (p = 0.002) was observed in the laparoscopic group. Finally, they concluded that the LPN is a feasible and safe alternative to the OPN with comparable oncologic, surgical, and functional outcomes. Against our results, they founded higher positive surgical margin rate in laparoscopic partial nephrectomy group. We believe the laparoscopic learning curve play an important role in this era. We performed all the partial nephrectomy surgeries in our referral hospital, as an Endourology-Laparoscopy Fellowship training center, the center of excellence in urology. All the surgeries were performed or supervised by endo-urology surgeons experienced in this field. Higher positive surgical margin in the laparoscopic group may also be related to differences in pathological stage and follow-up time; so further prospective studies with proper design is suggested.

Positive surgical margin was detected in 17/213 (7.9%) of the laparoscopic group and 35/450 (7.8%), overall. In a systematic review and meta-analysis study, Ficarra et al[20] evaluated the data of 45,786 patients of 36 retrospective studies who underwent partial nephrectomy and reported positive surgical margin in 3,093 (6.7%) patients (7%, 5%, and 4.3% in robot-assisted PN group, laparoscopic PN group, and open PN group, respectively). Further analysis showed that in comparison with minimally invasive approach, open PN approach had a significant advantage in terms of achieving negative surgical margin. They also found that positive surgical margin risk is more favorable in robot-assisted PN group compared with laparoscopic group. Against these findings, we didn't find any difference in terms of positive surgical margin between open and laparoscopic PN groups. Frozen section during surgery has been traditionally purposed to reduce positive surgical margin status following PN. However, the oncologic benefit remains unclear[22].

The impact of positive surgical margin following partial nephrectomy on recurrence free survival is controversial. Many studies have been conducted in this era and various results have been obtained. In the evaluation of multi-institutional database of patients who underwent robot-assisted partial nephrectomy, Rothberg et al[23] reported positive surgical margin in 42/839 (5.1%) patients. They showed that positive surgical margin was not associated with worse recurrence free survival. Instead, pT3a upstaging and advanced clinical stage associated with worse recurrence free survival. They concluded that patients with positive surgical margin should be carefully monitored for recurrence rather than undergo immediate secondary intervention. In a retrospective study of 314 patients who underwent partial nephrectomy with the median time of 24 months (IQR 12-40) follow up, Marchinena et al[24] reported positive surgical margin in 22(6.3%) patients. Recurrence was occurred in 2(9.1%) and 10 (3.5%) patients with positive and negative surgical margin, respectively. They concluded that positive surgical margin and pathological high grade (Fuhrman grade III or IV) were independent predictors of local recurrence in the multivariate analysis. In a similar retrospective study of 388 patients who underwent partial nephrectomy, Carvalho et al[25] reported positive surgical margin in 16 (3.8%) patients. they showed that positive surgical margin is associated with recurrence rate (18.7% vs 4.2% in PSM and NSM group, p = 0.007) and need for total nephrectomy but no impact on survival was noticed. In a retrospective study of 459 patients who underwent partial nephrectomy, PSMs were observed in 27 (5.9%) cases. Recurrence occurred in 36(7.8%) patients. A significantly higher incidence of recurrence was showed in PSM patients. recurrence rate was 22.2% in PSM and 6.9% in NSM patients (p = 0.013) in the median time of 96 months (IQR, 74-131) follow up[26]. Similar to 3 recently discussed studies, the rate of recurrence in positive surgical margin patients is also noticeable in our study (14.2% during median time of 36 months (IQR, 30-48) follow up) and closely monitoring of these patients is mandatory.

The aim of this study was to evaluate oncologic outcomes in patients with positive surgical margin who underwent open or laparoscopic partial nephrectomy. Due to low rate of positive surgical margin following partial nephrectomy, a large sample size was not available for us in this retrospective study; so further well-designed prospective studies with larger sample size and longer follow up time are recommended. There are some other minor factors that it would be better to consider but

unfortunately, there are not available for us to use them in this study. Some of them are including patients' BMI and RENAL nephrometry score.

CONCLUSIONS

In this study, we found that recurrence free survival was similar between positive surgical margin patients who underwent laparoscopic or open partial nephrectomy. Beside numerous advantages of minimally invasive techniques, laparoscopic approach would be comparable to conventional open partial nephrectomy in terms of oncologic outcomes. The rate of recurrence following partial nephrectomy in positive surgical margin patients is considerable and closely monitoring is mandatory.

REFERENCES

1. Bansal RK, Tanguay S, Finelli A, et al. Positive surgical margins during partial nephrectomy for renal cell carcinoma: Results from Canadian Kidney Cancer information system (CKCis) collaborative. Can Urol Assoc J. 2017;11:182-7.
2. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst. 2006;98:1331-4.
3. Rezaeetalab GH, Karami H, Dadkhah F, Simforoosh N, Shakhssalim N. Laparoscopic Versus Open Partial Nephrectomy for Stage T1a of Renal Tumors. Urol J. 2016;13:2903-7.
4. Borghesi M, Brunocilla E, Schiavina R, Martorana G. Positive surgical margins after nephron-sparing surgery for renal cell carcinoma: incidence, clinical impact, and management. Clin Genitourin Cancer. 2013;11:5-9.
5. Ani I, Finelli A, Alibhai SM, Timilshina N, Fleshner N, Abouassaly R. Prevalence and impact on survival of positive surgical margins in partial nephrectomy for renal cell carcinoma: a population-based study. BJU Int. 2013;111:E300-5.
6. Raz O, Mendlovic S, Shilo Y, et al. Positive surgical margins with renal cell carcinoma have a limited influence on long-term oncological outcomes of nephron sparing surgery. Urology. 2010;75:277-80.
7. Sundaram V, Figenshau RS, Roytman TM, et al. Positive margin during partial nephrectomy: does cancer remain in the renal remnant? Urology. 2011;77:1400-3.
8. Khalifeh A, Kaouk JH, Bhayani S, et al. Positive surgical margins in robot-assisted partial nephrectomy: a multi-institutional analysis of oncologic outcomes (leave no tumor behind). J Urol. 2013;190:1674-9.
9. Link RE, Bhayani SB, Allaf ME, et al. Exploring the learning curve, pathological outcomes and perioperative morbidity of laparoscopic partial nephrectomy performed for renal mass. J Urol. 2005;173:1690-4.
10. Allaf ME, Bhayani SB, Rogers C, et al. Laparoscopic partial nephrectomy: evaluation of long-term oncological outcome. J Urol. 2004;172:871-3.
11. Gill IS, Matin SF, Desai MM, et al. Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. J Urol. 2003;170:64-8.
12. Kassouf W, Siemens R, Morash C, et al. Follow-up guidelines after radical or partial nephrectomy for localized and locally advanced renal cell carcinoma. Can Urol Assoc J. 2009;3:73-6.
13. Lee CT, Katz J, Shi W, Thaler HT, Reuter VE, Russo P. Surgical management of renal tumors 4 cm. or less in a contemporary cohort. J Urol. 2000;163:730-6.
14. Trabulsi EJ, Kalra P, Gomella LG. New approaches to the minimally invasive treatment of kidney tumors. Cancer J. 2005;11:57-63.
15. Portis AJ, Yan Y, Landman J, et al. Long-term followup after laparoscopic radical nephrectomy. J Urol. 2002;167:1257-62.
16. Van Poppel H, Becker F, Cadeddu JA, et al. Treatment of localised renal cell carcinoma. Eur Urol. 2011;60:662-72.
17. Zazzara M, Carando R, Nazaraj A, Scarcia M, Romano M, Ludovico GM. Nephron sparing surgery for the treatment of renal masses: A single center experience. Urologia. 2021391560321993557.
18. Introini C, Di Domenico A, Ennas M, Campodonico F, Brusasco C, Benelli A. Functional and oncological outcomes of 3D clampless sutureless laparoscopic partial nephrectomy for renal tumors with low nephrometry score. Minerva Urol Nefrol. 2020;72:723-8.
19. Lane BR, Campbell SC, Gill IS. 10-year oncologic outcomes after laparoscopic and open partial nephrectomy. J Urol. 2013;190:44-9.
20. Ficarra V, Crestani A, Inferrera A, et al. Positive Surgical Margins After Partial Nephrectomy: A Systematic Review and Meta-Analysis of Comparative Studies. Kidney Cancer. 2018;2:133-45.
21. You C, Du Y, Wang H, et al. Laparoscopic Versus Open Partial Nephrectomy: A Systemic Review and Meta-Analysis of Surgical, Oncological, and Functional Outcomes. Front Oncol. 2020;10:583979.
22. Dagenais J, Mouracade P, Maurice M, et al. Frozen Sections for Margins During Partial Nephrectomy Do Not Influence Recurrence Rates. J Endourol. 2018;32:759-64.
23. Rothberg MB, Paulucci DJ, Okhawere KE, et al. A Multi-Institutional Analysis of the Effect of Positive Surgical Margins Following Robot-Assisted Partial Nephrectomy on Oncologic Outcomes. J Endourol. 2020;34:304-11.
24. Marchiñena PG, Tirapegui S, Gonzalez IT, Jurado A, Gueglio G. Positive surgical margins are predictors of local recurrence in conservative kidney surgery for pT1 tumors. International braz j urol. 2018;44:475-82.
25. Carvalho JAM, Nunes P, Tavares-da-Silva E, et al. Impact of Positive Surgical Margins After Partial Nephrectomy. European Urology Open Science. 2020;21:41-6.

26. Tellini R, Antonelli A, Tardanico R, et al. Positive Surgical Margins Predict Progression-free Survival After Nephron-sparing Surgery for Renal Cell Carcinoma: Results From a Single Center Cohort of 459 Cases With a Minimum Follow-up of 5 Years. Clin Genitourin Cancer. 2019;17:e26-e31.