

Partial nephrectomy and positive surgical margin, oncologic outcomes and predictors: a 15-year single institution experience

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Introduction The aim of this article was to compare oncological outcomes after partial nephrectomy between patients with positive (PSM) and negative (NSM) surgical margins.

Material and methods In this retrospective study, the data of 733 patients who underwent partial nephrectomy with diagnosis of renal cell carcinoma (RCC) were analyzed. A total of 80 patients from the NSM group were matched to 42 PSM patients. The Kaplan-Meier method was used to estimate freedom from local disease recurrence and metastatic progression and overall survival. Cox proportional hazards models were used to assess the predictors for recurrence/metastasis.

Results The mean age was 58.4 ± 11.4 years (range: 29 to 82). Median follow-up was 24 months (IQR₂₅₋₇₅: 15–36.2). A total of 5 patients from the PSM group (6.2%) developed local recurrence and metastasis was detected in 2 (2.5%) of them while no metastasis or recurrence was observed in the NSM group. In the multivariate analysis, positive surgical margin was the only independent predictor for recurrence/metastasis (HR[CI] = 0.19[0.04–0.75], p = 0.019). Recurrence-free survival was higher in the NSM group (100% for the NSM group vs 88.1%, p = 0.002) and recurrence/metastasis-free survival was also higher in the NSM group (100% for the NSM group vs 85.7%, p = 0.001), but there were no differences in overall survival between the two groups (96.3% for the NSM group vs 97.6% for the PSM group, p = 0.68).

Conclusions Although tumor recurrence was more prevalent in positive surgical margin patients who underwent partial nephrectomy, there were no differences in overall survival between the two groups. Therefore, active surveillance against further surgery would be a proper option after finding the tumor-involved margins.

Key Words: kidney neoplasms ↔ nephrectomy ↔ neoplasm recurrence
↔ neoplasm metastasis ↔ risk factors

INTRODUCTION

Recently, partial nephrectomy in the treatment of renal cell carcinoma (RCC) has received more attention as an attractive alternative to traditional radical nephrectomy. It became the first-line treatment owing to its multiple functions such as preserving normal renal parenchyma and kidney function, reducing risk

of chronic kidney disease and renal replacement therapy and improving surgical techniques in nephron sparing surgery [1, 2]. Tan et al. evaluated long-term survival in patients undergoing partial versus radical nephrectomy and found that the first group lived longer than the group who had total kidney removal [3]. Simple tumor enucleation during partial nephrectomy would be an option but many surgeons prefer

to remove the tumor with a rim of intact renal parenchyma to achieve a free surgical margin [4, 5, 6]. Although incomplete tumor removal may increase the risk of local recurrence or distant metastasis at least in theory, not all positive surgical margins (PSM) lead to cancer recurrence and it is unclear if positive surgical margin would impact recurrence-free survival, overall survival and cancer-specific survival. Some studies reported an equivalent survival rate between patients with PSM who underwent active surveillance compared to patients with complete surgical excision to achieve negative margins [7, 8, 9] and it could be concluded that the second step in treatment of patients with positive surgical margin is controversial.

The objective of our study was to compare recurrence-free survival and overall survival between two groups of patients who underwent partial nephrectomy in our referral center with positive and negative surgical margins (NSM). Also, the impact of perioperative factors on tumor recurrence or metastasis was investigated.

MATERIAL AND METHODS

In this retrospective study, 750 consecutive patients with renal cell carcinoma who underwent partial nephrectomy in our center (Department of Urology, Labbafinejad University hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran) between 2004 and 2018 were enrolled.

The inclusion criteria were a definite diagnosis of renal cell carcinoma (RCC) with partial nephrectomy during at least one-year of follow-up. Follow-up included history, physical examination, blood tests, chest X-ray, abdominal-pelvic computed tomography (CT) scan every 6 to 12 months in the first 5 years and then annually [10]. Patients with nodal invasion and presence of distal metastasis were excluded from the study. Patients' information including demographic findings, pathological and surgical data and their follow-up were collected. The study protocol was approved by the institutional board of research and ethics committee (ethics code: IR.SBMU.UNRC.1397.32). This study was conducted in accordance with the Declaration of Helsinki.

All the specimens were evaluated by a pathologist experienced in oncological urology in our center. Positive surgical margin was defined as extension of the tumor to the surface of the specimen in permanent pathology. Histological grade, pathological subtypes, tumor size, sarcomatoid changes and necrosis were also determined in pathological examination. The nuclear grade was determined based on the Fuhrman nuclear classification [11]. Local re-

currence was defined as new detection of the tumor mass in the same surgery site based on radiographic evidences on chest X-ray, CT scan, magnetic resonance imaging (MRI), or bone scan with or without pathologic confirmation. Metastasis was determined when imaging findings indicated new distant organ involvement during follow-up.

In total, 80 patients with negative surgical margin (NSM group) were matched to all 42 positive surgical margin patients (PSM group) in terms of age, sex, Fuhrman nuclear grade, pathological stage, pathological subgroup including papillary, chromophobe or clear cell carcinoma, single kidney, bilateral renal tumor, familial renal cancer, presence of sarcomatoid component or necrosis in the tumor, venous involvement and tumor thrombosis, surgical approach (open vs laparoscopic), comorbidities such as diabetes mellitus and chronic renal failure, smoking and body mass index (BMI) to compare recurrence-free survival and overall survival between these two groups and also demonstrate the impact of each of these factors on tumor recurrence.

Table 1. Clinical and pathological characteristics of PSM and NSM groups

	PSM group	NSM group	p-value
Number of patients	42	80	
Age (mean \pm SD)	58.7 \pm 9.8	58.27 \pm 12.2	0.821
Follow-up (months)	32.28 \pm 27.98	32.12 \pm 25.89	0.975
BMI (mean \pm SD)	27.38 \pm 4.4	26.32 \pm 3.3	0.180
Calcium (mean \pm SD)	9.7 \pm 0.6	9.6 \pm 0.5	0.417
Male/Female	28/14	49/31	0.693
DM (%)	9 (21.4%)	11 (13.7%)	0.276
HTN (%)	8 (19%)	13 (16.2%)	0.697
Smoking (%)	8 (19%)	12 (15%)	0.566
Tumor side (R/L/bilateral)	19/21/2	41/37/2	0.645
Surgery (Open/Laparoscopic)	17/24	38/42	0.528
Single kidney (%)	1 (2%)	0 (0%)	0.344
Pathology subtype (%)			
Clear cell	29 (69%)	51 (63.7%)	0.073
Chromophobe	4 (9.5%)	20 (25%)	
Papillary	9 (21.4%)	9 (11.2%)	
Lymphovascular invasion	1 (2.3%)	0 (0%)	0.344
Perineural invasion	1 (2.3%)	0 (0%)	0.344
Fuhrman grade			
Low-grade (1, 2)	28	57	0.601
High-grade (3, 4)	14	23	
Sarcomatoid change	1 (2%)	0 (0%)	0.344
Necrosis	2 (4.7%)	4 (5%)	1.000

PSM – positive surgical margin; NSM – negative surgical margin; SD – standard deviation; BMI – body mass index; DM – diabetes mellitus; HTN – hypertension; R – right; L – left

Quantitative data are shown as mean \pm standard deviation for data with normal distribution or median (interquartile range) for non-normally distributed data. Chi-square and Student t tests were used to compare proportions and means, respectively. Estimates of the cumulative distributions were calcu-

lated according to the Kaplan-Meier method, and log rank tests were used to compare the differences between the two groups. We used univariate and multivariate Cox proportional hazards regression analysis to recognize the predictors for recurrence/metastasis and reported them through hazard ratio with

Table 2. The association of recurrence/metastasis and risk factors

	Recurrent			Metastasis		
	No	Yes	p-value	No	Yes	p-value
Number of patients	117	5		120	2	
Margins						
(+)	37 (88.1)	5 (11.9)	.002	42 (95.2)	2 (4.8)	.048
(-)	80 (100)	0 (0)		80 (100)	0 (0)	
Age (mean \pm SD)	58.37 (11.36)	60 (14.2)	.782	58.34 (11.4)	64 (11.31)	.472
BMI (mean \pm SD)	26.63 (3.78)	28.12 (3.8)	.406	26.64 (3.79)	29.61 (2.17)	.304
Blood calcium (mean \pm SD)	9.65 (.57)	9.72 (.82)	.784	9.66 (.58)	9.1 (.001)	.286
Sex						
Male	74 (96.1)	3 (3.9)	.864	76 (98.7)	1 (1.3)	.696
Female	43 (95.6)	2 (4.4)		44 (97.8)	1 (2.2)	
DM						
No	98 (96.1)	4 (3.9)	.821	100 (98)	2 (2)	.529
Yes	19 (95.0)	1 (5)		20 (100)	0 (0)	
HTN						
No	97 (96)	4 (4)	.851	99 (98)	2 (2)	.515
Yes	20 (95.2)	1 (4.8)		21 (100)	0 (0)	
Smoking						
No	98 (96.1)	4 (3.9)	.830	100 (98)	2 (2)	.529
Yes	19 (95)	1 (5)		20 (100)	0 (0)	
Tumor side						
R	58 (96.7)	2 (3.3)	.810	60 (100)	0 (0)	.334
L	55 (94.8)	3 (5.2)		56 (96.6)	2 (3.4)	
Bilateral	4 (100)	0 (0.0)		4 (100)	0 (0)	
Surgery: Open	54 (98.2)	1 (1.8)	.238	54 (98.2)	1 (1.8)	
Laparoscopy	62 (93.9)	4 (6.1)		65 (98.5)	1 (1.5)	.859
Kidney						
Single	1 (100)	0 (0)	.829	1 (100)	0 (0)	.891
Double	116 (95.9)	5 (4.1)		119 (98.3)	2 (1.7)	
Pathology						
Clear cell	72 (93.5)	5 (6.5)	.267	75 (97.4)	2 (2.6)	.590
Chromophobe	22 (100)	0 (0)		22 (100)	0 (0)	
Papillary	17 (100)	0 (0)		17 (100)	0 (0)	
Lymphovascular invasion	117 (96.7)	4 (3.3)	0.041	119 (98.3)	2 (1.7)	.928
	0 (0)	1 (100)		1 (100)	0 (0)	
Perineural invasion	117 (96.7)	4 (3.3)	0.041	119 (98.3)	2 (1.7)	.928
	0 (0)	1 (100)		1 (100)	0 (0)	
Fuhrman						
Low-grade (1, 2)	81 (95.3)	4 (4.7)	.612	83 (97.6)	2 (2.4)	.357
High-grade (3, 4)	36 (97.3)	1 (2.7)		37 (100)	0 (0)	
Sarcomatoid change						
No	116 (95.9)	5 (0)	.829	119 (98.3)	2 (1.7)	.891
Yes	1 (100)	0 (0)		1 (100)	0 (0)	
Necrosis						
No	112 (96.6)	4 (3.4)	.116	114 (98.3)	2 (1.7)	.758
Yes	5 (83.3)	1 (16.7)		6 (100)	0 (0)	

SD – standard deviation; BMI – body mass index; DM – diabetes mellitus; HTN – hypertension; R – right; L – left

95% CI. All p values were two-sided and $p < 0.05$ was considered statistically significant. SPSS software version 21.0 (IBM Corporation, Armonk, NY, USA) was applied for statistical analysis.

RESULTS

Among 750 patients who underwent partial nephrectomy, 733 patients met the inclusion criteria and their data were analyzed. The mean age was 58.4 ± 11.4 years (range: 29 to 82). Median follow-up was 24 months (IQR: 15–36.2). All the clinical and pathological characteristics of PSM group and NSM matched groups are shown in Table 1 separately. A total of 5 patients from the PSM group (6.2%) developed local recurrence and metastasis was detected in 2 (2.5%) of them while no metastasis or recurrence was observed in the NSM group. Mean time to recurrence was 9 ± 6.24 months (range: 2 to 18) while mean time to metastasis was 8.5 ± 9.19 months (range: 2 to 15). Pathology evaluation manifested that all recurrences and metastases belonged to subtype of clear cell carcinoma. In total, there were four deaths, one in the positive margin group and three in the negative margin group. All deaths were due to non-cancer causes. Four cases of recurrence were at PT1a stage and one remaining was at PT1b stage in pathology. One case of metastasis was at PT1a stage and the other was at PT1b stage in pathology. Recurrence had correlation with positive surgical margin ($p = 0.002$), lymphovascular ($p < 0.001$) and perineural ($p < 0.001$) invasion, while metastasis was correlated with only positive surgical

margin ($p = 0.048$). The relationships between all these factors and the P values are shown in Table 2. In the univariate analysis, positive surgical margin (HR[CI] = 0.22 [0.05–0.85], $p = 0.028$), lympho-vascular invasion ($p < 0.001$) and peri-neural invasion ($p < 0.001$) could significantly predict the occurrence of recurrence/metastasis. In the multivariate analysis, positive surgical margin was the only independent predictor for recurrence/metastasis (HR[CI] = 0.19[0.04–0.75], $p = 0.019$).

Recurrence-free survival was higher in the NSM group (100% for the NSM group vs 88.1%, $p = 0.002$) and recurrence/metastasis-free survival was also higher in the NSM group (100% for the NSM group vs 85.7%, $p = 0.001$), but there were no differences in overall survival between the two groups (96.3% for the NSM group vs 97.6% for the PSM group, $p = 0.68$). Figure 1A shows the recurrence/metastasis-free survival and Figure 1B shows the overall survival of NSM patients and PSM patients.

DISCUSSION

One of the important points to keep in mind during partial nephrectomy is that the margin of the surgery would be free of tumor. Many studies were performed on this subject and reported the incidence of positive margin after partial nephrectomy to be about 0–10% [12, 13, 14], while the rate of tumor recurrence is lower (0 to 6%) [15, 16]. However, it is controversial whether positive surgical margin may affect progression-free survival, overall survival, cancer-specific survival and subsequent surgery

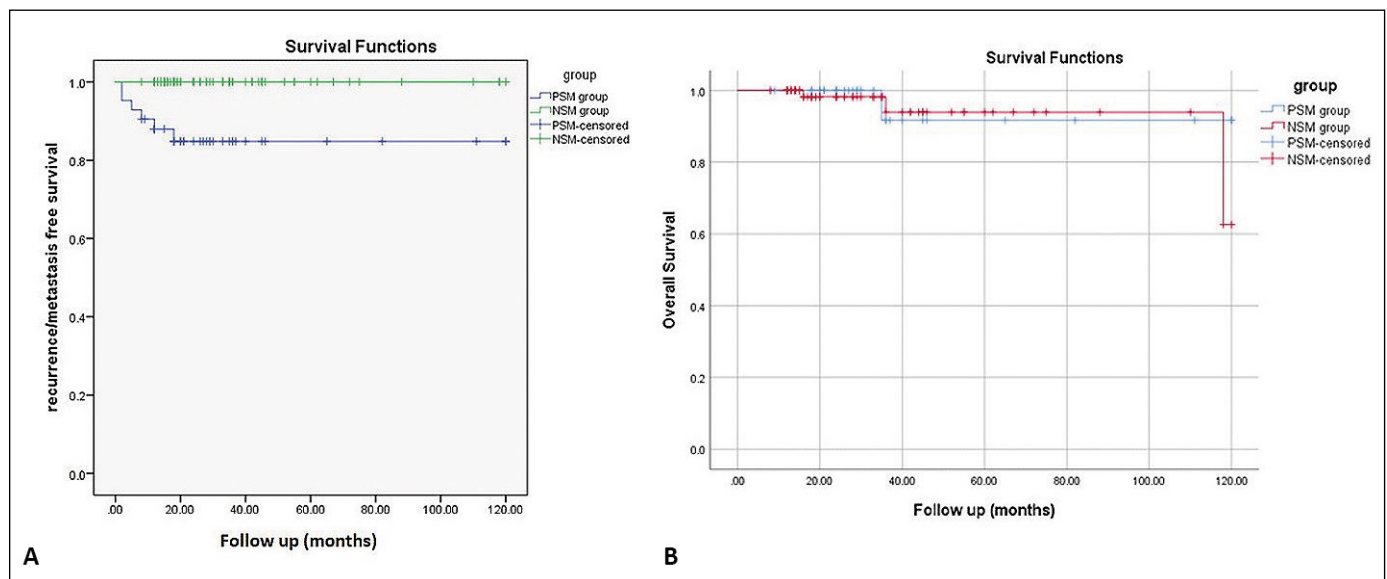


Figure 1A shows the recurrence/metastasis free survival and **Figure 1B** shows the overall survival of NSM versus PSM group.

PSM – positive surgical margins; NSM – negative surgical margins

is mandatory after finding positive margin or not. In this study, it was found that tumor recurrence occurred more in positive surgical margin group but it did not affect the overall survival in comparison with the negative surgical margin group. This is totally similar to the findings of Bensalah et al. [17]. They matched 102 patients with negative and 101 with positive surgical margin and achieved the same findings. They also did not find any difference in cancer-specific survival estimates between two groups; in this study, such comparison was not performed because no patients died due to renal cancer during the follow-up. Although positive surgical margin did not predict lower overall survival in similar studies [9, 17, 18] and ours, it seems that studies with longer follow-up time are needed to confirm this finding.

Repeat partial nephrectomy, radical nephrectomy and active surveillance are three options available in our center after finding positive surgical margin. According to our results and the findings of other studies mentioned above about the similar overall survival in margin positive and negative groups, active surveillance would be a proper option especially in elderly patients with poor general condition. Bensalah et al. [17] stated that only in 39% of patients who underwent second surgery, residual tumor was found in the pathology examination and they considered it necessary to use new techniques or tumor markers to evaluate the problem more accurately. According to the findings, it seems that repeat excision or radical nephrectomy after finding positive surgical margin is not mandatory in all patients and further surgery besides overtreatment can be avoided especially in patients with no proper condition to tolerate subsequent surgery.

There was a correlation between tumor recurrence and positive surgical margin, lymphovascular and perineural invasion in a univariate analysis. It is more effective to use Cox proportional hazard regression analysis to test the independent effect of variables on survival but due to the low number of recurrences, this model was not used in the current research. In a multivariate Cox regression analysis, Bensalah et al. [17] showed indication (imperative vs elective) and tumor location (peripheral vs hilar) are two independent factors that could predict tumor recurrence. Takagi et al. [19] in the retrospective study of 1227 patients who underwent partial nephrectomy, demonstrated that high-grade tumor and upstaging to PT3a are two independent factors that could predict worse recurrence-free survival. RENAL score (radius, exophytic/endophytic properties, nearness of deepest tumor portion to collecting system or sinus, ante-

rior/posterior and location relative to polar line) was the only factor that could predict the tumor recurrence in a study of 830 cases who underwent partial nephrectomy [20]. In the evaluation of 314 patients, Marchinena et al. [21] found that positive surgical margin and high-grade tumors (Fuhrman grade 3 and 4) were independent predictors of local recurrence and Fuhrman grade was the independent predictor for distant recurrence. Petros et al. matched 100 patients with negative margin to 34 positive surgical margin cases and showed multifocal tumor would be an independent risk factor for tumor recurrence and they concluded that maybe the recurrence occurred due to new primary tumors as opposed to secondary and positive surgical margin [22]. All these studies and different results demonstrate the need for conducting systematic reviews and meta-analysis in this regard.

The guidelines have suggested that the subtype of clear cell in RCC shows worse oncological outcomes than papillary and chromophobe cells [23, 24]. Also, in our study, all patients with recurrence and metastasis had clear cell type of RCC. Wagener et al. in a large retrospective cohort study of 1943 patients with papillary RCC and 5600 with clear cell RCC also found a significantly higher cancer-specific mortality rate in the first group ($p = 0.007$) [25]. Yoo et al. evaluated 759 patients with clear cell RCC and 84 patients with papillary RCC and found that 10-year recurrence-free survival was significantly higher in the clear cell group (96.1% vs 73%, $p < 0.001$) which was different from our results [26]. One main reason is that they demonstrated that recurrence after at least five years following the surgery was more prevalent in the papillary group in comparison with the clear cell group (0.3% vs 4.8%, $p < 0.001$) but the mean duration of follow-up in our patients was only 32 months and so the recurrence of the tumor and its relationship with the pathology could not be assessed after 5 years of surgery.

Pathologic features including lymphovascular, perineural invasion and Fuhrman nuclear grade of the tumor have a correlation with aggressive behavior and worse oncologic outcomes in RCC [27, 28, 29]. Although most relapses occur within the first 5 years after the surgery, lymphovascular invasion (LVI) besides other pathological features such as nuclear grade can help us predict which patients need longer follow-up even more than 5 years due to increased risk of late recurrences [30, 31]. Bel-sante et al. in the study of 333 patients with organ-confined clear cell RCC found that lymphovascular invasion was a significant predictor of cancer-specific survival ($p = 0.01$) and disease-free survival

($p = 0.026$) [32]. Sorbellini et al. [33] in the multivariate analysis of 833 patients with RCC found that only LVI ($P 0.012$) and Fuhrman grade ($P 0.002$) were independent predictors of recurrence. Lymphovascular invasion was strongly associated with adverse outcomes in the study of 841 patients with RCC in the univariate analysis by Katz et al. [34]. In a retrospective study of 213 patients with RCC by Minervini et al., cancer-specific survival was 95.9%, 86.8%, and 60.1% in patients with Fuhrman grade 1, 2 and 3–4, respectively. They found that nuclear grade is an important morphologic variable for predicting long-term survival especially in tumors greater than 7 cm [35]. Also, a relationship was found between recurrence/metastasis and these pathologic features in our study. In some studies, tumor recurrence occurred more in patients with imperative indication of partial nephrectomy in comparison with elective groups. The reason is that maybe the imperative tumors are larger in size and higher grade and more often classified

as clear cell carcinoma [17]. However, no differences were found between recurrence and imperative indication in this study.

CONCLUSIONS

In this study, positive surgical margin, lymphovascular and perineural invasion had correlation with tumor recurrence. It was also concluded that although tumor recurrence was more prevalent in positive surgical margin patients who underwent partial nephrectomy however, there were no differences in overall survival between the two groups. Therefore, active surveillance rather than further surgery would be a proper option after finding the tumor-involved margins. However, studies with larger sample size and longer follow-up are necessary to confirm this conclusion.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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