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Predictors of positive surgical margins in patients undergoing partial nephrectomy: A large single-center experience

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ABSTRACT

Objective: To identify preoperative factors that predict positive surgical margins in partial nephrectomy.

Material and methods: Using our institutional partial nephrectomy database, we investigated the patients who underwent partial nephrectomy for malignant tumors between January 2011 and December 2015. Patient, tumor, surgeon characteristics were compared by surgical margin status. Multivariable logistic regression was used to identify independent predictors of positive surgical margins.

Results: A total of 1025 cases were available for analysis, of which 65 and 960 had positive and negative surgical margins, respectively. On univariate analysis, positive margins were associated with older age (64.3 vs. 59.6, p<0.01), history of prior ipsilateral kidney surgery (13.8% vs. 5.6%, p<0.01), lower preoperative eGFR (74.7 mL/min/1.73 m^2 vs. 81.2 mL/min/1.73 m^2, p=0.01), high tumor complexity (31.8% vs. 19.0%, p=0.03), hilar tumor location (23.1% vs. 12.5%, p=0.01), and lower surgeon volume (p<0.01). Robotic versus open approach was not associated with the risk of positive margins (p=0.79). On multivariable analysis, lower preoperative eGFR, p=0.01), hilar tumor location (p=0.01), and lower surgeon volume (p<0.01) were found to be independent predictors of positive margins.

Conclusion: In our large institutional series of partial nephrectomy cases, patient, tumor, and surgeon factors influence the risk of positive margins. Of these, surgeon volume is the single most important predictor of surgical margin status, indicating that optimal oncological outcomes are best achieved by high-volume surgeons.

Keywords: Nephrectomy; partial nephrectomy; positive surgical margin; robotic surgical procedures.

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Introduction

Partial nephrectomy (PN) is the gold standard treatment option for clinical T1 renal masses.[1,2] During PN, the complete removal of the tumor with a small margin of normal parenchyma is considered to be sufficient to provide local cancer control.[1] Although the impact of surgical margin status on clinically significant oncological outcomes is still controversial, positive surgical margins (PSM) may increase the risk of local recurrence, especially in patients with high-grade tumors.[3-7]

In the literature, the generally accepted rate of PSM after PN ranges between 0% to 11%[3,7-12]; however, higher rates up to 28% have been reported in some series.[4,13,14] Several risk factors for PSM have been suggested, including age,[15] tumor location,[15] tumor size,[9,10] tumor stage,[9] tumor grade,[5,15] and tumor invasion into the perinephric fat.[9] The aim of this study was to identify predictors of PSM in PN while taking into account surgeon factors, namely surgical approach and surgeon volume. Only preoperative characteristics were assessed in order to inform patient counseling and prevention of PSM.

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Table 1. Patient characteristics

Variables	PSM [n=65 (6.3%)]	NSM [n=960 (93.7%)]	p
Mean age, year (±SD)	64.3 (±11.1)	59.6 (±11.9)	<0.01
Male, n (%)	41 (63.1)	602 (62.7)	0.95
Body mass index, median (IQR)	28.5 (25.9-33.3)	30.1 (26.4-34.2)	0.28
CCI ≥2, n (%)	27 (41.5)	332 (34.6)	0.25
Solitary kidney, n (%)	4 (6.2)	56 (5.8)	0.91
Prior ipsilateral kidney surgery, n (%)	9 (13.8)	54 (5.6)	<0.01
Preoperative eGFR, median (IQR)	74.7 (54.4-90.2)	81.2 (64.4-96.9)	0.01
Chronic kidney disease, n (%)	20 (30.8)	182 (19)	0.02

PSM: positive surgical margin; NSM: negative surgical margin; CCI: Charlson Comorbidity Index; IQR: interquartile range; SD: standard deviation

Table 2. Tumor characteristics

Variables	PSM (n=65)	NSM (n=960)	p
Clinical T stage, n (%)			0.71
T1a	38 (58.5)	579 (60.3)	
T1b	23 (35.4)	342 (35.6)	
T2	4 (6.1)	39 (4.1)	
Multiple Ipsilateral Tumors, n (%)	7 (10.8)	58 (6)	0.07
Tumor size, cm (IQR)	3.5 (2.7-5)	3.5 (2.5-4.6)	0.36
R.E.N.A.L score, median (IQR)	8 (7-10)	8 (6-9)	0.07
Tumor complexity			0.03
Low, n (%)	13 (20.6)	272 (29.2)	
Moderate, n (%)	30 (47.6)	484 (51.8)	
High, n (%)	20 (31.8)	178 (19)	
Endophytic property			0.46
<50% endophytic	19 (32.8)	341 (41)	
50-99% endophytic	28 (48.3)	353 (42.5)	
100% endophytic	11 (19)	137 (16.5)	
Hilar location, n (%)	15 (23.1)	120 (12.5)	0.01

PSM: positive surgical margin; NSM: negative surgical margin; IQR: interquartile range

Material and methods

After receiving Institutional Review Board approval (IRB number 5065), we identified patients who had undergone PN for malignant disease (based on final pathology) between January 2011 and December 2015. Written informed consent was obtained from the patients. Overall 15 surgeons were included in the study, all with fellowship training or at least one year of staff experience. The PN approach for robotic and open cases was standardized, as previously described.[16,17] The present study was conducted in compliance with the Helsinki Declaration.

Study endpoint

The primary endpoint of the study was surgical margin status. PSM was defined as cancer present at the inked parenchymal margin of the final pathological specimen. According to this definition, perinephric or renal sinus fat invasion (pT3a stage) was not considered as a PSM.

Study variables

Patient, tumor, and surgeon characteristics as well as operative and pathological outcomes were compared based on surgical margin status. Patient characteristics included age, gender, body mass index (BMI), Charlson Comorbidity Index (CCI), prior ipsilateral kidney surgery, presence of a solitary kidney, and preoperative estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) equation.[18] Chronic kidney disease was defined as GFR less than 60 mL/min/1.73 m^2. Tumor characteristics included clinical T stage, multiple ipsilateral tumors within the operated kidney (based on preoperative imaging), clinical tumor size, tumor complexity based on the R.E.N.A.L. nephrometry classification system (low, 4-6; moderate, 7-9; and high, 10-12),[19] endophytic properties, and hilar location.[20] Surgeon characteristics included approach (robotic or open) and PN volume. Surgeon volume was categorized into quartiles by annual surgeon case volume as high (≥25 cases/year), intermediate high (5-24 cases/year), intermediate low (3-4 cases/year), and low (≤2 cases/year). Operative outcomes included operative time, ischemia time, estimated blood loss (EBL), intraoperative blood transfusion, and intraoperative complications. Pathological outcomes included histology, grade, pathological T stage, presence of renal sinus invasion, and perinephric fat invasion.

Statistical analysis

The Pearson chi-square test for categorical variables and the Mann-Whitney U test for continuous variables were used to as-

sess the associations with surgical margin status. Variables significant on univariate analysis were included in the multivariate model. Logistic regression was used to evaluate the independent effect of age, prior ipsilateral kidney surgery, preoperative eGFR, tumor complexity, hilar tumor location, and surgeon volume on PSM. Analyses were performed with Statistical Package for the Social Sciences 20.0 (IBM SPSS Statistics Corp.; Armonk, NY, USA), and statistical significance was considered at $p<0.05$.

Results

A total of 1025 cases were available for analysis, of which 65 (6.3%) had PSM. Mean age (64.3 vs. 59.6 yrs., $p<0.01$), incidence of prior ipsilateral kidney surgery (13.8 vs. 5.6%, $p<0.01$), and incidence of CKD (30.8 vs. 19%, $p=0.02$) were higher in PSM patients (Table 1). Incidence of hilar involvement (23.1 vs. 12.5%, $p<0.01$) was higher in PSM arm however; median RENAL Score did not differ between groups ($p=0.07$) (Table 2). The median ischemia time was 29 minutes for PSM cases versus 23.1 minutes for negative-surgical-margin cases ($p=0.02$). The rate of intraoperative blood transfusion (10.8% vs. 3.9%, $p<0.01$) was higher in PSM cases, but EBL was similar. Intraoperative complications (7.7% vs. 2.4%, $p=0.01$) were higher for PSM cases. No differences in tumor histology or grade were detected based on margin-positivity status. Pathological T stage was higher ($p=0.01$) for the PSM group, primarily due to higher rates of sinus fat involvement (18.5% vs. 5.8, $p<0.001$) (Table

Table 3. Operative and pathological information

Variables	PSM (n=65)	NSM (n=960)	p
Operative details			
Mean operative time, min (±SD)	155 (90)	160 (84)	0.8
Median ischemia time, min (IQR)	29 (17.5-38)	23.1 (17.5-30)	0.02
Median estimated blood loss, mL (IQR)	200 (100-300)	200 (100-300)	0.25
Intraoperative blood transfusion, n (%)	7 (10.8)	37 (3.9)	<0.01
Intraoperative complications, n (%)	5 (7.7)	23 (2.4)	0.01
Pathological findings			
Histology, n (%)			0.11
Clear cell RCC	35 (53.8)	637 (66.4)	
Papillary RCC	14 (21.5)	186 (19.4)	
Chromophobe RCC	10 (15.4)	84 (8.8)	
Other RCC	6 (9.2)	53 (5.5)	
Nuclear grade, n (%)			0.44
1-2	25 (50)	476 (55.6)	
3-4	25 (50)	380 (44.4)	
Pathological T stage, n (%)			0.01
T1a	30 (46.2)	630 (65.6)	
T1b	18 (27.7)	211 (22)	
T2a	3 (4.6)	17 (1.8)	
T2b	0	5 (0.5)	
T3a	14 (21.5)	96 (10)	
Sinus fat involvement	12 (18.5)	56 (5.8)	<0.01
Perirenal fat involvement	3 (4.6)	46 (4.8)	0.97

PSM: positive surgical margin; NSM: negative surgical margin; IQR: interquartile range; RCC: renal cell carcinoma

Table 4. Surgeon characteristics

Variables	PSM (n=65)	NSM (n=960)	p
Surgical approach			0.79
Robotic, n (%)	44 (67.7)	635 (66.1)	
Open, n (%)	21 (32.3)	325 (33.9)	
Surgeon volume			<0.01
High, n (%)	25 (38.5)	651 (67.5)	
Intermediate high, n (%)	35 (53.8)	212 (22.0)	
Intermediate low, n (%)	3 (4.6)	73 (7.6)	
Low, n (%)	2 (3.1)	29 (3.0)	

PSM: positive surgical margin; NSM: negative surgical margin

Table 5. Multivariate analysis of predictors of positive surgical margins after partial nephrectomy

Variables	OR	95% CI	p
Age, y	1.01	0.99-1.04	0.16
Preoperative eGFR	0.98	0.97-0.99	<0.01
Prior ipsilateral kidney surgery, n (%)	1.60	0.69-3.69	0.27
Tumor complexity			0.67
Low	Ref		
Moderate	1.06	0.53-2.11	0.86
High	1.43	0.62-3.28	0.39
Hilar versus non-hilar location	2.22	1.18-4.16	0.01
Surgeon volume			<0.01
High, n (%)	Ref		
Intermediate high, n (%)	4.50	2.63-7.92	<0.01
Intermediate low, n (%)	1.05	0.30-3.67	0.93
Low, n (%)	1.63	0.36-7.39	0.52

eGFR: estimated glomerular filtration rate; OR: odds ratio; CI: confidence interval

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3). The highest-volume surgeons had a PSM rate of 3.7% compared to 14.1% for lower-volume surgeons (p<0.01); however, no difference in PSM was detected by approach used (p=0.79) (Table 4).

On multivariate analysis, lower preoperative eGFR (p<0.01), hilar tumor location (p=0.01), and surgeon volume (p<0.01) were found to be independent predictors of PSM (Table 5). In particular, surgeon volume was the strongest predictor of PSM, such that lower-volume surgeons (high intermediate group) had 4.5-fold higher odds of PSM than the highest-volume surgeons (OR 4.50, 95%CI 2.63-7.92, p<0.01).

Discussion

The aim of this study was to predict the risk of PSM associated with PN based on preoperative factors which aids in preoperative counseling and primary prevention. The overall incidence of PSM ranges from 0% to %7 in patients undergoing PN.[21] The incidence of PSM in our series, including open and robotic PN, was 6.3%, which is comparable with previously published series regardless of the surgical technique.[9] To our knowledge, this is the largest single-center study to evaluate predictors of PSM after PN, taking into account patient, tumor, and surgeon factors. In our analysis, we found that surgeon volume, hilar tumor location, and preoperative eGFR were independent predictors of PSM. Above all, surgeon volume was the most important factor influencing surgical margin status, with higher-volume surgeons having significantly lower rates of PSM. Notably, at our center of experienced open and robotic surgeons, surgical approach did not influence PSM rates. This finding differs from prior research by Tabayoyong et al.[22], which reported higher PSM rates associated with robotic PN compared to open PN; however, this study did not account for surgeon experience or volume, potentially explaining their contradictory results.

The volume-outcome relationship in PN has been previously established; however, few studies that have investigated the volume effect on PSM rates have had conflicting results.[9,23,24] In a population-based study using the Ontario Cancer Registry of 664 PNs performed over a 10-year period, Ani et al.[9] did not detect a correlation between surgeon volume and surgical margin status. In contrast, in a multi-institutional study of 570 PNs, Couapel et al.[24] showed that higher-volume centers had lower PSM rates. Unlike the present study, neither of these studies accounted for tumor complexity in their analyses.

Tumor complexity, as assessed by R.E.N.A.L. nephrometry score and hilar tumor location, has been previously linked to malignant and high-grade pathology;[19] however, the association between tumor complexity or hilar designation and PSM status is poorly studied.[25-27] In our study, R.E.N.A.L. score was not a predictor of PSM status, but hilar location increased the odds of PSM two-fold. In support of our findings, Bensalah et al.[5] showed that central tumor location was a significant predictor of local recurrence following PN, a phenomenon that may be explained by PSM.

Parenchymal volume loss is a surgically modifiable factor that predicts functional preservation after PN.[28,29] In our multivariable model, preoperative renal function was a significant predictor of PSM. It is probable that efforts to maximize volume preservation, especially in patients with preexisting renal dysfunction, may predispose to a higher risk of PSM. Our results are supported by the research of Couapel et al.[24], which showed that patients with preoperative chronic kidney disease had a four-fold increased risk of PSM.

The major limitation of this study is its retrospective nature, which can be a source of bias. Also, given the high level of expertise of surgeons in this study, our results may not be generalizable to other surgeons.

In conclusion, at our high-volume center, PSM occurs infrequently after PN but can be influenced by patient, tumor, and surgeons' factors. Surgeon volume is the primary, and only modifiable, predictor of PSM, but hilar tumor location and preoperative renal function also influence surgical margin status.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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