Original Article

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Impact of Positive Surgical Margins on Renal Cell Carcinoma Recurrence

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Abstract

Objective: To investigate the impact of positive surgical margins (PSM) on local relapse and metastasis in patients undergoing partial nephrectomy (PN).
Materials and Methods: We retrospectively analyzed the data of 43 patients who underwent PN between June 2019 and January 2024 and met the inclusion criteria. Patients were divided into two groups: PSM and negative surgical margin (NSM). We analyzed preoperative patient characteristics, surgical details, and pathological findings. We compared the incidences of local relapse, ipsilateral radical nephrectomy, and metastasis between the two groups during follow-up.
Results: The median follow-up duration was 24.5 months in the PSM group and 16 months in the NSM group, with no significant difference in follow-up duration (p>0.05). Ischemia times were significantly longer in the PSM group (26.5 minutes vs. 18 minutes, p=0.04) and there was greater intraoperative blood loss (700 mL vs. 300 mL, p<0.001). No significant differences were observed between the groups regarding local relapse, metastasis, or ipsilateral radical nephrectomy (p>0.05). Histological type, Fuhrman grade, and pathological T-stage did not differ significantly between the groups (p>0.05).
Conclusion: PSM is associated with longer ischemia times and increased intraoperative bleeding. However, despite the higher recurrence rates associated with PSM, no statistically significant differences were observed in local relapse or metastasis when compared to NSM. Future research should focus on larger cohorts and extended follow-up to better understand the impact of surgical margins on patient outcomes.
Keywords: Local recurrence, metastasis, negative surgical margins, partial nephrectomy, positive surgical margins

Introduction

In recent years, due to advancements and the widespread use of imaging techniques, the detection of smaller and earlier-stage renal masses, both incidentally and symptomatic, has increased. The standard curative treatment for localized renal tumors is surgery. However, the choice of surgical procedure depends on the tumor's size, location, and stage. For cT1 and selected cT2 tumors, partial nephrectomy (PN) is preferred when considering the importance of preserving kidney function to maintain oncological outcomes and quality of life (1). It has been reported that in localized renal tumors, kidney function is better preserved after PN than after radical nephrectomy (RN), and morbidity related to cardiovascular disorders is reduced (2). In patients undergoing PN, positive surgical margins (PSM) can be observed at rates ranging from 0% to 11%, regardless of the surgical technique used (open, laparoscopic, robotic) (3,4). PSM are a subject of debate in terms of prognosis and follow-up plans because they may lead to poor outcomes in certain histological subtypes.

Some researchers have reported that PSM in renal cell carcinoma (RCC) does not affect cancer-free survival (5). The oncological outcomes of PSM remain controversial. PSM, especially in high-grade patients, increases the risk of local relapse. In patients with PSM, the incidence of local relapse is 16% compared with 3% in patients with negative surgical margins (NSM) (6).

The aim of this study was to investigate the impact of surgical margins on local relapse and metastasis in patients with PN.

Materials and Methods

This study retrospectively examined the data of 57 patients who underwent preoperative thoracoabdominopelvic computed tomography (CT) or abdominal magnetic resonance imaging

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(MRI) combined with thoracic CT between June 2019 and January 2024 and who underwent PN due to a preliminary diagnosis of localized renal malignancy.

The inclusion criteria were as follows: minimum follow-up of 6 months, malignant pathology, PSM, NSM, and complete follow-up data. The exclusion criteria were benign pathologies, such as oncocytoma and angiomyolipoma, clinical stage cT3-4, cN+, or cM+, and incomplete or missing data for the study. After excluding 14 patients who met the exclusion criteria, the study was designed with 43 patients.

Preoperative factors evaluated in the included patients included age, sex, laterality, clinical tumor size and location, renal nephrometry score, and serum creatinine levels. Perioperative renal ischemia status, surgical technique, intraoperative bleeding, and non-bleeding intraoperative complications were also assessed.

All specimens were evaluated by uro-pathologists at our institution for analysis. Pathological findings included histological types, such as clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC, as well as pathological T-stage, tumor size, Fuhrman grade, and surgical margins. During follow-up, local relapse, ipsilateral RN, and metastasis were evaluated. Patients with PSM were grouped into group 1, and patients with NSM were grouped into group 2. Between-group comparisons were made regarding age, sex, laterality, tumor size and location, renal nephrometry score, preoperative serum creatinine levels, histological type, pathological T-stage, Fuhrman grade, pathological tumor size, surgical margins, and occurrence of local relapse, ipsilateral RN, and metastasis. The median follow-up duration was calculated as the median time from surgery to the last follow-up visit.

The study protocol was approved by the Clinical Research Ethics Committee of Gazi University Faculty of Medicine (approval number: 23/01/2023-82, date: 27.01.2023).

Surgical Technique

Open PN: A subcostal incision was made in the lateral decubitus position to free the kidney from surrounding tissues transabdominally. After controlling the renal hilum, the renal artery and vein were clamped en bloc. The tumor was then resected under cold ischemia. Post-resection, the tumor bed and parenchyma were repaired in two layers. Hemostasis was achieved using a hemostatic matrix kit (Surgiflo, ETHICON) and absorbable hemostat (Surgicel, ETHICON). A drain was placed in the renal bed, and the procedure was concluded.

Laparoscopic PN: In the lateral decubitus position, insufflation was performed with a Veress needle to achieve an intra-abdominal pressure of 15 mmHg. After placing a total of four trocars, including one for the camera, the kidney was freed from surrounding tissues, and control of the renal hilum was established. The renal artery and vein were clamped en bloc, and the tumor was resected under warm ischemia. Post-resection, the tumor bed and parenchyma were repaired in two layers. Hemostasis was achieved using a hemostatic matrix kit (Surgiflo, ETHICON) and absorbable hemostat (Surgicel, ETHICON). A drain was placed in the renal bed, and the procedure was concluded.

Robot-assisted laparoscopic PN (RAPN): In the lateral decubitus position, insufflation was achieved using a Veress needle to reach an intra-abdominal pressure of 15 mmHg. After placing a total of five trocars, including one for the camera, the kidney was freed from surrounding tissues, and control of the renal hilum was established. The renal artery and vein were clamped en bloc, and the tumor was resected under warm ischemia. Post-resection, the tumor bed and parenchyma were repaired in two layers. Hemostasis was achieved using a hemostatic matrix kit (Surgiflo, ETHICON) and absorbable hemostat (Surgicel, ETHICON). A drain was placed in the renal bed, and the procedure was concluded.

Patients were evaluated every 3 months during the first year after surgery and then every 6 months thereafter. Follow-up evaluations included medical history taking, physical examinations, routine laboratory blood tests, chest radiography, and abdominal imaging (CT or MRI). Follow-up assessments for both PSM and NSM cases were conducted at the same time-points.

Statistical Analysis

Statistical analysis was performed using SPSS software version 22. Categorical data across groups were compared using Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test. Statistical significance was set for p-values less than 0.05.

Results

The median age of patients in the PSM group was 52.5 years (range: 44-58), while in the NSM group it was 57 years (range: 32-77). There were no statistically significant differences between the groups regarding age, sex, laterality, or median preoperative serum creatinine levels (all $p>0.05$; Table 1).

The median follow-up duration was 24.5 months (7-47) in the PSM group and 16 months (6-60) in the NSM group. There was no statistically significant difference between the groups in terms of follow-up duration ($p>0.05$) (Table 1).

The median ischemia time was 26.5 minutes (23-32) in the PSM group and 18 minutes (8-33) in the NSM group. The ischemia time was significantly longer in the PSM group ($p=0.04$) (Table 1).

The median intraoperative blood loss was 700 mL (600-900) in the PSM group and 300 mL (200-700) in the NSM group. Intraoperative blood loss was significantly higher in the PSM group ($p<0.001$) (Table 1).

There were no statistically significant differences between the two groups regarding intraoperative complications, tumor location, renal nephrometry score, endophytic nature of the tumor, or imaging-based tumor size ($p>0.05$, $p>0.05$, $p>0.05$, $p>0.05$ and $p>0.05$, respectively) (Table 1).

There were no statistically significant differences between the groups regarding histological tumor type, Fuhrman grade, pathological T-stage, or pathological tumor size ($p>0.05$, $p>0.05$, $p>0.05$ and $p>0.05$, respectively) (Table 2).

In the PSM group, during a median follow-up of 24.5 months, 1 patient (25%) experienced local relapse, and the same patient 1 (25%) also had synchronous metastases. Patient 1 (25%) underwent ipsilateral RN surgery. In the NSM group, during a median follow-up of 16 months, none of the patients experienced local relapse, but 1 patient (2.6%) had metastasis, and no patients (0%) underwent ipsilateral RN. There were no significant differences between the groups in terms of local relapse, metastasis, and ipsilateral RN (p>0.05, p>0.05 and p>0.05, respectively) (Table 3).

Discussion

PSMs can be considered residual cancer cells in the resection area. However, these residual cells might undergo necrosis due to renal ischemia, making them potentially clinically insignificant. Additionally, because pathologists can only examine one side of the specimen, cancer cells corresponding to PSM might not be present in the resection bed. In NSM, although there is a

Table 1. Patient characteristics and perioperative findings

		PSM n (4)	NSM n (39)	p-value
Age, year (median, min-max)		52.5 (44-58)	57 (32-77)	0.319
Follow-up, month (median, min-max)		24.5 (7-47)	16 (6-60)	0.454
Gender n (%)	Female	0 (0%)	17 (43.6%)	0.140
	Male	4 (100%)	22 (56.4%)	
Tumor side n (%)	Right	3 (75%)	21 (53.8%)	0.618
	Left	1 (25%)	18 (46.2%)	
Renal nephrometry score (median, min-max)		5.5 (4-7)	5 (4-8)	0.479
Endophytic biomass, n (%)		2 (50%)	12 (30.8%)	0.585
Imagiological tumor size, cm (median, min-max)		37.5 (19-57)	37 (12-75)	0.762
Tumor location n (%)	Superior pole	1 (25%)	9 (23.1%)	0.996
	Inferior pole	2 (50%)	20 (51.3%)	
	Mezorenal area	1 (25%)	10 (25.6%)	
Surgical approach n (%)	Open	2 (50%)	31 (79.5%)	0.374
	LPN	1 (25%)	3 (7.7%)	
	RAPN	1 (25%)	5 (12.8%)	
Ischemia time, minute (median,min-max)		26.5 (23-32)	18 (8-33)	0.04*
Preoperative creatinine mg/dL (median, min-max)		0.9 (0.9-1.6)	0.9 (0.5-2.8)	0.361
Intraoperative blood loss, mL (median, min-max)		700 (600-900)	300 (200-700)	<0.001*
Intraoperative complications, n (%)		3 (75%)	10 (25.6%)	0.075

PSM: Positive surgical margin, NSM: Negative surgical margin, LPN: Laparoscopic partial nephrectomy, RAPN: Robotic-assisted laparoscopic partial nephrectomy, min-max: Minimum-maximum, *Statistically significant p-value

Table 2. Pathological findings

		PSM n (4)	NSM n (39)	p-value
Histology n (%)	ccRCC	4 (100%)	35 (89.7%)	0.798
	pRCC	0 (0%)	3 (7.7%)	
	chrRCC	0 (0%)	1 (2.6%)	
T stage n (%)	T1a	2 (50%)	28 (71.8%)	0.571
	T1b	2 (50%)	10 (25.6%)	
	T2a	0 (0%)	1 (2.6%)	
Fuhrman grade n (%)	I	2 (50%)	10 (25.6%)	0.824
	II	1 (25%)	15 (38.5%)	
	III	1 (25%)	13 (33.3%)	
	IV	0 (0%)	1 (2.6%)	
Tumor size, cm (median, min-max)		37.5 (15-55)	35 (8-73)	0.763

PSM: Positive surgical margin, NSM: Negative surgical margin, ccRCC: Clear cell renal cell carcinoma, pRCC: Papillary renal cell carcinoma, chrRCC: Chromosomal renal cell carcinoma

Table 3. Follow-up variables

	PSM n (4)	NSM n (39)	p-value
Local relapse, n (%)	1 (25%)	0 (0%)	0.093
Metastasis, n (%)	1 (25%)	1 (2.6%)	0.179
Ipsilateral RN, n (%)	1 (25%)	0 (0%)	0.093

PSM: Positive surgical margin, NSM: Negative surgical margin, RN: Radical nephrectomy possibility of up to 5% false-negative reports, NSM does not guarantee the absence of local relapse (7,8).

Bensalah et al. (9) reported that only 39% of patients who underwent reoperation due to PSM had residual tumors identified on pathological examination. They stated that new techniques or tumor markers are necessary to more accurately assess surgical margins in their studies.

PSM after PN has been reported at rates ranging from 0.1% to 10.7% (10). In our study, the rate of PSM was 9.3%, which is consistent with the literature. Takagi et al. (11) reported that the average time to recurrence after PN was 19 months. In our study, the time to recurrence in one of the four patients with PSM was 16 months. However, due to the limited number of patients, we could not determine a threshold value.

In the literature, there is no consensus on whether there is a statistical relationship between positive and NSM and recurrence rates or specific survival. Bernhard et al. (12) conducted multivariate analysis during an average follow-up of 27 months and demonstrated an association between PSM and local recurrence. Similarly, Wood et al. (6) showed a strong association between PSM and local relapse after PN, with an average follow-up of 23 months. They reported a relapse rate of 15.9% in the PSM group compared with 3% in the control group. Khalifeh et al. (3) reported in their study that during an average follow-up of 13 months, 9 out of 21 patients with PSM (42.9%) experienced recurrence, and 4 patients (19.1%) developed metastases. They interpreted these findings as indicating a strong association between PSM and recurrence (3). In our study, only 1 recurrence occurred in the PSM group. Due to the limited number of patients, statistically strong results were not obtained.

Shah et al. (13) demonstrated that PSM is an independent risk factor for recurrence. Their subgroup analysis revealed that PSM was a risk factor for recurrence in pathologically high-risk tumors (pT2-3a or Fuhrman grade III-IV) but not in low-risk tumors (pT1 or Fuhrman grade I-II) (13). Similarly, Marchiñena et al. (14) found that PSM and high-grade tumors (Fuhrman grade III-IV) are independent predictors of local recurrence. It is known that tumors with a high Fuhrman grade are more aggressive and are thought to have a higher risk of recurrence. However, due to the limited number of patients in our study cohort, we were unable to evaluate the correlation between Fuhrman grade and recurrence.

In a study by Carvalho et al. (15), it was concluded that high-risk tumors and limited surgical experience are risk factors for PSM. Although they could not demonstrate a negative impact of PSM on survival, they observed a trend toward increased local recurrence and metastasis.

In a matched pair analysis study by Bensalah et al. (9), which included 101 patients with PSM and 102 patients with NSM, they found that PSM had no impact on 5-year recurrence-free survival (RFS), 5-year cancer-specific survival (CSS), or 5-year overall survival (OS). Rothberg et al. (16) reported that, during an average follow-up of 18.8 months, the oncological outcomes were not worse in patients with PSM than in those with NSM.

Morrone et al. (17) evaluated patients undergoing RAPN and found no statistical relationship between PSM and RFS or OS. However, multivariate analysis showed that higher RENAL scores were associated with NSM. They proposed that this paradoxical finding might be due to the difficulty in detecting small masses in the renal parenchyma or increased surgeon confidence in easier cases (17). In our study, the longer ischemia time and increased intraoperative blood loss in the PSM group could be attributed to the difficulties encountered during tumor resection, which could prevent the achievement of NSM.

In a matched pair analysis study by Radfar et al. (18), with an average follow-up period of 24 months, they found that tumor recurrence occurred more frequently in the PSM group. However, the authors also noted that this did not affect OS compared with the NSM group (18).

Yoo et al. (19) found that 10 year RFS was significantly higher in patients with ccRCC than in those with pRCC. They attributed this finding to the greater prevalence of recurrence in the pRCC group compared with the ccRCC group at least 5 years after surgery (19). In our study, the average follow-up period was only 20 months, and all patients with PSM had ccRCC. Therefore, we were unable to evaluate tumor recurrence and its relationship with histological type beyond the 5-year postoperative period.

Study Limitations

First, as this was a retrospective study, there was a possibility of selection bias and information inaccuracies. Second, the small number of patients and short follow-up durations may have limited our ability to obtain objective results. Additionally, because our data represent results from a single center, they may not be generalizable. Additionally, because our data reflected the experience of multiple surgeons, varying levels of surgical expertise might have influenced our results. The use of different ischemia techniques (warm vs. cold) might have affected the results. Importantly, key parameters, such as CSS, RFS, and OS, were not evaluated in relation to PSM. An analysis of survival might have provided more in-depth insights into the influence of PSM on recurrence. Furthermore, the size of the PSM area was not assessed.

Conclusion

The current study aimed to investigate the impact of PSM and NSM on local relapse and metastasis among patients undergoing PN. Although our results support some findings in the literature, the limited number of patients prevented us from reaching definitive conclusions in some statistical assessments. We hypothesized that the high incidence of surgical margins in patients with prolonged ischemia time and increased intraoperative blood loss may be due to difficulties encountered during tumor resection.

In conclusion, the effect of PSM on local relapse and metastasis remains controversial. However, our study revealed higher recurrence rates in the PSM group. It should be noted that PSM poses a higher risk in high-grade tumors, and careful monitoring of this patient group is necessary. When supported by larger patient cohorts and long-term follow-up studies, our findings provide clearer insights into the impact of surgical margins on oncological outcomes.

Footnote

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Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.C.B., B.E., M.K., N.K., Ç.C., U.A., S.Ç., S.S., Concept: E.C.B., B.E., S.Ç., S.S., Design: E.C.B., M.K., Ç.C., U.A., S.Ç., Data Collection or Processing: B.E., M.K., N.K., Ç.C., U.A., Analysis or Interpretation: E.C.B., B.E., Ç.C., U.A., Literature Search: M.K., N.K., Ç.C., U.A., S.Ç., S.S., Writing: E.C.B., B.E., S.Ç., S.S.

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