



## Does Margin Length Predict Recurrence After Partial Nephrectomy, or Is Presence Alone Sufficient?

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### Abstract

To evaluate whether the length of positive surgical margin carries a risk for recurrence, data of patients that underwent partial nephrectomy (PN) from six centers were evaluated. Fifty-three patients with positive surgical margins (PSMs) (the PSM group) and 438 patients with negative surgical margin (the NSM group) were included in the present study. Pathologic reevaluations were performed, and surgical margins were measured in micrometers. The number of positive margin areas, and the length of the maximum and total positive margins were evaluated. Data were analyzed using SPSS 27 package program. A p-value less than 0.001 was considered statistically significant. Local recurrence occurred in 16.98% of patients in the PSM group and 4.24% of patients in the NSM group. ( $p < 0.001$ ). Patients with PSM were at fourfold increased risk for recurrence. Age, gender, tumor location, tumor side and size, and fuhrman grade were not associated with local recurrence of the tumor ( $p > 0.01$ ). However, positive surgical margin was an important risk factor for local recurrence ( $p < 0.01$ ). No relationship was found between positive margin length and local recurrence ( $p = 0.044$ ). Logistic regression analysis did not identify any parameters associated with local recurrence. The presence of a PSM was significantly associated with an increased risk of local recurrence following PN. The number of positive margin foci and total or maximum length of margin involvement were not associated with recurrence. These findings suggest that it is the presence of PSM, rather than its extent, that may be the primary factor influencing oncological risk.

**Keywords:** Length of margin, Partial nephrectomy, Recurrence

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## Introduction

Partial nephrectomy (PN) is the preferred treatment option for localized renal tumors, particularly T1 lesions, due to its oncological efficacy and renal function preservation. A key component of postoperative evaluation is the assessment of surgical margins. Although a positive surgical margin (PSM) does not always indicate residual tumor or necessitate additional surgical intervention, its presence has been associated with increased risk of local recurrence in some studies (1).

PSMs occur in approximately 2–8% of patients undergoing PN for T1 renal masses (2). Recurrence rates are significantly higher in patients with PSMs, reaching up to 16%, compared to 3% in those with negative surgical margins (3). Despite this known association, there remains limited understanding of whether specific characteristics of PSMs, such as the number of involved foci or the linear extent of margin positivity influence recurrence risk.

To address this gap, the present multicenter retrospective study investigates the association between PSMs and local recurrence after PN, with a particular focus on whether the length of the positive margin serves as a predictive factor. By evaluating quantitative pathological features of margin involvement, we aim to provide further clarity on the prognostic implications of PSMs and inform both surgical decision-making and postoperative surveillance strategies.

## Methods

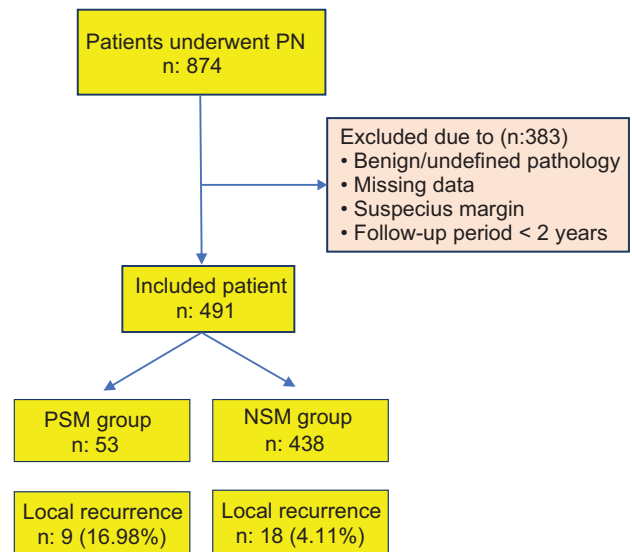
### Study design

After obtaining Institutional Ethics Committee approval from Necmettin Erbakan University (ethic number: 2023/4104), a retrospective data analysis was performed by the authors from 6 tertiary hospitals in different regions of Türkiye. Data of 874 patients that underwent PN from 6 centers were evaluated. Patients with benign or undefined pathology, suspicious surgical margins, or incomplete data, as well as those with a follow-up period of less than 2 years, were excluded from the study. Finally, 53 patients with PSMs (the PSM group) and 438 patients with NSM (the NSM group) were included to the present study (Figure 1).

Age, gender, size, side and location of tumor, pathologic subtype, and Fuhrman grade were evaluated. In addition, pathologic reevaluation for all patients were performed, and surgical margins were measured in micrometers by the pathologists. The number of positive margin areas, and the length of the maximum and total positive margins were evaluated. The effect of the length of surgical margin on local recurrence was evaluated in the present study.

### Pathologic evaluation

PN specimens were fixed in 10% buffered formaldehyde solution. Following fixation, the entire specimen was stained



**Figure 1:** Study flow chart. PSM: Positive surgical margin; NSM: Negative surgical margin.

with surgical margin dye, and its dimensions and weight were recorded. The specimen was then serially sectioned for macroscopic examination, including assessment of tumor size and gross characteristics. Tissue samples were obtained to include the entire parenchymal surgical margin.

Given the multicenter nature of the study, each participating laboratory processed the samples using their standard protocols and available equipment. After routine tissue processing, paraffin blocks were prepared. Sections with a thickness of 5 micrometers were cut from the paraffin blocks using a microtome and stained with hematoxylin and eosin (H&E) for histopathological evaluation. Microscopic examination was performed using a light microscope, and the length of tumor-positive foci at the surgical margin was measured in micrometers.

For this study, the margin status and measurements were reevaluated by dedicated genitourinary pathologists at each institution. Although a centralized pathology review was not feasible due to the retrospective, multicenter design, participating pathologists adhered to widely accepted histopathological processing principles, including inking of margins and microscopic measurement in micrometers, to enhance consistency across centers.

### Statistical analysis

Data were analyzed using the SPSS 27 package program. The Kolmogorov–Smirnov test first checked the normal distribution of data, and in descriptive statistics, mean  $\pm$  standard

deviation and median (minimum–maximum) were used to express data with and without normal distribution, respectively. Student's *t*-test was used for normally distributed parameters, and Mann–Whitney U test was used for nonnormally distributed parameters to compare numeric variables. Pearson's chi-square test or Fisher's exact test was used to compare the observed frequencies with the expected frequencies. A *p*-value less than 0.01 was considered statistically significant. Given the relatively small number of recurrence events and multiple comparisons among clinicopathological variables, a more conservative threshold for statistical significance was prespecified as  $\alpha = 0.01$  in order to reduce the risk of type I error.

## Results

Of the 874 patients in the entire cohort who underwent PN, the overall PSM rate was 6.08% (53 out of 874). Following application of the predefined exclusion criteria, including benign or indeterminate histology, suspicious margins, missing variables, and inadequate follow-up, 491 patients were eligible for analysis. Consequently, the proportion of PSMs within the analyzed cohort increased to 10.79% (53 out of 491). The local recurrence rate following PN was 5.49% ( $n=27$ ), with a median recurrence time of 48 months (IQR=35). The mean follow-up duration was  $53.87 \pm 36.44$  months for the PSM group and  $53.59 \pm 23.88$  months for the NSM group ( $p=0.157$ ). The male-to-female ratios were 1.4 and 1.9 in the PSM and NSM groups, respectively ( $p=0.353$ ). The mean ages were  $62.43 \pm 12.40$  years for the PSM group and  $59.16 \pm 12.32$  years for the NSM group ( $p=0.064$ ). The mean tumor sizes were  $3.34 \pm 1.44$  cm for the PSM group and  $3.69 \pm 1.78$  cm for the NSM group ( $p=0.165$ ) (Table 1).

Pathological high-grade tumors (Fuhrman grade III or IV) were identified in 20.7% of the PSM group and 14.15% of the NSM group. Although the incidence of high-grade tumors was higher in the PSM group, it was not statistically significant ( $p=0.302$ ). Local recurrence occurred in 16.98% of patients in the PSM group compared to 4.11% in the NSM group ( $p<0.001$ ). Patients with PSM had a fourfold increased risk of recurrence according to the odds ratio from logistic regression analysis.

Positive margins were detected in a single area in 31 (58.5%) patients and in multiple areas in 22 (41.5%) patients. The median total length of the surgical margin in the PSM group was 4340 micrometers (IQR=9697). Among the PSM group, the median total length of the surgical margin was 1700 micrometers (IQR=6400) in patients with local recurrence ( $n=9$ ) and 5237.5 micrometers (IQR=10738) in patients without local recurrence ( $n=44$ ) ( $p=0.044$ ). However, this value did not reach the predefined level of statistical significance ( $\alpha = 0.01$ ) and was therefore interpreted as a nonsignificant trend (Table 2). Moreover, no consistent gradient

suggesting increasing recurrence risk with increasing margin length was observed.

Our results indicate that age, gender, tumor location, tumor side, size, and Fuhrman grade were not associated with local recurrence of the tumor ( $p>0.01$ ). However, positive surgical margins were found to be an important risk factor for local recurrence ( $p<0.001$ ) (Table 1). The number of positive margin areas and the length of the maximum and total positive margins were not associated with local recurrence. According to our data, no relationship was found between positive margin length and local recurrence ( $p=0.044$ ,  $\alpha=0.01$ ). Furthermore, logistic regression analysis did not identify any parameters associated with local recurrence.

## Discussion

PN has become a standard treatment modality especially for T1 renal tumors due to better preservation of renal function and decreasing the risk for cardiovascular disorders (4, 5). The main concern of the nephron sparing surgery is the inability to achieve NSMs. Local recurrence may not only be attributable to local spread of the tumor by microvascular embolization, or true multifocality, but also to incomplete resection of the primary tumour (6). It is well known that positive surgical margin is associated with increased risk for recurrence. The risk of local recurrence increases from 3% to 16% in patients with PSMs (3). However, the more nuanced question, "which specific characteristics of positive surgical margins contribute most to recurrence?" remains largely unanswered in the existing literature. Thus, the present study aimed to explore this further by examining the length and number of positive surgical margins and their impact on local recurrence.

The majority of recurrences tend to happen within the first 2 years following surgery. It has been demonstrated that local recurrences were mostly detected within the first 2–5 years following surgery (7). Therefore, we included patients with at least 2 years of follow-up reports in the present study.

In the light of our data, PSMs are the most important risk factors for local recurrence. However, a relationship was not found between the length of positive margin and local recurrences. Therefore, the absence of a robust and biologically plausible dose–response relationship further supports the interpretation that margin length alone should not be used as a determinant of recurrence risk. On the other hand, Fuhrman grade and tumor size were not statistically associated with local recurrence.

Anatomic complexity may affect the outcomes of PN. However, studies mostly did not evaluate whether a nephrometry-score (PADUA or RENAL) was associated with local recurrence. Matos et al. revealed that RENAL score was not related to PSM, which is similar to our data (8).

**Table 1:** Baseline patient, disease, and operation characteristics.

		PSM group N=53	NSM group N=438	p
Age at Surgery – Mean ± SD		62.43±12.40	59.16±12.32	0.064 <sup>a</sup>
Gender	Female	22 (12.9%)	149 (87.1%)	0.353 <sup>b</sup>
	Male	31 (9.7%)	289 (90.3%)	
Tumor Size (cm)		3.34±1.44	3.69±1.78	0.165 <sup>a</sup>
Fuhrman Grade		2.00±0.83	1.90±0.68	
Fuhrman – Noninformed		9 (13%)	60 (87%)	0.302 <sup>b</sup>
Fuhrman – 1 or 2		316 (90.5%)	33 (9.5%)	
Fuhrman – 3 or 4		62 (84.99%)	11 (15.1%)	
Histological Type – Clear cell		23 (11.10%)	185 (88.90%)	0.989 <sup>b</sup>
Histological Type – Other		30 (10.6%)	253 (89.4%)	
Follow Up (Month)		51.60±36.44	-	-
Local Recurrence (+)		9 (39.1%)	14 (60.9%)	0.000 <sup>b</sup>
Local Recurrence (-)		44 (9.6%)	413 (90.4%)	
Polar Localization – Upper		19 (15.6%)	103 (84.4%)	0.137 <sup>b</sup>
Polar Localization – Middle		16 (9.9%)	146 (90.1%)	
Polar Localization – Lower		18 (8.7%)	189 (91.3%)	
Tumor Side – Left		26 (10.8%)	215 (89.2%)	0.997 <sup>b</sup>
Tumor Side – Right		27 (10.8%)	223 (89.2%)	
Renal Score		5.15±1.89	5.50±1.56	0.060 <sup>a</sup>
Resection Technique – Enucleation		17 (15.9%)	90 (84.1%)	0.161 <sup>b</sup>
Resection Technique – Enucleoresection		1 (9.1%)	10 (90.9%)	
Resection Technique – Standard Resection		35 (9.4%)	337 (90.6%)	
EBL-mL		59.25±110.412	91.38±144.82	0.093 <sup>a</sup>
Operation Technique – Open		28 (11.7%)	212 (88.3%)	0.064 <sup>b</sup>
Operation Technique – Laparoscopic		17 (15.00%)	96 (85.00%)	
Operation Technique – Robotic		8 (5.9%)	127 (94.1%)	

<sup>a</sup>Mann–Whitney U test; <sup>b</sup>Chi square test.

PSM: Positive surgical margin; NSM: Negative surgical margin; EBL: Estimated blood loss.

**Table 2:** Association between surgical margin and local recurrence in patients with positive surgical margins.

	Local recurrence (+)		Local recurrence (-)		p-value	Mann–Whitney U statistics
	Median	IQR	Median	IQR		
Number of involved foci	1	2	1	1	0,917	193
Total length of the positive margin	1700	6400	5237,5	10738	0,044	113
Maximum length of the positive margin	950	5150	4575,5	9038	0,017	98

Effect of surgical techniques such as enucleation, enucleoresection, or resection have also been investigated as to whether they have any impact on surgical margins. The only prospective data published by Minervini et al. showed that resection technique significantly impacts PSM rates (9). However, in recent meta-analysis, it has been revealed that, similar to our study, surgical technique (simple enucleation versus standard PN) has no impact on surgical margin and local recurrence (10, 11).

It is well established that tumor size and histologic Fuhrman grade are important prognostic factors for kidney cancers (12). European Association of Urology RCC Guidelines suggest using the Leibovich model for clear cell RCC to evaluate risk for recurrence and to propose a follow-up schedule (13, 14). Fuhrman grade and tumor size are both important risk factors for recurrence after PN, as suggested in Leibovich model (14, 15). However, it was also revealed in the literature that they were not related to PSMs and local recurrence as it is in the present study (16). It was also investigated in the literature that the pathologic upstaging to T3a after PN is another important risk factor for local recurrence (17, 18). However, due to the low number of patients with pT3a tumor in our series, we could not evaluate the effect of upstaging to T3a on local recurrence.

Interestingly, univariable analysis revealed a trend toward shorter margin lengths in patients who experienced recurrence. However, this observation should be interpreted with extreme caution. Firstly, the study included a limited number of recurrence events, increasing the susceptibility to random variation. Secondly, the tumor's biological behavior and mere violation of tumor boundaries may be more important than the measured linear extent of involvement. For these reasons, and in accordance with our prespecified conservative significance threshold ( $\alpha = 0.01$ ), we did not interpret  $p = 0.044$  as evidence of a true association.

Although the pathologic reevaluation was performed according to the same standards in all centers, the retrospective nature of the study could be considered as a limitation of this study. Despite this shortcoming, this is a unique article investigating the relationship between tumor length in the positive margin and local recurrence. We believe that the present study may contribute to the improvement of the writing guidelines of pathology reports especially by supporting with further postoperative studies with larger series.

## Conclusion

In this multicenter study, the presence of a PSM was significantly associated with an increased risk of local recurrence following PN. However, the number of positive margin foci, as well as the total or maximum length of margin involvement, did not show a statistically significant association with recurrence in the multivariable analysis. These findings

suggest that it is the presence of PSM, rather than its extent, that may be the primary factor influencing oncological risk. Further prospective studies with larger cohorts are needed to determine whether the characteristics of margins should impact postoperative surveillance or treatment strategies.

## Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that AI-assisted tools (ChatGPT or Gemini) were used only for minor language editing during the revision process. No AI tools were used in the drafting of the manuscript. All references have been manually verified for accuracy and relevance.

## Author Contributions

All authors contributed equally to this article.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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