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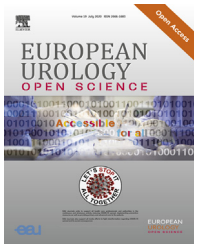

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Kidney Cancer

# Impact of Positive Surgical Margins After Partial Nephrectomy

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**Abstract**

***Background:*** The impact of positive surgical margins (PSMs) after partial nephrectomy (PN) is controversial.

***Objective:*** To evaluate the risk factors for a PSM and its impact on overall survival.

***Design, setting, and participants:*** This is a retrospective study of 388 patients were submitted to PN between November 2005 and December 2016 in a single centre. Two groups were created: PSM and negative surgical margin (NSM) after PN. A $p$ value of $<0.05$ was considered significant.

***Outcome measurements and statistical analysis:*** Relationships with outcome were assessed using univariable and multivariable tests and log-rank analysis.

***Results and limitations:*** The PSM rate was 3.8% ($N = 16$). The mean age at the time of surgery (PSM group: $64.1 \pm 11.3$ vs NSM group: $61.8 \pm 12.8$ yr, $p = 0.5$) and the mean radiological tumour size ($4.0 \pm 1.5$ vs $3.4 \pm 1.8$ cm, $p = 0.2$) were similar. Lesion location ($p = 0.3$), surgical approach ($p = 0.4$), warm ischaemia time ($p = 0.9$), and surgery time ($p = 0.06$) had no association with PSM. However, higher surgeon experience was associated with a lower PSM incidence (2.6% if $\geq$30 PNs vs 9.6% if $<$30 PNs; $p = 0.02$). Higher operative blood loss ($p = 0.02$), higher-risk tumours ($p = 0.03$), and larger pathological size ($p = 0.05$) were associated with an increase in PSM. In the PSM group, recurrence rate (18.7% vs 4.2%, $p = 0.007$) and secondary total nephrectomy rate (25% vs 4.4%, $p < 0.001$) were higher. However, overall survival was similar. Multivariate analysis revealed that high-risk tumour ($p = 0.05$) and low experience ($p = 0.03$) could predict a PSM. Limitations include retrospective design and reduced follow-up time.

***Conclusions:*** PSMs were mainly associated with high-risk pathological tumour ($p = 0.05$) and low-volume surgeon experience. Recurrence rate and need for total nephrectomy were higher in that group, but no impact on survival was noticed.

***Patient summary:*** The impact of positive surgical margins (PSMs) after partial nephrectomy is a matter of debate. In this study, we found that PSMs were mainly associated with aggressive disease and low surgeon experience.



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## 1. Introduction

Renal cell cancer (RCC) represents 2–3% of all cancers, and its incidence increased by 2% over the past 2 decades, due to improved detection of tumours by cross-sectional imaging. These tumours are usually smaller and of lower stage [1,2]. International guidelines support the use of partial nephrectomy (PN) as the preferred treatment for clinical T1 disease, even if >4 cm, whenever possible [3]. Multiple retrospective series have demonstrated comparable cancer-specific survival (CSS) for PN versus radical nephrectomy (RN), with better preserved kidney function, lowering the risk of development of cardiovascular diseases [4–11] and eventually leading to lower cardiovascular mortality.

One pitfall of nephron-sparing approaches is the possibility of positive surgical margins (PSMs). They occur in 2–8% of PNs [12] and theoretically correspond to residual tumour left in the kidney bed. However, its potentially negative impact is still unclear [13–15]. Some retrospective studies reported that PSMs do not translate into a higher tendency towards the development of metastases or decreased CSS [16,17].

The objective of our work was to evaluate the risk factors for PSMs after PN and for their impact on overall survival.

## 2. Patients and methods

This study was conducted in compliance with the Declaration of Helsinki. A retrospective analysis of the files of 388 patients who underwent 424 PN surgeries at our institution between November 2005 and December 2016 was performed. Written informed consent was obtained from patients. PNs were performed by 16 urologists, all with at least 3 yr of staff experience, either by laparoscopy ($n = 375$) or by open approach ($n = 49$).

PSMs were defined as cancer presented at the inked parenchymal margin of the surgical specimen. Patient, tumour, surgeon, operative, and pathological variables were compared based on surgical margin status. Two groups were created: PSM and negative surgical margin (NSM) after PN.

Patient characteristics included age at PN, gender, initial symptoms (if any), and preoperative serum creatinine values.

Tumour characteristics included the number of tumours, imagiological tumour size, solitary kidney, bilateral tumours, tumour side, location, endophytic properties, and renal sinus invasion.

Operative characteristics included surgery indication, surgical approach, surgery duration, warm ischaemia time, estimated blood loss, intraoperative complications, type of haemostatic agents used intraoperatively, and length of hospital stay. The total individual surgeon volume was categorised as high (≥30 PNs) or low (<30 PNs).

Pathological characteristics included histology, pathological T stage, and diameter. A pathological high-risk tumour was defined as one of stage pT2–3 and/or Fuhrman grades III–IV.

Follow-up variables included postoperative serum creatinine values, complete remission, local relapse, metastisation, need for radical ipsilateral nephrectomy, and overall survival.

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) 23.0 (IBM SPSS Statistics Corp., Armonk, NY, USA), and statistical significance was considered at $p < 0.05$. Pearson chi-square test for categorical variables, independent sample $t$ test for continuous variables, logistic regressions, and Kaplan-Meier survival curves with log-rank test were used to verify associations considering the two groups created above.

## 3. Results

The PSM rate was 3.8% ($N = 16$). The mean age at surgery (PSM group: 64.1 ± 11.3 vs NSM group: 61.8 ± 12.8 yr, $p = 0.5$) was not different between groups. A male prevalence was seen in both groups (68.8% vs 63.5%, $p = 0.7$). Patients were mostly asymptomatic (93.8% [$n = 15$] vs 85.8% [$n = 350$], $p = 0.8$). Serum creatinine values were similar before surgery (PSM group: 1.0 ± 0.5 mg/dl vs NSM group: 0.9 ± 0.3 mg/dl, $p = 0.3$).

Tumour characteristics are shown in Table 1. There was a nonstatistical trend for the increased risk of PSMs in bigger tumours on imagiological evaluation ($p = 0.2$).

Concerning surgery, the laparoscopic approach (Table 2) was the mainstay treatment. Lower surgeon experience was associated with an increased rate of PSMs: PSM rates were 9.6% ($n = 5$) and 2.6% ($n = 11$) in low- and high-volume surgeons, respectively ($x^2$ [1] = 5.57, $p = 0.018$).

Operative details (Table 3) revealed an association between surgeries with intraoperative blood loss ≥100 ml and PSM ($p = 0.02$) and a trend towards PSM in longer surgeries ($p = 0.06$). The most used haemostatic materials in the PSM group were *Surgicel* and the combination between *Surgicel* and *Floseal*, while in the NSM group it was just *Surgicel* ($p = 0.07$).

Pathological findings (Table 4) revealed clear cell RCC predominance in both groups. There were no PSMs in cases of benign lesions ($x^2$ [1] = 5.83, $p = 0.02$).

The global analysis revealed that most lesions in the PSM group were pT1b (50%, $n = 8$), whereas pT1a (68.9%, $n = 281$) was the most common finding in the NSM group. Considering only pT1, PSMs were mostly found in pT1b (pT1a [2.4%, $n = 6$] vs pT1b [8.3%, $n = 8$], $x^2$ [1] = 6.07, $p = 0.01$).

High-risk tumours (pT2 or pT3, or Fuhrman grades III or IV) were mostly seen in the PSM group ($x^2$ [1] = 4.7, $p = 0.03$), with a bigger pathological size ($p = 0.05$).

Postoperative serum creatinine did not differ between groups (PSM: 1.4 ± 0.9 vs NSM: 1.1 ± 0.6 mg/dl, $p = 0.1$).

Concerning follow-up (Table 5), the overall recurrence rate was higher ($x^2$ [1] = 7.3, $p = 0.007$), local relapse was higher ($x^2$ [1] = 5.7, $p = 0.02$), as well as metastasis development ($x^2$ [1] = 11.3, $p = 0.001$) and need for total ipsilateral nephrectomy ($x^2$ [1] = 13.3, $p < 0.001$), in the PSM group. However, overall survival was not different between groups ($x^2$ [1] = 0.894, $p = 0.3$; Fig. 1).

Concerning data from the PSM group, secondary total nephrectomy was performed in the following four cases:

- Focal surgical margin (R1) was found after an open PN for an endophytic tumour (pT1bNxM0 clear cell). Surveillance had been adopted, but after 9 mo, local relapse and lung metastisation developed. Ipsilateral RN was undertaken and histology revealed pT3aN0 clear-cell carcinoma.
- Focal surgical margin (R1) in one of five tumours was excised from a solitary kidney (pT1bN1M0). Hilar lymphadenectomy revealed three out of three positive

**Table 1 – Differences in tumour characteristics between groups**

| Variables | PSM group (*n* = 16) | NSM group (*n* = 408) | *p* value |
|---|---|---|---|
| Number of tumours, *n* (%) | | | <0.001 |
| 1 | 15 (93.8) | 388 (95.1) | |
| ≥2 | 1 (6.3) | 20 (4.9) | |
| Imagiological tumour size, cm (IQR) | 4.0 ± 1.5 (0.8–6.3) | 3.4 ± 1.8 (0.8–14.7) | 0.2 |
| Solitary kidney, *n* (%) | 2 (12.5) | 20 (4.9) | 0.2 |
| Bilateral tumours, *n* (%) | 0 (0) | 24 (5.9) | 0.4 |
| Tumour location, *n* (%) | | | |
| Superior pole | 2 (12.5) | 130 (31.9) | 0.3 |
| Inferior pole | 7 (43.8) | 137 (33.6) | |
| Mesorenal area | 7 (43.8) | 141 (34.6) | |
| Renal sinus invasion, *n* (%) | 5 (31.3) | 66 (16.2) | 0.2 |
| Endophytic, *n* (%) | 5 (35.7) | 64 (18.8) | 0.1 |
| Tumour side, *n* (%) | | | |
| Right | 8 (50) | 207 (50.7) | 0.9 |
| Left | 8 (50) | 201 (49.3) | |

IQR = Interquartile range; NSM = negative surgical margin; PSM = positive surgical margin.

**Table 2 – Surgery characteristics between groups**

| Variables | PSM group (*n* = 16) | NSM group (*n* = 408) | *p* value |
|---|---|---|---|
| Surgery indication, *n* (%) | | | 0.9 |
| Elective | 14 (87.5) | 357 (87.5) | |
| Absolute | 2 (12.5) | 51 (12.5) | |
| Surgical approach, *n* (%) | | | 0.4 |
| Open | 3 (18.8) | 46 (11.3) | |
| Laparoscopic | 10 (62.5) | 316 (77.5) | |
| Conversion | 3 (18.8) | 46 (11.3) | |
| Laparoscopic approach, *n* (%) | | | 0.6 |
| Transperitoneal | 10 (100) | 304 (96.5) | |
| Retroperitoneoscopic | 0 (0) | 12 (3.5) | |
| Laparoscopic approach, *n* (%) | | | 0.9 |
| LESS | 0 (0) | 7 (2.2) | |
| 3 ports | 9 (90) | 280 (88.1) | |
| 4 ports | 1 (10) | 29 (9.7) | |

LESS = laparoendoscopic single site; NSM = negative surgical margin; PSM = positive surgical margin.

**Table 3 – Operative issues between groups**

| Operative issues | PSM group (*n* = 16) | NSM group (*n* = 408) | *p* value |
|---|---|---|---|
| Surgery time (min), mean ± SD | 140.3 ± 56.5 | 119.2 ± 43.5 | 0.06 |
| Mean warm ischaemia time (min), mean ± SD (IQR) | 13.8 ± 8.6 (0–26) | 13.5 ± 9.8 (0–35) | 0.9 |
| Off-clamp technique, *n* (%) | 3 (18.8) | 103 (25.2) | 0.6 |
| Warm ischaemia time (min), *n* (%) | | | 0.8 |
| ≤10 | 2 (15.4) | 41 (10.1) | |
| >10–≤20 | 10 (61.5) | 232 (56.9) | |
| >20–≤30 | 4 (23.1) | 124 (30.3) | |
| >30 | 0 (0) | 11 (2.7) | |
| Intraoperative blood loss (ml), *n* (%) | | | 0.02 |
| <100 | 6 (37.5) | 267 (65.4) | |
| 100–500 | 6 (37.5) | 110 (27.0) | |
| >500 | 4 (25.0) | 31 (7.6) | |
| Intraoperative complications, *n* (%) | 1 (6.3) | 24 (5.9) | 0.9 |
| Other surgeries done at the same time, *n* (%) | 0 (0) | 12 (2.9) | 0.5 |
| Intraoperative haemostatic materials used, *n* (%) | | | 0.07 |
| Not used/not specified | 1 (6.3) | 92 (22.5) | |
| Floseal | 3 (18.8) | 36 (8.8) | |
| Surgicel | 4 (25) | 141 (34.6) | |
| Hemopatch | 0 (0) | 21 (5.1) | |
| Tachosyl | 2 (12.5) | 16 (3.9) | |
| Surgicel + Floseal | 4 (25) | 90 (22.1) | |
| Surgicel + Tachosyl | 2 (12.5) | 12 (2.9) | |
| Length of hospital stay (d) | 5.1 ± 1.9 | 5.6 ± 1.9 | 0.8 |

IQR = interquartile range; NSM = negative surgical margins; PSM = positive surgical margin; SD = standard deviation.

**Table 4 – Pathological findings between groups**

| Pathological findings | PSM group ($n$ = 16) | NSM group ($n$ = 408) | $p$ value |
|---|---|---|---|
| Histology, $n$ (%) | | | 0.3 |
| Clear cell RCC | 7 (43.8) | 162 (39.7) | |
| Chromophobe RCC | 6 (37.5) | 63 (15.4) | |
| Papillary RCC | 3 (18.8) | 65 (15.9) | |
| Angiomyolipoma | 0 (0) | 41 (10) | |
| Oncocytoma | 0 (0) | 35 (8.7) | |
| Others | 0 (0) | 42 (10.3) | |
| Malignancy, $n$ (%) | | | 0.02 |
| Malign | 16 (100) | 298 (73.0) | |
| Benign | 0 (0) | 110 (27.0) | |
| Pathological T stage, $n$ (%) | | | 0.06 |
| T1a | 6 (37.5) | 281 (68.9) | |
| T1b | 8 (50) | 104 (25.4) | |
| T2a | 0 (0) | 7 (1.7) | |
| T3a | 2 (12.5) | 15 (3.7) | |
| T3b | 0 (0) | 1 (0.3) | |
| Pathological risk disease, $n$ (%) | | | 0.03 |
| Low risk (pT1 and Fuhrman grade I–II) | 10 (62.5) | 341 (83.6) | |
| High risk (pT2-pT3 or Fuhrman grades III–IV) | 6 (37.5) | 67 (16.4) | |
| Pathological diameter, cm (IQR) | 4.2 ± 1.7 (0.5–7) | 3.2 ± 1.9 (0.3–16) | 0.05 |

IQR = interquartile range; NSM = negative surgical margins; PSM = positive surgical margin; RCC = renal cell carcinoma.

**Table 5 – Follow-up data between groups**

| Follow-up variables | PSM group ($n$ = 16) | NSM group ($n$ = 408) | $p$ value |
|---|---|---|---|
| Recurrence rate, $n$ (%) | 3 (18.8) | 17 (4.2) | 0.007 |
| Local relapse, $n$ (%) | 2 (12.5) | 10 (2.5) | 0.02 |
| Metastisation, $n$ (%) | 3 (18.8) | 12 (2.9) | 0.001 |
| Need for ipsilateral RN, $n$ (%) | 4 (25) | 18 (4.4) | <0.001 |
| Death, $n$ (%) | 2 (12.5) | 30 (7.4) | 0.4 |
| Overall survival since the first surgery (yr), $n$ (%) | 10.4 ± 0.8 | 11.5 ± 0.2 | 0.344 |

NSM = negative surgical margin; PSM = positive surgical margin; RN = radical nephrectomy.

ganglia metastisation. Surveillance was adopted, but after 1 yr, local relapse and adrenal metastisation developed. RN with ipsilateral adrenalectomy was performed, and histology revealed pT4N0M0 clear cell tumour with adrenal invasion.

- A PSM (R2) was found after a converted PN for an endophytic tumour (pT1bN0M0). During hospital stay, a perirenal abscess with high-output urinary fistula developed. RN was performed, but histology did not reveal residual tumour.
- A PSM (R2) was found in the final pathological report of clear cell with paraganglioma-like areas (pT1bNxM0) despite a negative perioperative frozen section. RN was subsequently performed, but histology did not reveal residual tumour.

On multivariate analysis (Table 6), the only risk factors for PSMs were high-risk tumour ($p$ = 0.05) and low-volume experience of the surgeon ($p$ = 0.03). On the contrary, PSMs were not associated with the risk of recurrence rate, local relapse, metastisation, and need for an ipsilateral RN.

## 4. Discussion

The increasing use of imaging led to an increase in the diagnosis of renal tumours in earlier stages. The role of PN in dealing with renal masses increased, being the gold standard to handle small renal lesions [3]. The ideal PN must result from a balance of a warm ischaemia time of <25 min, NSMs, and no perioperative complications, allowing oncological control and maximising renal preservation [18].

However, despite surgeon efforts, PSMs may occur. Our findings of 3.8% PSMs in PNs are in line with the 2–8% incidence reported in the literature [12]. A PSM is believed to correspond to the tumour left in the remaining kidney. However, this assumption may not be entirely correct, as only one side of the margin is seen by the pathologist. In fact, there is conflicting evidence concerning the significance of PSMs, and protection from recurrence is not ensured by NSMs [13].

On the contrary, it is conceivable that, in cases of minimal PSMs, the remaining tumour may suffer from cautery or ischemia-induced necrosis. Alternatively, false-positive PSMs can be created by rupture of the tumour capsule during or after resection. By contrast, a frozen section during surgery leads to up to 5% of false-negative results. The relatively high false-negative rate, controversy over the prognosis of a positive margin, and inconsistency in influencing intraoperative management are arguments against its routine use [19].

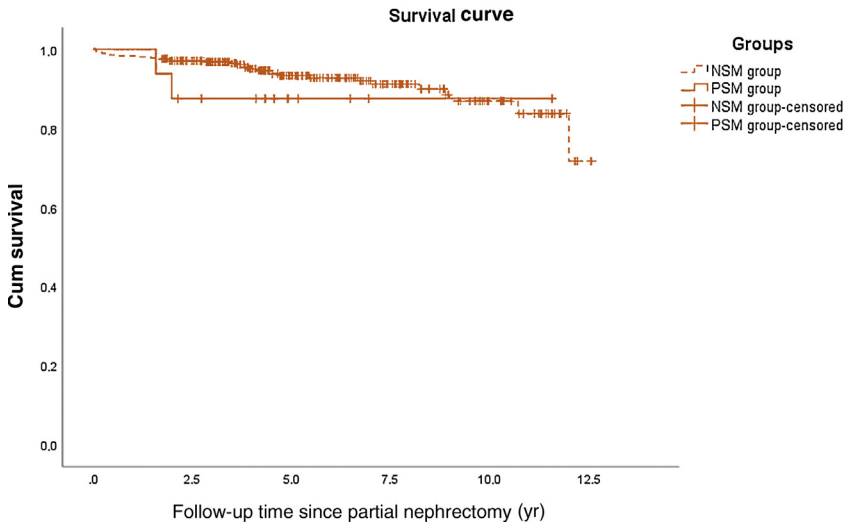


**Figure 1 – Kaplan-Meier survival curve since partial nephrectomy between groups ($x^2$ [1] = 0.894, $p$ = 0.3]. Cum = cumulative; NSM = negative surgical margin; PSM = positive surgical margin.**

**Table 6 – Multivariate analysis of factors possibly related to positive surgical margins**

| Multivariate analysis | OR | 95% CI | *p* value |
|---|---|---|---|
| High risk (pT2-pT3 or Fuhrman grades III–IV) | 3.0 | 1–9.2 | 0.05 |
| Low-volume surgeon (<30 PNs) | 3.5 | 1.2–10.5 | 0.03 |
| Complete remission | 0.09 | 0.001–5.6 | 0.3 |
| Local relapse | 4.0 | 0.2–76.4 | 0.4 |
| Metastases | 8.0 | 0.4–159 | 0.2 |
| Need for ipsilateral RN | 5.7 | 0.7–44.7 | 0.1 |

CI = confidence interval; OR = odds ratio; PN = partial nephrectomy; RN = radical nephrectomy.

Some studies revealed a weak association between PSMs and disease survival or recurrence [16,20–24], while others have shown opposing results [25,26]. Khalifeh et al [26] showed an association between PSMs and higher local recurrence and metastasis rate ($p <$ 0.001). Our analysis supported that association, but with no impact on the overall survival after surgery.

Only a small percentage of patients with PSMs will develop recurrence. For that reason, RN or re-resection of margins can result in overtreatment in many cases [27]. In our series, two out of four patients with PSMs who were submitted to secondary nephrectomy did not harbour residual tumour. All other patients with PSMs who were submitted to a surveillance (imaging) programme did not develop local recurrence.

Univariable associations revealed that PSMs were associated with longer operative time, larger pathological size, and higher blood loss during surgery. However, multivariable analysis showed that the most important factors associated with PSMs were higher pathological risk disease (pT2-pT3 or Fuhrman grades III–IV) and lower surgical volume rate (<30 PNs). Shah et al [28] found the same results: PSM were mostly found in patients with adverse pathological features (pT2-pT3 or Fuhrman grades III–IV). On the contrary, surgical volume has also been a matter of debate. In a population-based study using the Ontario Cancer Registry of 664 PNs performed over a 10-yr period, Ani et al [29] did not detect an association between surgeon volume and surgical margin status. In contrast, Couapel et al [30], in a multi-institutional study of 570 PNs, showed that higher-volume centres had lower PSM rates.

The major limitations of this study are its retrospective, single-centre nature and a short follow-up time. Other limitations are the absence of a standardised tumour nephrometric score and the scarcity of data concerning the technique adopted for resection.

## 5. Conclusions

In our series, PSMs occurred infrequently after PN, being mainly associated with a high-risk pathological lesion and low surgeon volume. No impact on patient survival was noticed, although there seems to be a tendency to a higher overall recurrence and local relapse rates and metastases in the PSM group.

***Author contributions*:** João André Mendes Carvalho had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design*: Carvalho, Tavares-da-Silva.
*Acquisition of data*: Carvalho, Jarimba, Caetano, Sousa, Cipriano.
Analysis and interpretation of data: Carvalho, Tavares-da-Silva.
Drafting of the manuscript: Carvalho, Moreira.
Critical revision of the manuscript for important intellectual content: Carvalho, Nunes, Tavares-da-Silva, Figueiredo.
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