



## Kidney Cancer

# Positive Surgical Margin Appears to Have Negligible Impact on Survival of Renal Cell Carcinomas Treated by Nephron-Sparing Surgery

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## Abstract

**Background:** The occurrence of positive surgical margins (PSMs) after partial nephrectomy (PN) is rare, and little is known about their natural history.

**Objective:** To identify predictive factors of cancer recurrence and related death in patients having a PSM following PN.

**Design, setting, and participants:** Some 111 patients with a PSM were identified from a multicentre retrospective survey and were compared with 664 negative surgical margin (NSM) patients. A second cohort of NSM patients was created by matching NSM to PSM for indication, tumour size, and tumour grade.

**Measurements:** PSM and NSM patients were compared using student *t* tests and chi-square tests on independent samples. A Cox proportional hazards regression model was used to test the independent effects of clinical and pathologic variables on survival.

**Results and limitations:** Mean age at diagnosis was  $61 \pm 12.5$  yr. Mean tumour size was  $3.5 \pm 2$  cm. Imperative indications accounted for 39% (43 of 111) of the cases. Some 18 patients (16%) underwent a second surgery (partial or total nephrectomy). With a mean follow-up of 37 mo, 11 patients (10%) had recurrences and 12 patients (11%) died, including 6 patients (5.4%) who died of cancer progression. Some 91% (10 of 11) of the patients who had recurrences and 83% of the patients (10 of 12) who died belonged to the group with imperative surgical indications. Rates of recurrence-free survival, of cancer-specific survival, and of overall survival were the same among NSM patients and PSM patients. The multivariable Cox model showed that the two variables that could predict recurrence were the indication ( $p = 0.017$ ) and tumour location ( $p = 0.02$ ). No other variable, including PSM status, had any effect on recurrence. None of the studied parameters had any effect on the rate of cancer-specific survival.

**Conclusions:** PSM status occurs more frequently in cases in which surgery is imperative and is associated with an increased risk of recurrence, but PSM status does not appear to influence cancer-specific survival. Additional follow-up is needed.

## 1. Introduction

With the widespread use of modern imaging techniques, a growing number of small renal tumours are being diagnosed and managed by nephron-sparing surgery (NSS). It is now well established that the long-term cancer-specific survival of patients treated by open partial nephrectomy (OPN) is similar to that of patients who underwent radical nephrectomy [1]. Laparoscopic PN (LPN) has recently emerged as an alternative to OPN with equivalent intermediate surgical and oncologic outcomes [2].

Initially, concerns were raised regarding the oncologic safety of NSS due to high rates of local recurrence being reported [3,4]. The surgical technique improved over time, and recurrence rates after partial nephrectomy (PN) are now <5% and are equivalent to those of radical nephrectomy [1,5,6]. The presence of a positive surgical margin (PSM) on the tumour resection has traditionally been considered as a surrogate end point for tumour recurrence; however, PSM incidence has become rare, and little is known about its natural history. Not all PSMs lead to cancer recurrence; therefore, there is no precise consensus regarding the management of the remaining kidney.

The objective of our study was to better appraise the natural course of PSM by comparing PSM and negative surgical margin (NSM) tumours recorded in a large, multi-institutional database. We also aimed to identify predictive factors of recurrence and of death from cancer in PSM patients.

## 2. Methods

This was a retrospective study including data from 26 centres in Europe and North America. After approval by institutional review boards in all centres, records of patients who underwent either OPN or LPN for a localised renal tumour between December 1987 and August 2006 were reviewed. A total of 119 PSM cases were identified; of these, eight patients with nodal invasion and/or distant metastasis were excluded. PSM status was defined as the presence of tumoural tissue on the inked surface of the tumour on final pathologic assessment. The following variables were assessed: age at diagnosis, NSS indication (ie, elective vs imperative; imperative indication refers to patients with solitary kidneys, bilateral renal tumours, or renal insufficiency), presence of symptoms at presentation, Eastern Cooperative Oncology Group (ECOG) performance status, tumour size, TNM stage, Fuhrman grade, histologic subtype, immediate (ie, as soon as pathologic exam confirmed the presence of a PSM) or delayed (ie, as a consequence of a tumour recurrence) secondary surgery, presence of residual tumour on the

pathologic specimen in case of a nephrectomy, local or distant recurrence, and cancer-specific survival. Follow-up was specific to each institution's practice but usually included a physical exam and a computed tomography scan of the abdomen and chest every 6 mo.

PSM data were acquired by direct mailing to the 26 centres included in the study. NSM data were extracted from a multi-institutional database that does not include all 26 centres. Most of the centres that provided data on PSM patients did not supply any information about their NSM patients.

Patients with PSM were first compared with a group of unmatched NSM patients. Then a second matched cohort of NSM patients was created by matching NSM patients to PSM patients for PN indication, tumour size, and Fuhrman grade. Student *t* tests and chi-square tests of independent samples were used respectively to compare means and proportions. Estimates of the cumulative survival distributions were calculated according to the Kaplan-Meier method, and log-rank tests were used to compare the differences between groups. A Cox proportional hazards regression model was used to test the independent effects of clinical and pathologic variables on survival. The following variables were entered into the model: age (continuous), tumour size (continuous), indication (categorical: imperative vs elective), tumour location (categorical: hilar vs peripheral), T stage (categorical), histologic subtype (recoded as categorical: clear cell carcinoma vs other) and Fuhrman grade (recoded as categorical: grade 1–2 vs grade 3–4). Graphical methods suggested that the proportional hazards assumptions were reasonable for all selected variables. A stepwise selection procedure was used to select the final optimal model. All *p* values were 2-sided, and *p* < 0.05 was considered to indicate significance.

### 3. Results

#### 3.1. Description of the positive surgical margin population

Of the 119 patients with PSM on final pathologic assessment, 8 patients with nodal invasion and/or distant metastasis were removed, yielding a total of 111 patients for final analysis. Characteristics of PSM patients are depicted in Table 1. Mean age was 61 ± 12.5 yr. Mean follow-up was 37 mo. Mean tumour size was 3.5 ± 2 cm. The majority of the patients (95 of 111, 86%) were operated through an open incision. The indication was imperative in 43 patients (39%). The majority of the tumours were of low stage (93 of 111, 84% of T1 tumours). The tumour was discovered incidentally in 89 patients (80%), and 87 patients (79%) had a normal performance status (ECOG score: 0).

#### 3.2. Patient management and outcome

The following approaches were used to manage PSM patients: 93 patients (83.8%) were closely followed, 3 patients (2.7%) underwent repeated PN, and 15 patients (13.5%) underwent a radical nephrectomy. The decision for observation versus immediate delayed surgery was made by the surgeon according to his own practice patterns. Among the 18 patients who underwent a second surgery, residual tumour was found in seven cases (39%). With a mean follow-up of 37 mo, 11 patients (10%) had recurrences and 12 patients (11%) died, including 6 patients (5.4%) whose deaths were related to cancer progression. Seven recurrences were local, and four were discovered by distant

**Table 1 – Comparison of positive surgical margin (PSM) patients and unmatched negative surgical margin (NSM) patients**

	PSM (n = 111)	NSM (n = 664)	<i>p</i> value
Age, yr, mean ± SD	61 ± 12.5	59.5 ± 12.6	0.10
Tumour size, cm, mean ± SD	3.5 ± 2	3.4 ± 1.8	0.20
Symptoms at diagnosis, n (%)	22 (19.8)	96 (23.6)	0.40
Indication			0.90
Imperative, n (%)	43 (39)	252 (38)	
Elective, n (%)	68 (61)	412 (62)	
Central location, n (%)	29 (26)	51 (9.1)	<0.0001
Operative technique			–
Laparoscopic, n (%)	16 (14)	NA	
Open, n (%)	95 (86)		
T stage:			0.09
T1, n (%)	93 (83.8)	598 (90)	
T2, n (%)	4 (3.6)	21 (3)	
T3, n (%)	14 (12.6)	45 (7)	
Histology			0.80
Clear cell, n (%)	75 (67.6)	457 (71)	
Papillary, n (%)	29 (26.1)	135 (21)	
Chromophobe, n (%)	7 (6.3)	49 (7.6)	
Fuhrman grade			0.02
1–2	75 (70)	535 (80.6)	
3–4	32 (30)	129 (19.4)	
Length of follow-up, mo	37	35.4	0.70
Recurrence, n (%)	11 (10.1)	14 (2.2)	<0.0001
Death, n (%)	12 (10.8)	58 (8.7)	0.47
Death from cancer, n (%)	6 (5.4)	27 (4.1)	0.45

NA = not applicable.

metastases. Time to recurrence was significantly shorter in patients with a PSM compared with NSM patients (21.4 ± 19 mo vs 24.7 ± 17 mo, *p* = 0.004). Some 91% of the patients who recurred (10 of 11), and 83% (10 of 12) of those who died belonged to the imperative group. Among the 68 patients who had an elective indication, only 1 patient had a recurrence and was further treated by total nephrectomy. None of the patients who had an immediate second surgery had a recurrence. Among the six patients who had salvage surgery for a recurrence, one died of cancer. This patient belonged to the imperative group.

#### 3.3. Comparison of positive and negative margin patients

When comparing PSM patients with a population of unmatched NSM patients (Table 1), we did not find any difference regarding age or tumour size. Patients with PSMs more frequently had a centrally located tumour than patients with NSMs (26% vs 9.1%, *p* < 0.0001). There was a higher frequency of high-grade tumours in the PSM subset than in the NSM subset (30% of grade 3–4 tumours vs 19.4%, *p* = 0.02). With a comparable follow-up, the recurrence rate was more important in the case of a PSM than in the case of an NSM (10.1% vs 2.2%, *p* < 0.0001); however, rates of cancer-specific survival and overall survival were similar (Table 1). To avoid selection bias, we constructed a new cohort of NSM patients matched for surgical indication, tumour size, and Fuhrman grade. At the end of the matching

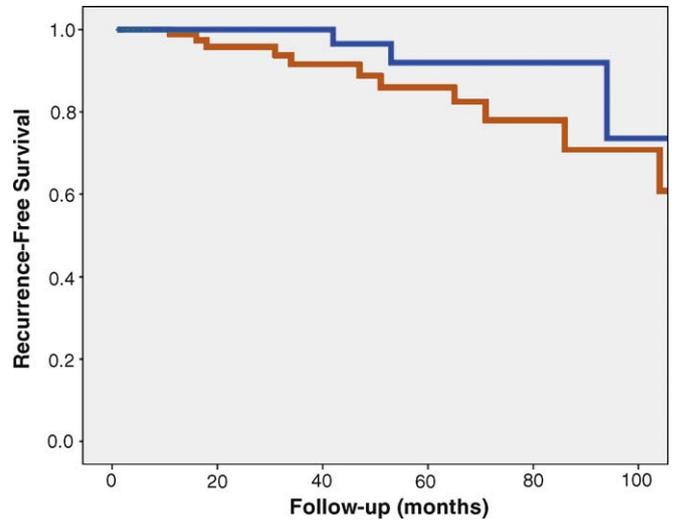
**Table 2 – Comparison of positive surgical margin (PSM) patients and matched negative surgical margin (NSM) patients**

	PSM (n = 101)	NSM (n = 102)	p value
Age, yr, mean ± SD	61.4 ± 12.2	59 ± 13.1	0.10
Tumor size, cm, mean ± SD	3.3 ± 1.6	3.2 ± 1.5	0.60
Symptoms at diagnosis, n (%)	21 (20.8)	14 (23.7)	0.70
Indication			0.99
Imperative, n (%)	40 (39.6)	41 (40)	
Elective, n (%)	61 (60.4)	61 (60)	
Central location, n (%)	26 (26)	4 (4.9)	<0.0001
T stage:			0.50
T1, n (%)	86 (85)	83 (81.4)	
T2, n (%)	2 (2)	1 (1)	
T3, n (%)	13 (13)	18 (17.6)	
Histology:			0.80
Clear cell, n (%)	69 (68.3)	66 (67.3)	
Papillary, n (%)	27 (26.7)	25 (25.5)	
Chromophobe, n (%)	5 (5)	7 (7.1)	
Fuhrman grade:			0.98
1–2, n (%)	74 (73.3)	76 (74.5)	
3–4, n (%)	27 (26.7)	26 (25.5)	
Follow-up, mo	38.5	31	0.11
Recurrence, n (%)	11 (10.9)	3 (2.9)	0.03
Death, n (%)	10 (9.9)	9 (8.8)	0.80
Death of cancer, n (%)	5 (5)	6 (5.9)	0.98

process, we obtained 101 PSM tumours and 102 NSM tumours (Table 2). Due to the matching process, there were no other significant differences regarding age, tumour size, tumour stage, or tumour grade. Mean follow-up was similar in both groups. We still observed a higher rate of tumour recurrence (10.9% for PSM and 2.9% for NSM,  $p = 0.03$ ); however, there was no impact on overall survival or cancer-specific survival.

**3.4. Comparative survival of negative and positive margin patients**

Fig. 1 shows the recurrence-free survival of NSM patients and PSM patients. We did not find any difference between PSM patients and NSM patients (log-rank test,  $p = 0.113$ ) (Table 3). In the subgroups of imperative and elective PN, rates of recurrence-free survival of NSM patients and PSM patients were also similar (log-rank tests,  $p = 0.2$  and  $p = 0.9$ , respectively). Mean follow-up after recurrence was shorter in PSM patients than in NSM patients ( $27 \pm 37$  mo vs  $41 \pm 45$



**Fig. 1 – Recurrence-free survival according to margin status. There is no difference between negative (blue) and positive (orange) margin patients, which is significant (log-rank test,  $p = 0.113$ ).**

mo,  $p = 0.009$ ). Concerning cancer-specific survival, we did not observe any difference according to the margin status (Fig. 2;  $p = 0.42$ ).

The multivariable Cox model showed that the two variables that could predict recurrence were the indication and tumour location (Table 4). None of the other variables included in the model (eg, age, tumour size, T stage, histology, Fuhrman grade, margin status), notably including the presence of a PSM, had any impact on the occurrence of a recurrence. When assessing cancer-specific survival or global survival as the dependent variable, none of the parameters, including the presence of a PSM, were significant predictors of cancer death.

**4. Discussion**

NSS is now considered the standard of care for the treatment of small renal tumours, with long-term oncologic results equivalent to that of radical nephrectomy [1]. Indications once reserved for imperative cases (ie, solitary kidneys, bilateral tumours, or impairment of renal function) have been extended to patients with a normal contralateral kidney. Moreover, there is growing evidence that PN can be safely recommended for larger renal tumours, provided that

**Table 3 – Rates of recurrence-free survival, cancer-specific survival, and overall 5-yr survival in patients with positive surgical margins (PSM) and negative surgical margins (NSM)**

	5-yr recurrence-free survival rate, %	p value	5-yr cancer-specific survival rate, %	p value	Overall survival rate, %	p value
PSM	79	–	88	–	81	–
Matched NSM	92	0.113	91	0.40	88	0.70
Unmatched NSM	95	<0.001	92	0.13	86	0.22

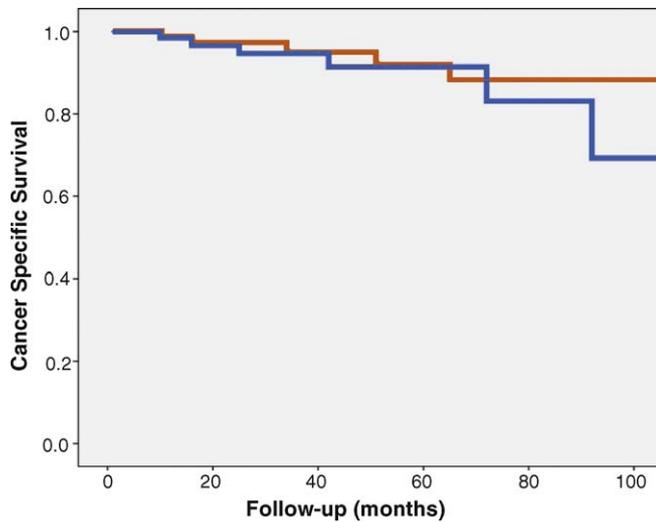


Fig. 2 – Cancer-specific survival curves according to margin status. Survival of negative (blue) and positive (orange) margin patients is similar (log-rank test,  $p = 0.42$ ).

Table 4 – Multivariable Cox proportional hazards regression model for the prediction of recurrence

Variable	<i>p</i> value	Hazard ratio	95% confidence interval
Tumour location (central vs peripheral)	0.02	1.2	1.06–1.8
Indication (imperative vs elective)	0.017	14.3	1.6–21.2

surgical resection is technically feasible [7,8]. A primary goal of NSS is to remove the tumour with an adequate normal parenchyma margin, and there is no doubt that every effort should be made to guarantee an NSM. The long-term prognostic significance of a PSM, however, has not yet been clearly determined [9]. PSM rates vary from 0.8% to 6.9% in contemporary OPN and LPN series [10], while recurrence rates range between 0% and 6% [1,6,11].

Our study suggests that the presence of a PSM has no impact on overall survival and cancer-specific survival of patients treated by NSS for a localised tumour. To our knowledge, this matched series of PSM patients is the largest reported to date. Although the presence of PSM is associated with more recurrences, survival rates of NSM patients and PSM patients are equivalent. Furthermore, in the multivariable model, the margin status is not a significant predictor of recurrence or survival. This finding is in accordance with recent series that have addressed the influence of PSM on oncologic outcome [12,13]. Yossepovitch et al combined the data from two important tertiary centres and reported 77 cases of PSM out of 1344 patients who underwent PN [12]. PSM was not associated with an increased risk of recurrence or metastatic progression in that study. Kwon et al reported a series of 57 PSMs from operations performed between 1989 and 2005 [13]. With a

median follow-up of 22 mo, only 2 PSM patients (4%) had recurrences, compared with 4 of 713 NSM patients (0.5%). Those six recurrences occurred in patients with tumours considered to have a high potential for malignancy. The 5-yr probability of recurrence was significantly higher in patients with a PSM, but there was no difference in terms of long-term risk of metastatic progression. These results and ours show that not all PSMs lead to tumour recurrence and/or cancer progression. A PSM, however, increases the risk of tumour recurrence; therefore, longer follow-up is needed to make sure that the incidence of recurrence and progression remains stable over time. Additionally, we observed a shorter time to recurrence in case of a PSM (21.3 mo vs 27.7 mo,  $p = 0.004$ ). This finding might be an incentive to justify a closer follow-up during the initial years of surveillance in cases of PSMs.

There is no precise consensus regarding the appropriate management of the remaining kidney in case of a PSM. Therapeutic options include active surveillance, repeated PN, or radical nephrectomy. The majority of the patients of our series (93 of 111, 84%) was closely followed. Among the patients who underwent a second surgery, residual tumour was found in only seven cases (39%). This result highlights the fact that residual disease might not be present, even if it is reported on the pathologic exam. The process of renal reconstruction, including coagulation of the tumour bed, suture of the renal parenchyma edges, and use of haemostatic agents, probably leads to ischaemic and immunologic damage of the superficial layer of the tissue abutting the resection bed, thereby destroying potentially remaining tumour cells. Therefore, it is difficult to give a specific recommendation to the physician who has to deal with a PSM. There is a clear need for new techniques or tumour markers that could assist the physician in predicting the course of a disease in order to make a decision based on reliable prognostic variables.

In that setting, the value of frozen-section analysis can be questioned. Several authors have found important discrepancies between the results of frozen sections and final pathologies [14,15]. In the series from Kwon et al, the 7% rate of PSM was observed despite the systematic use of frozen-section analysis [13]. In another series of 301 PNs, Duvdevani et al found a PSM on final pathology in four patients who had perioperative negative findings [15]. Furthermore, in the laparoscopic era, frozen section is not used routinely, and one can foretell that the technique will be utilised less and less in the future. Finding of PSM after resection does not mean that there will be evidence of residual tumour on final pathology. Any urologist should be aware of the limitations of frozen-section analysis before embarking on a wider resection or a radical nephrectomy that can lead to unnecessary kidney damage and increased surgical morbidity. Additional tools are clearly needed to better assess the quality of the resection during NSS [16].

An important finding is that we observed a high discrepancy in terms of outcome between the imperative and elective groups. The vast majority (10 of 11) of the

recurrences occurred in the imperative group. Similarly, 10 of the 12 patients who died had an imperative indication. In the elective group, only one patient recurred and is still alive at the time of data acquisition, thanks to an adequate salvage therapy. Moreover, there was no difference regarding recurrence rates according to the margin status in the survival analysis (Fig. 1). It has been demonstrated that imperative tumours are of larger diameter, higher stage, and higher grade than their elective counterparts [17]. Patients with elective tumours were clearly selected (ie, for good performance status and low stage) and therefore had better cancer control. Multivariable analysis showed that the two factors that could predict recurrence were tumour location (central vs peripheral) and an imperative indication; however, none of the variables included in the Cox model had any impact on cancer survival.

We acknowledge several limitations to the present study. First, this study is retrospective, with all the attendant imprecision associated with the large recollection of data. Data were collected in many centres from different countries, and there are certainly biases related to differences among health care systems, patient selection, surgical techniques, and pathologic assessment. Finally, our follow-up was relatively short, and additional observation would be mandatory before we could confirm that the higher incidence rate of PSM does not translate into a worse survival rate.

## 5. Conclusions

PSM following NSS occurs more frequently in cases of imperative surgery and may be associated with an increased risk of recurrence; however, it does not appear to influence cancer-specific survival. Additional follow-up is needed to confirm these data.

**Author contributions:** Karim Bensalah 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:** Bensalah, Pantuck, Beldegrun, Patard.

**Acquisition of data:** Bensalah, Pantuck, Thuret, Montorsi, Karakiewicz, Motet, Zini, Bertini, Salomon, Villers, Soulie, Bellec, Rischmann, De La Taille, Avakian, Crepel, Ferriere, Bernhard, Dujardin, Pouliot, Rigaud, Pfister, Albouy, Guy, Joniau, van Poppel, Lebret, Culty, Saint, Zisman, Raz, Lang, Spie, Wille, Roigas, Aguilera, Rambeaud, Martinez Pifeiro, Nativ, Farfara, Richard, Roupert, Doehn, Bastian, Muller, Tostain, Beldegrun, Patard.

**Analysis and interpretation of data:** Bensalah, Patard.

**Drafting of the manuscript:** Bensalah, Patard.

**Critical revision of the manuscript for important intellectual content:** Pantuck, Beldegrun.

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### Editorial Comment on: Positive Surgical Margin Appears To Have Negligible Impact on Survival of Renal Cell Carcinomas Treated by Nephron-Sparing Surgery

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A fundamental and long-standing goal of surgical oncology is complete gross and microscopic removal of the cancer. Regarding partial nephrectomy for renal masses, the historical recommendation of a 1–2-cm circumferential margin remains safe, conservative, and appropriate. Contemporary data, however, suggest that margins <5 mm [1] or even tumor enucleation [2] both result in similarly favorable outcomes. Although every effort should be made to achieve negative margins, large series show a positive margin will occur in 2–6% of patients [3].

The accompanying international, multi-institutional study by Bensalah et al [4], along with similar work from others [3], suggests that kidney cancer now uniquely joins prostate cancer as a condition in which a positive surgical margin does not invariably precede and predict a cancer recurrence. Why might this be? Falsely positive margins can exist due to tissue processing, variability in pathologic assessment, and inadvertent tumor incisions. Additionally, a legitimate microfocus of residual cancer may never result in clinical recurrence if adequately treated by intraoperative fulguration or argon-beam application to the tumor base. Moreover, since the average annual growth rate of radiographically visible but small renal masses is 0.28 cm/yr [5], residual cancer cells may require many years to become clinically apparent. Therefore, a

median follow-up of 3 yr in this study [4] and in others [3] is likely inadequate to ascertain the true long-term oncologic impact of a positive surgical margin.

Despite the suggestion that a positive surgical margin does not affect long-term cancer control, it cannot be overemphasized that the kidney surgeon's intent and obligation is to secure negative margins. Nevertheless, the presence of a positive surgical margin should prompt more frequent and intensive surveillance. This study suggests that only a small proportion of patients with a positive margin will exhibit a clinical recurrence at short follow-up and that if timely salvage measures are instituted, cancer-specific survival does not appear to be adversely affected.

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### Editorial Comment on: Positive Surgical Margin Appears To Have Negligible Impact on Survival of Renal Cell Carcinomas Treated by Nephron-Sparing Surgery

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The authors conducted a retrospective study involving 26 centers and identified 111 patients without metastatic disease who had a positive surgical margin (PSM) at the time of partial nephrectomy (PN) for a renal cortical tumor (RCT) [1]. The overall denominator of patients undergoing PN at these centers is unknown, but the authors estimated PSM patients were 1–3.5% of the total.

Of these patients, 43 (39%) had an imperative indication, 93 (84%) had a T1 tumor, and 89 (80%) were discovered incidentally. After a mean follow-up of 37 mo, 11 patients (10%) recurred and 12 patients died, including 6 (5.4%) who died from metastatic renal cancer. Ten of the 12 (83%) deaths occurred in patients who were operated on for imperative indications. Recurrence-free, cancer-specific, and overall survival was the same for PSM patients compared with matched and unmatched cohorts of negative-surgical-margin patients. Only one elective PN patient recurred. Most PSM patients underwent continued surveillance ( $n = 93$ , 83.8%), 3 (2.7%) underwent repeat PN, and 15 (13.5%) underwent radical nephrectomy (RN), with residual tumor found in 7 of 18 cases (39%).

This study confirms recent reports suggesting that a PSM is an uncommon event and that, in the vast majority of cases, careful surveillance is sufficient management [2].

Our contemporary understanding of RCT tumors stresses oncologic efficacy of PN to RN for T1 RCT [3] and an appreciation of the prognostic importance of tumor histology (with approximately 20% of tumors benign [eg, renal oncocytoma, fat-poor angiomyolipoma] and 25% indolent [eg, papillary and chromophobe carcinoma] with limited metastatic potential).

In this report, renal oncocytomas were not analyzed, yet 29.4% of the cases were the more indolent papillary ( $n = 29$ , 26.1%) and chromophobe ( $n = 7$ , 6.3%), which are far less likely to develop metastatic disease than the conventional clear cell carcinoma. Technical factors, particularly those seen in imperative cases such as tumor in a solitary kidney, renal sinus tumor, perihilar tumor, and tumor multifocality and bilaterality, can lead to a PSM. Additionally, the condition of the surgical specimen and the manner in which it is prepared by the pathologists could also lead to a PSM. Interestingly, in our experience, small renal tumors are more likely than larger tumors to have a PSM, particularly when the mass is endophytic [2]. This study, and others like it, should give urologists courage to perform PN, even if the anticipated resection margin is close and the tumor abuts the collecting system or renal hilum. A PSM only rarely progresses to a clinical local recurrence. The recently described benefits of PN in terms of preventing chronic kidney disease and its associated cardiovascular morbidity and potential mor-

tality are increasingly clear [4,5]. A close surgical margin, or even positive one, at the time of PN, should no longer trigger a secondary PN or RN but simply close, long-term surveillance.

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