Published in final edited form as:

J Urol. 2008 June ; 179(6): 2158–2163. doi:10.1016/j.juro.2008.01.100.

Predictors and oncological outcomes following positive surgical margins at partial nephrectomy

Ofer Yossepowitch, R. Houston Thompson, Bradley C. Leibovich, Scott E. Eggener, Joseph A. Pettus, Eugene D. Kwon, Harry W. Herr, Michael L. Blute, and Paul Russo

From the Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center (OY, RHT, SEE, JAP, HWH, PR), New York, New York and the Department of Urology, Mayo Clinic and Mayo Medical School (BCL, EDK, MLB), Rochester, Minnesota

Abstract

Purpose—The prognostic significance and optimal management of patients with positive surgical margins (PSMs) following partial nephrectomy remain ill-defined. We combine data from two tertiary-care intuitions and report predictors of PSMs and long-term oncological outcomes for patients with PSMs.

Methods—Clinical, pathologic, and follow-up data on 1344 patients undergoing 1390 partial nephrectomies for kidney cancer were analyzed. Patients with PSMs on final pathology were managed expectantly. Univariate and multivariable logistic regression models were fit to determine clinicopathologic features associated with PSMs. The Kaplan-Meier method was used to estimate freedom from local disease recurrence and metastatic progression. Cox proportional hazards models were used to assess whether PSM predicted local recurrence or metastatic disease adjusting for tumor size, pathologic stage, histologic subtype and presence of a solitary kidney.

Results—PSM were documented in 77 cases (5.5%). Decreasing tumor size and presence of a solitary kidney carried a significantly higher risk of PSMs. The overall 10-year probability of freedom from local disease recurrence was 93% (95% CI 89, 95), and from metastatic progression 93% (95% CI 90, 95), with no significant difference between patients with positive vs. negative margins ($p=0.97$ and 0.18, respectively). PSMs were not associated with an increased risk of local recurrence or metastatic disease.

Conclusions—PSMs in partial nephrectomy specimens do not uniformly portend an adverse prognosis. While every effort should be taken to ensure clear margins, our data suggest that select patients with a PSM can be safely offered vigilant monitoring without compromising their long-term disease-free survival.

Keywords

kidney neoplasms; partial nephrectomy; positive surgical margins; local recurrence; metastasis

Introduction

Partial nephrectomy (PN) is the standard of care for small renal cortical tumors.^{1–4} Numerous studies have established its oncological efficacy with the added benefit of preserving long-term

Address correspondence to: Paul Russo, MD, Department of Urology, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, 353 East 68th Street, New York, New York 10021, e-mail: E-mail: russop@mskcc.org, Telephone: 646-422-4391, Fax: 212-988-0760.

All authors report no potential conflicts of interest

renal function and minimizing the risk for chronic kidney disease.^{2, 5} Emerging data further suggest that PN may be safely offered to appropriately selected patients with larger tumors, 4 to 7 cm in size, without a significant increase in postoperative morbidity or compromise of long-term disease-free survival.^{1, 3, 6}

The standard surgical technique of PN entails removal of the tumor with an additional rim of uninvolved renal parenchyma. While simple tumor enucleation has been proposed as a safe alternative,⁷ excising a wide margin of normal parenchyma will ensure absence of malignancy in the preserved portion of the kidney. Yet the optimal margin required for oncological safety remains an area of contention. Recent observations suggest that a tumor-free margin, regardless of size, is sufficient to achieve complete local excision.^{8, 9} Conversely, tumor at the inked margin implies, at least in theory, incomplete cancer removal, potentially increasing the risk of local or distant recurrence. Therefore, the management of patients with a positive surgical margin (PSM) remains a challenge, with controversy persisting over the need for more rigorous follow-up or for immediate adjunctive therapy, including repeat partial nephrectomy or completion of nephrectomy. Moreover, given the multicentric nature of renal cortical tumors, particularly of the papillary subtype, local recurrence emanating from incomplete resection of the primary tumor can be difficult or impossible to distinguish from occult multicentric disease or *de novo* tumor formation, further obfuscating the interpretation of the effects of PSM on oncologic outcomes.

Recent studies addressing the impact of PSM in PN specimens have suggested that a PSM does not necessarily indicate residual disease.^{10–12} However, these reports generally were limited by small numbers of patients with positive margins, few disease recurrences, and relatively short follow-up times. In this study we combine data from two tertiary care institutions to determine potential predictors for PSM following PN and investigate long-term oncological outcomes.

Materials and Methods

After institutional review board approval was obtained from both participating sites, the renal cancer registries were queried to identify patients undergoing PN. Details regarding these prospectively-maintained registries have been provided in earlier reports.^{2, 4} Institutional data use agreements were signed and de-identified datasets were transferred between institutions. Because our primary goal was to analyze the impact of PSM on oncological outcomes, we excluded all patients with benign histology (including metanephric adenomas, angiomyolipomas, and oncocytomas). The queries identified 1344 patients with complete clinical and pathologic information available from 1390 PNs for malignant renal cortical tumors at the Mayo Clinic (n=619, between 1972 and 2004) or Memorial Sloan Kettering Cancer Center (n=771, between 1989 and 2005).

All specimens were analyzed by dedicated urologic pathologists. A positive surgical margin was defined as extension of tumor to the inked surface of the resected specimen on final pathology. Therefore, any benign tissue overlying the tumor, regardless of thickness, rendered the margin negative. The standard practice during the study period at both institutions was to achieve complete tumor extirpation. Thus, when frozen section revealed microscopically positive margins or when the surgeon was concerned about a grossly involved margin, re-resection of the PN bed or completion of nephrectomy were carried out at the time of surgery. The latter patients were excluded from this study. Tumor size was determined by measuring the maximal diameter of the tumor at the time of pathologic examination, and the histologic subtype was assigned in accordance with the Heidelberg classification of renal cortical tumors.

Follow-up was conducted according to accepted clinical practice at each institution. In general, follow-up consisted of physical examination, chest radiographs, and kidney imaging every 6–12 months during the first 5 years and annually thereafter. Patients with PSM on final pathology were observed at similar intervals with serial imaging and no patient was treated with immediate adjunctive therapy.

Local disease recurrence was defined as new tumor formation at a prior PN site and included all cases in which a renal tumor developed in the previously operated pole, regardless of whether the mass was unequivocally abutting the PN bed. For all cases of local recurrence, imaging studies were re-reviewed to confirm the diagnosis. Metastatic progression was defined as unequivocal imaging findings indicating distant organ involvement with or without a confirmatory diagnostic biopsy. A metachronous contralateral renal neoplasm was not considered metastatic disease. We chose metastatic progression as the measure of oncological efficacy because metastatic renal cancer is the primary determinant of survival, often causes substantial morbidity, has no proven cure, and antedates cancer-specific mortality by an average of 2 years.¹³

Statistical Analysis

Univariate and multivariable logistic regression analyses were used to determine features associated with PSM. For this analysis we included all 1390 PNs in the study cohort, with covariates including tumor size, pathologic stage, and whether the surgery was performed in the setting of a solitary kidney. To adjust for the possibility of stage migration and improvements in surgical technique over time, we included as a covariate the year that the surgery was performed. Moreover, because the difference between pathologic stages T1a, T1b, and T2 is entirely accounted for by tumor size, stage was coded as a dichotomous variable, $\leq$ pT2 vs. pT3. Data pertaining to tumor location or percent parenchyma involvement were unavailable for the majority of patients and were not included in the final model.

Estimates of the probability of local disease recurrence and metastatic progression were calculated with the Kaplan-Meier method. The log-rank test was used to compare outcomes of patients with positive versus negative surgical margins on final pathology. In these analyses, patients who presented with bilateral synchronous tumors or developed a metachronous renal mass were included only once using the initial PN as an index case. Multivariable Cox proportional hazard regression models were fit to test whether a positive surgical margin was associated with each of the study endpoints, controlling for year of surgery, tumor size, pathologic stage ($\leq$ pT2 vs. pT3), histological subtype, and whether the surgery was performed on a solitary kidney. Tumor histology was modeled as a categorical variable, namely clear cell carcinoma, papillary carcinoma (type I and II), chromophobe carcinoma, and unclassified renal cancer. The 15 patients with miscellaneous histology were excluded from this analysis. Histologic coagulative necrosis was not routinely recorded at Memorial Sloan Kettering and tumor grade was unavailable for all histologic subtypes. All decisions with respect to the coding of the variables were made before modeling the data. Categorical variables were compared between subgroups with a chi-square test for proportions. Continuous variables were compared with a t-test for differences in means. All statistical analyses were two-sided and performed using Stata version 8.2 with $p < 0.05$ considered significant.

Results

The clinical and pathologic features of the study cohort are summarized in Table 1. PSM were documented in 77 patients (5.5%). Of the PNs, 114 (8.1%) were performed in the setting of a solitary kidney. While tumor size was significantly greater in patients with a solitary kidney than in those with a normal contralateral kidney ($p = 0.001$), the rate of PSM ($p = 0.25$) and the distribution of pathologic stage ($p = 0.34$) and tumor histology ($p = 0.1$) did not differ between

these two groups. The overall median follow-up was 3.4 years (IQR 1.4, 6.1). For patients with no evidence of disease recurrence at last visit, median follow-up was 3.3 years (IQR 1.4, 5.9); 459 patients (33%) were followed more than 5 years and 136 patients (10%) more than 10 years. There were 39 local recurrence events, and 57 patients developed metastatic progression. Nineteen (33%) of the patients with metastatic progression had previously experienced a local recurrence.

Table 2 depicts results from logistic regression analyses to find factors associated with PSM. Increasing tumor size was associated with lower incidence of positive margins (odds ratio 0.86 for each 1 cm increase in maximal tumor diameter; 95% CI 0.72, 0.97, $p=0.05$). This association was maintained (odds ratio 0.82, 95% CI 0.69, 0.93, $p=0.03$) after controlling for year of surgery, pathologic stage, and whether the surgery was performed in a solitary kidney. Interestingly, PN in a solitary kidney was not associated with an increased incidence of PSM in univariate analysis, but it was significantly associated in multivariable analysis (Table 2). This phenomenon appears to be primarily related to interaction between covariates: patients with solitary kidneys generally harbored larger tumors compared to those with a healthy contralateral kidney (mean tumor diameter $4.54 \text{ cm} \pm 0.23$ vs. $3.13 \text{ cm} \pm 0.04$, respectively, $p=0.001$) and larger tumors exhibited a lower likelihood of PSM; once tumor diameter was adjusted for (i.e., the model assumes that all tumors are of the same size), surgery performed in a solitary kidney did carry a significantly higher risk of PSMs. The year of surgery and advanced pathologic stage were not significantly associated with the risk of PSM.

The overall 5- and 10-year freedom from local disease recurrence was 97% (95% CI 95, 98) and 93% (95% CI 89, 95), respectively, and freedom from metastatic progression 96% (95% CI 94, 97) and 93% (95% CI 90, 95), respectively. When stratified by the surgical margin status, the 5-year freedom from local recurrence for patients with negative margins was 97% (95% CI 95, 98) and for those with positive margins 98% (95% CI 89, 97) ($p \text{ log rank} = 0.97$; Figure 1). Likewise, the 10-year probability of freedom from metastatic progression was 93% (95% CI 89, 95) for patients with negative margins and 95% (95% CI 84, 98) for those with positive margins ($p \text{ log rank} = 0.18$; Figure 2). In a multivariable analysis the only predictor of local disease recurrence was tumor size (hazard ratio 1.2 for each 1 cm increase in tumor size, $p=0.01$; Table 3). Increasing tumor size was similarly associated with higher likelihood of metastatic disease, as were surgery in a solitary kidney (compared to surgery in a patient with a healthy contralateral kidney), pathologic stage T3 (compared to $\leq \text{pT2}$) and clear cell histology (compared to papillary renal cell carcinoma). PSM was not associated with increased risk of local recurrence or metastatic progression (Table 3).

Discussion

Excising tumors with an adjacent rim of normal-appearing tissue is a key tenet in surgical oncology. The importance of achieving negative surgical margins to reduce the risk of recurrence has been demonstrated in numerous types of cancer, including melanoma, sarcoma, prostate, bladder, colon, pancreas, and breast cancer.^{14–16} This standard should also be applied to kidney cancer and hence PSMs during surgery for renal cortical tumors should invariably be discouraged and undisputedly be avoided. However, PSMs occur on rare occasions following PN,^{9–11} and the clinical impact of a PSM on long-term disease progression and its optimal management remain ill-defined and were thus the subject of our study.

Relative to the adverse outcome associated with PSM in other solid tumors, our results indicate that PSM in PN specimens do not uniformly portend an ominous prognosis. In a relatively large cohort of patients with PSMs managed expectantly, no association was apparent between a PSM on final pathology and either local disease recurrence or metastatic progression. While

we emphasize that surgeons should strive to achieve clear margins during PN, the status of the surgical margin should not be used as an endpoint to assess oncological safety or efficacy. Likewise, our study suggests that select patients with positive margins can be safely offered vigilant monitoring with serial imaging without compromising their long-term disease-free survival.

With prostate, breast, and pancreatic cancer, the technique used by the individual surgeon has been associated with the rate of positive margins.^{14, 15, 17} Therefore, we hypothesized that greater technical PN complexity might affect the rate of positive margins in kidney cancer as well. This notion is supported by the observed association between PSM and surgery in a solitary kidney. While neither year of surgery nor pathologic stage was associated with PSM in univariate and multivariable analyses, an intriguing and unexpected finding was the association between positive margins and smaller tumors. If one assumes that excision of smaller lesions would be less technically difficult than excision of larger lesions, one would expect smaller lesions to be associated with a decreased rather than increased incidence of PSM. A possible explanation for this incongruent finding is that surgeons might have been more reluctant to incise a generous rim of adjacent renal parenchyma in cases of small, exophytic lesions, perhaps to avoid segmental vessel injury, entry into the collecting system or the need for renal artery clamping. Likewise, a demarcation line between the tumor and normal parenchyma may be more evident in cases of large compared to small tumors. Alternatively, this finding might be related to tissue processing and pathologic sampling. Finally, size alone may not be an adequate surrogate for the technical complexity of PN in an individual patient. Controlling for other factors such as tumor location, ischemia time, and percent parenchyma involvement might render our association between PSM and tumor size statistically insignificant.

Compared to surgery for other solid cancer types, PN has several unique features that might account for our inability to demonstrate that positive margins adversely affect clinical outcome. First, to achieve adequate renal parenchymal hemostasis following tumor excision, surgeons often fulgurate the cortical rim of the PN bed (avoiding thermal injury to the renal medulla or collecting system) using electrocautery or argon beam coagulation. This may potentially eradicate any residual cancer cells by virtue of thermal destruction and attain an “additional margin.” Second, renal ischemia induced by clamping of the renal artery might extirpate cells with high metabolic requirements, specifically cancer cells. Third, the natural history of a residual microscopic focus of renal cancer might be considerably protracted, such that it requires a longer follow-up to manifest clinically. Additionally, tumors in this study were relatively small (median tumor diameter 3.3 cm) and previous observations suggest that smaller tumors tend to have a favorable phenotype associated with an indolent biological behavior.¹⁸ Lastly, false positive margins may result from inadvertent capsulotomy during specimen processing, and false negative margins may result from a sampling error. False positives or false negatives might explain, in part, our favorable oncologic outcomes for patients with PSM.

One aspect of this study warrants further emphasis. The PSMs reported herein represent patients in whom the resection was deemed complete by the surgeon at the time of PN. Complete tumor extirpation is paramount, and the finding that PSM on final pathology was not independently associated with poor outcome should not be misinterpreted. We do not advocate expectant management for patients who have gross positive margins. However, we provide evidence that microscopic PSMs on final pathology can be managed expectantly without immediate additional treatment or compromised long term outcome.

Conclusions

Every effort should be taken to ensure clear margins during partial nephrectomy, particularly in the setting of a solitary kidney. However, positive surgical margins do not appear to increase the long-term risk of local recurrence or metastatic progression and thus the status of the surgical margin should not be used as a measure of oncological efficacy. Select patients with positive margins can be safely offered vigilant monitoring without compromising their long-term disease-free survival.

Abbreviations

PSM, positive surgical margin; PN, partial nephrectomy; CI, confidence interval; IQR, interquartile range.

References

1. Patard JJ, Shvarts O, Lam JS, Pantuck AJ, Kim HL, Ficarra V, et al. Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. *J Urol* 2004;171:2181. [PubMed: 15126781]
2. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006;7:735. [PubMed: 16945768]
3. Leibovich BC, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol* 2004;171:1066. [PubMed: 14767272]
4. Thompson RH, Leibovich BC, Lohse CM, Zincke H, Blute ML. Complications of contemporary open nephron sparing surgery: a single institution experience. *J Urol* 2005;174:855. [PubMed: 16093969]
5. Lau WK, Blute ML, Weaver AL, Torres VE, Zincke H. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin Proc* 2000;75:1236. [PubMed: 11126830]
6. Dash A, Vickers AJ, Schachter LR, Bach AM, Snyder ME, Russo P. Comparison of outcomes in elective partial vs radical nephrectomy for clear cell renal cell carcinoma of 4–7 cm. *BJU Int* 2006;97:939. [PubMed: 16643474]
7. Carini M, Minervini A, Masieri L, Lapini A, Serni S. Simple enucleation for the treatment of PT1a renal cell carcinoma: our 20-year experience. *Eur Urol* 2006;50:1263. [PubMed: 16787695]
8. Castilla EA, Liou LS, Abrahams NA, Fergany A, Rybicki LA, Myles J, et al. Prognostic importance of resection margin width after nephron-sparing surgery for renal cell carcinoma. *Urology* 2002;60:993. [PubMed: 12475656]
9. Timsit MO, Bazin JP, Thiounn N, Fontaine E, Chretien Y, Dufour B, et al. Prospective study of safety margins in partial nephrectomy: intraoperative assessment and contribution of frozen section analysis. *Urology* 2006;67:923. [PubMed: 16635521]
10. Permpongkosol S, Colombo JR Jr, Gill IS, Kavoussi LR. Positive surgical parenchymal margin after laparoscopic partial nephrectomy for renal cell carcinoma: oncological outcomes. *J Urol* 2006;176:2401. [PubMed: 17085113]
11. Breda A, Stepanian SV, Liao J, Lam JS, Guazzoni G, Stifelman M, et al. Positive margins in laparoscopic partial nephrectomy in 855 cases: a multi-institutional survey from the United States and Europe. *J Urol* 2007;178:47. [PubMed: 17574057]
12. Gill IS, Matin SF, Desai MM, Kaouk JH, Steinberg A, Mascha E, et al. Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. *J Urol* 2003;170:64. [PubMed: 12796646]
13. Eggener SE, Yossepowitch O, Pettus JA, Snyder ME, Motzer RJ, Russo P. Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. *J Clin Oncol* 2006;24:3101. [PubMed: 16809736]

14. Eastham JA, Kattan MW, Riedel E, Begg CB, Wheeler TM, Gerigk C, et al. Variations among individual surgeons in the rate of positive surgical margins in radical prostatectomy specimens. *J Urol* 2003;170:2292. [PubMed: 14634399]
15. Tseng JF, Pisters PW, Lee JE, Wang H, Gomez HF, Sun CC, et al. The learning curve in pancreatic surgery. *Surgery* 2007;141:694. [PubMed: 17511115]
16. Swallow CJ, Catton CN. Local management of adult soft tissue sarcomas. *Semin Oncol* 2007;34:256. [PubMed: 17560988]
17. Blair SL, O'Shea KE, Orr RK. Surgeon variability in treating nonpalpable breast cancer: surgical oncology as a value-added specialty. *Ann Surg Oncol* 1998;5:28. [PubMed: 9524704]
18. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. *J Urol* 2003;170:2217. [PubMed: 14634382]

Figure 1.
Local recurrence-free survival.

Figure 2.
Metastatic-progression-free survival

Table 1

Clinical and pathologic characteristics of 1344 patients undergoing 1390 partial nephrectomies.

Characteristic	Mayo clinic (n=619)	Memorial Sloan Kettering (n=771)
Age at surgery, years		
Median (IQR)	63 (53, 71)	61 (52, 69)
Mean (range)	61.8 (22–86))	59.6 (12–84)
Patient gender (%)		
Female	179 (29)	257 (33)
Male	440 (71)	514 (67)
Side (%)		
Right	291 (47)	392 (51)
Left	328 (53)	379 (49)
Tumor in solitary kidney (%)		
Yes	59 (10)	55 (7)
No	560 (90)	716 (93)
Maximal tumor diameter (cm)		
Mean $\pm$ SD	3.5 $\pm$ 1.9	3.1 $\pm$ 1.4
Median (IQR)	3 (2.2, 4.3)	2.6 (2.0, 3.7)
Pathologic stage (%) *		
T1a	448 (72)	597 (77)
T1b	139 (22)	98 (13)
T2	16 (3)	11 (2)
T3	16 (3)	63 (8)
Surgical margin status (%)		
Negative	606 (98)	707 (92)
Positive	13 (2)	64 (8)
Tumor histology (%)		
Clear cell	402 (65)	478 (62)
Papillary	175 (28)	168 (22)
Chromophobe	38 (6)	92 (12)
Unclassified	-	22 (3)
Miscellaneous **	4 (<1)	11 (1)

* Unavailable for 2 patients.

** Including mixed epithelial and stromal tumors, lymphoma, collecting duct carcinoma, cellular mixoma, hemangioendothelioma, transitional cell carcinoma, and unavailable for 2 patients.

Table 2

Predictors of positive surgical margins in partial nephrectomy

	Univariate Analysis		Multivariable Analysis	
	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)
Year of surgery	0.77	1 (0.96, 1.05)	0.81	1 (0.96, 1.05)
Solitary vs. bilateral kidneys	0.11	1.5 (0.93, 3.13)	0.05	1.8 (1.19, 3.94)
Maximal tumor diameter	0.05	0.86 (0.72, 0.97)	0.03	0.82 (0.69, 0.93)
Pathologic stage (T3 vs. $\leq$ T2)	0.19	1.7 (0.76, 3.88)	0.13	1.9 (0.82, 4.35)

Table 3

Predictors of local disease recurrence and metastatic progression in 1344 patients undergoing partial nephrectomy for renal cortical tumors.

	Local recurrence		Metastatic progression	
	P-Value	HR (95% CI)	P-Value	HR (95% CI)
Year of surgery	0.74	0.99 (0.93, 1.04)	0.6	1.01 (0.96,1.06)
Solitary kidney (vs. bilateral kidneys)	0.13	1.9 (0.82, 4.5)	<0.001	3.4 (1.7,6.5)
Maximal tumor diameter	0.01	1.2 (1.06, 1.36)	0.001	1.2 (1.1, 1.4)
Positive surgical margins	0.99	1 (0.23, 4.3)	0.36	1.6 (0.6, 4.1)
Pathologic stage (≤ T2 vs. T3)	0.14	2.1 (0.8, 5.7)	0.08	1.9 (0.9, 4.3)
Histologic subtype				
Clear cell *	—	—	—	—
Papillary	0.34	0.67 (0.3, 1.5)	0.006	0.27 (0.1, 0.7)
Chromophobe	0.39	0.52 (0.1, 2.3)	0.21	0.45 (0.13, 1.6)
Unclassified	1.00		0.36	2.5 (0.33,19.1)

* Defined as reference category

HR, hazard ratio