

Positive Surgical Margins Increase Risk of Recurrence after Partial Nephrectomy for High Risk Renal Tumors

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Purpose: The clinical significance of a positive surgical margin after partial nephrectomy remains controversial. The association between positive margin and risk of disease recurrence in patients with clinically localized renal neoplasms undergoing partial nephrectomy was evaluated.

Materials and Methods: A retrospective multi-institutional review of 1,240 patients undergoing partial nephrectomy for clinically localized renal cell carcinoma between 2006 and 2013 was performed. Recurrence-free survival was estimated using the Kaplan-Meier method and evaluated as a function of positive surgical margin with the log rank test and Cox models adjusting for tumor size, grade, histology, pathological stage, focality and laterality. The relationship between positive margin and risk of relapse was evaluated independently for pathological high risk (pT2-3a or Fuhrman grades III-IV) and low risk (pT1 and Fuhrman grades I-II) groups.

Results: A positive surgical margin was encountered in 97 (7.8%) patients. Recurrence developed in 69 (5.6%) patients during a median followup of 33 months, including 37 (10.3%) with high risk disease (eg pT2-pT3a or Fuhrman grade III-IV). A positive margin was associated with an increased risk of relapse on multivariable analysis (HR 2.08, 95% CI 1.09–3.97, $p=0.03$) but not with site of recurrence. In a stratified analysis based on pathological features, a positive surgical margin was significantly associated with a higher risk of recurrence in cases considered high risk (HR 7.48, 95% CI 2.75–20.34, $p<0.001$) but not low risk (HR 0.62, 95% CI 0.08–4.75, $p=0.647$).

Abbreviations and Acronyms

CSS = cancer specific survival
CT = computerized tomography
NSM = negative surgical margin
NSS = nephron sparing surgery
PN = partial nephrectomy
PSM = positive surgical margin
RCC = renal cell carcinoma
RFS = recurrence-free survival

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Editor's Note: This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 626 and 627.

Conclusions: Positive surgical margins after partial nephrectomy increase the risk of disease recurrence, primarily in patients with adverse pathological features.

Key Words: nephrectomy; laparoscopy; carcinoma, renal cell; kidney neoplasms

PARTIAL nephrectomy has emerged as the treatment of choice for clinically localized renal masses.¹ Although oncologic outcomes comparable to those of radical nephrectomy have been demonstrated, a realistic concern is violation of the tumor during resection, leaving residual disease in the nephrectomy bed.² A positive surgical margin has been shown to increase the recurrence risk for many solid organ malignancies.^{3–9} However, several studies evaluating outcomes after PN for renal cell carcinoma have failed to demonstrate the prognostic significance of a PSM.^{10,11}

Lack of consensus surrounding the clinical relevance of a PSM may result from broad interstudy variability in the pathological characteristics of the populations studied. Similar to prostate cancer, our appreciation for the heterogeneous behavior of RCC has matured in recent years.^{12–14} Lesions low in Fuhrman grade and stage follow a relatively indolent course, whereas tumors of advanced pathological phenotype exhibit a higher proclivity for growth and systemic spread, warranting early intervention.^{15–17} It seems plausible, then, that residual tumor in the context of PSM mimics the primary lesion rather than universally signifying disease meant to progress.

The low incidence of positive surgical margins and the relative infrequency of pathologically aggressive lesions treated with NSS limits the high risk patients evaluated in many series.^{10,11} Contemporary studies often lack the statistical power to discern differences between high risk patients with and without PSM as well as between high and low risk patients with PSM. We evaluated the impact of PSM on recurrence-free survival after NSS, using a multi-institutional cohort comprised of greater numbers of pathological high risk cases. Oncologic outcomes stratified by margin status and patient risk group were also analyzed.

METHODS

After institutional review board approval, data from patients (age 18 years or older) undergoing PN for clinically localized renal masses (clinical stage T1 or T2) between 2006 and 2013 at 4 high volume centers (University of California Irvine, North Shore LIJ, University of Southern California, University of Chicago) were collected. Patient demographics, surgical approach (minimally

invasive vs open), tumor pathology (laterality, histology, Fuhrman grade, focality, pathological stage, size and margin status), duration and disease status at followup, and time and site of recurrence were evaluated. Patients with clinical stage T3 or greater disease, solitary kidney, benign pathology, familial RCC or RCC treated before 2006 were excluded from analysis. Institutional databases were prospectively collected, with de-identified data merged and analyzed.

Laparoscopic, robotic and open PN techniques have been previously described.^{18–20} Based on surgeon preference, extirpation was completed with tumor enucleation or sharp excision, and intraoperative biopsy of the resection bed was evaluated using frozen section. Specimens were sent for pathological evaluation, where margins were stained before manipulation. Malignant cells at the stained margin were reported as PSM. A negative surgical margin was defined as the absence of malignancy at the stained margin.

All patients had more than 1 year of postoperative surveillance, consisting of an initial visit between 6 and 12 months, followed by semiannual or annual visits. History, examination, laboratory testing, and imaging of the abdomen, pelvis and chest were performed at each visit. Imaging included the exclusive use of cross-sectional imaging or baseline CT followed by alternating use of ultrasound and CT based on surgeon preference. X-ray was used to screen the chest, except for pT3a disease, for which CT may have been obtained. Recurrence was considered if imaging demonstrated new lesions, with definitive diagnosis assigned only after tissue confirmation of histological congruence with the original tumor. Lesions in tissue adjacent to the resection site were classified as local recurrence, whereas metachronous lesions in the ipsilateral kidney away from the nephrectomy bed or in the contralateral kidney were not considered recurrence. Lesions in distant organs were considered metastatic. Patients with a PSM received no adjuvant intervention.

Patients were divided into 2 groups based on the presence of cancer at the surgical margin. Univariable comparisons of baseline characteristics between margin groups were performed using the Fisher exact test and the Student t-test. Time to recurrence was estimated using the Kaplan-Meier method. The primary objective was to compare the relapse risk after NSS between patients with and those without a PSM. The association of margin status with time to recurrence was evaluated with the log rank test on univariable analysis and the Cox proportional hazards model on multivariable analysis, adjusting for age, gender, tumor size, pathological stage (pT1, pT2, pT3a), histology (clear cell, papillary, chromophobe, other), Fuhrman grade (I-IV) and laterality.

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