Original Study

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Positive Surgical Margins Predict Progression-free Survival After Nephron-sparing Surgery for Renal Cell Carcinoma: Results From a Single Center Cohort of 459 Cases With a Minimum Follow-up of 5 Years

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Abstract

The presence of positive surgical margins (PSMs) after partial nephrectomy has been associated with an increased risk of disease recurrence, but conclusive evidence is lacking. The aim of this study is to examine the prognostic role of PSMs in a large retrospective cohort with long-term follow-up. PSMs were associated with disease recurrence, both local and distant, and decreased progression-free survival. Patients with PSMs should undergo a more intense follow-up.

Background: The role of positive surgical margins (PSMs) on the recurrence of renal cell carcinoma (RCC) after partial nephrectomy (PN) is debated, and available evidence lacks long-term data. The aim of this study was to evaluate the predictive role of PSMs on progression-free survival (PFS) in a large cohort followed for at least 5 years. **Methods:** This study was a retrospective analysis of a prospectively compiled single-institution database collecting complete information on more than 2700 patients who had undergone surgery for renal tumor. The data of all the patients submitted to PN for RCC and with least 5 years follow-up were extracted. Surgical specimens were examined at the time of surgery only by 2 expert uro-pathologists. A PSM was defined as the presence of cancer cells at the inked surface of the specimen. The role of PSMs on survival was estimated by Cox regression models adjusted for influent covariates. **Results:** A total of 459 patients fulfilled the inclusion criteria and were evaluated. PSMs were observed in 27 (5.9%) cases. No differences in preoperative and pathologic data were found comparing patients with and without PSMs. At a median follow-up of 96 months (interquartile range, 74-131 months), a clinically evident relapse of RCC was diagnosed in 36 (7.8%) patients at a median interval of 36 months from PN. Among these, 6 had a PSM for an incidence of relapse of 22.2% in the PSM group, whereas 30 had negative margins, for an incidence of 6.9% ($P = .013$). The sites of relapse were distant organs in 18 cases, and the kidney underwent PN in 21. The patients with PSMs showed a borderline significantly higher incidence of distant metastasis (11.1% vs. 3.5%; $P = .071$) and a significantly higher incidence of renal relapses (14.8% vs. 3.9%; $P = .029$). Multivariable Cox models confirmed that the presence of PSMs was an independent predictor of PFS (odds ratio, 3.127; $P = .013$). **Conclusions:** PSMs are an independent predictor of PFS in patients who underwent PN for RCC, owing to a higher incidence of distant and local relapses. Surveillance in presence of PSMs should be intensified and extended for a long time.

Clinical Genitourinary Cancer, Vol. 17, No. 1, e26-31
Keywords: Partial nephrectomy, Predictors, Prognosis, Recurrence, Renal Cell Carcinoma

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Submitted: May 21, 2018; Revised: Aug 12, 2018; Accepted: Aug 14, 2018; Epub: Aug 23, 2018

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1558-7673/$ - see frontmatter
https://doi.org/10.1016/j.clgc.2018.08.004

Introduction

Renal cell carcinoma (RCC) represents 2% to 3% of solid tumors, and its incidence is increasing, especially in young patients.[1] According to international guidelines,[2,3] partial nephrectomy (PN) represents the standard of care for organ-confined RCC because it offers excellent oncologic results[4] and better preservation of renal function[5] that could reduce cardiovascular and probably also cancer-specific mortality.[6-8]

Urologists are fairly concerned of the risk of positive surgical margins (PSMs) because this could jeopardize patients' survival, as happens for most oncologic surgeries.[9,10] Thus, avoiding a PSM is paramount, and this goal has been included among all the composite tools designed to objectivize the outcomes of PN, like the Trifecta or the Margin Ischemia Complications score.[11,12] However, the role of PSMs on the risk of recurrence of RCC is still under debate because the available evidence is made by retrospective studies with conflicting results. Several authors reported that a PSM could be relevant on prognosis only for RCC with pathologic aggressive features,[13] but the majority undermined the potential negative role of PSMs.[14] Nevertheless, almost all these studies provided a relatively short follow-up time that could have masked the prognostic role of PSMs, especially in case of the more indolent cancers for which relapses could occur at a very long distance.[15]

The aim of this study is to evaluate the oncologic impact of PSMs in a large single center cohort of patients who underwent PN followed for at least 5 years.

Materials and Methods

This study was a retrospective review of a prospectively maintained institutional database including all clinical, surgical, pathologic, and follow-up data of more than 2700 consecutive patients who underwent surgery for a renal tumor since 1983. The indication of radical nephrectomy versus PN followed international guidelines contemporary to the date of surgery. Operations were performed through open retroperitoneal, laparoscopic, or robot-assisted approaches, depending on the period of the study and surgeon's preference. After resection, at the discretion of the surgeon, punch biopsies of the tumor bed were taken and sent for frozen sections to assess the presence of residual disease and consistently proceed to wider resection or nephrectomy. According to institutional policy, the resection strategy for PN intended to leave a thin layer of healthy parenchyma around the tumor, by performing an enucleo-resection. Across the period of the study, 2 dedicated expert uro-pathologists (R.T. and S.F.) examined surgical specimens and defined PSM as the presence of cancer cells at the inked surface. RCC subtyping was updated to contemporary World Health Organization classification of renal tumors,[16] nuclear grading was attributed according to Fuhrman criteria,[17] and pathologic staging was assigned according to the Union for International Cancer Control TNM staging, 2017 edition.[18]

Patients underwent periodical follow-up controls at a dedicated outpatient office according to a schedule tailored on staging and grading, as previously reported.[19] Briefly, a computed tomography scan was required at 4 months and then alternated with abdomen ultrasound plus chest x-rays every 6 months for 2 years, and then yearly for an indefinite time. Recurrence was defined by the clinical evidence of lesions with features compatible with relapsing RCC, eventually confirmed at pathologic examination by biopsy or resection. A local recurrence was intended as the presence of a new tumor that arose from the previous site of PN identified by computed tomography by the hyper-dense plugs or clips used for the renorrhaphy. Both local recurrences and distant metastasis were generally candidates for surgical treatment whenever deemed as technically resectable, otherwise medical therapy was indicated.

All patients who underwent PN for nonmetastatic RCC with at least 5 years of follow-up were included in the present analysis. The prognostic role of the presence of PSMa at final pathology was investigated, accounting for other predictors of progression-free survival (PFS).

Statistical Analysis

Continuous variables were reported as median and interquartile range (IQR), and categorical variables as number and proportions. The Student t test or Mann-Whitney U test were used to compare continuous variables, and the Pearson χ^2 test was used for categorical variables. The endpoint of the study was PFS, defined as the time between PN and the first event of a clinically documented recurrence or death owing to RCC, censoring the cases with recurrence. The status of patients who disregarded controls was updated by consultation of hospital or administrative online registries or phone calls. Univariate Cox models estimated the association between predictors, among which PSM was one, and PFS; multivariable models assessed the association between PSMs and PFS, accounting for other influent covariates selected by univariable analysis. Differences were considered statistically significant with $P \leq .05$, and all P values were 2-sided. Analyses were performed using SPSS (IBM Corp, IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY).

Results

Over 1055 PNs for a renal tumor were performed after 1983; the data of 459 patients with final pathology consistent with RCC and a minimum follow-up of 5 years were reviewed. Across the long time span of the study, the majority of patients were operated on during the more recent years, as the cumulative incidence of 50% of cases was reached in 2004. A PSM was found in 27 patients (prevalence of PSMs, 5.9%), with a higher rate in more recent cases (year of surgery 1983-2004 vs. 2005-2014, prevalence of PSM 3.8% vs. 8.1%; $P = .072$). No differences were found in preoperative and pathologic features according to the status of surgical margins (Table 1). The cohort was followed for a median time of 96 months (IQR, 74-131 months) from PN to death or last control. Overall, 39 events of progression were diagnosed in 36 (7.8%) patients, of whom 6 had a PSM (22% of 27 with PSMs) and 30 a negative margin (6.9% of 432 with negative margins) ($P = .013$). The relapse occurred at distant sites in 18 patients and in the kidney that previously underwent PN in 21. The incidence of distant metastasis in patients with PSMs was higher, with borderline statistical significance (3/27 vs. 15/432, or 11.1% vs. 3.5%; $P = .071$), whereas the higher incidence of local relapse in the patients with

Table 1 Preoperative and Pathologic Features of Patients

	PSMs 27 Patients (5.9%), n (%)	No PSMs 432 Patients (94.1%), n (%)	*P* Value
Gender			.982
Male	18 (66.7)	310 (66.9)	
Female	9 (33.3)	153 (33.1)	
Mean age at surgery, y (SD)	62.2 (±10.2)	60.7 (±12.7)	.719
Mean clinical diameter, cm (SD)	3.2 (±1.3)	3.1 (±1.3)	.832
pT stage			.221
pT1a	21 (77.7)	349 (80.8)	
pT1b	3 (11.1)	61 (14.1)	
pT2	1 (3.8)	6 (1.4)	
pT3a	2 (7.4)	16 (3.7)	
RCC subtype			.361
Clear cell	18 (66.7)	319 (73.8)	
Papillary	5 (18.5)	74 (17.1)	
Chromophobe	3 (11.1)	28 (6.5)	
Others	1 (3.7)	11 (2.6)	

Abbreviations: PSMs = Positive surgical margins; RCC = renal cell carcinoma.

PSM reached statistical significance (4/27 vs. 17/432, or 14.8% vs. 3.9%; $P = .029$). The median time to distant metastasis was 46 months (IQR, 11-80 months) in the PSM group and 39 months (IQR, 15-50 months) in other patients ($P = .147$), whereas the median time to local recurrence was, respectively, 43 months (IQR, 17-68 months) and 56 months (IQR, 26-96 months) ($P = .56$). Multivariable models showed that tumor diameter (odds ratio [OR], 1.269; $P < .001$), pathologic staging and, in particular, pT3a stage (OR, 5.734; $P < .001$), high Fuhrman grading (OR, 5.346; $P = .006$), and PSMs (OR, 3.127; $P = .013$) were independently predictive of PFS (Table 2).

At the diagnosis of relapse, 23 patients underwent surgical treatment (16 radical nephrectomies, 7 metastasectomies), 7 patients had medical therapy, and 6 patients received supportive care. Among the patients who underwent surgery for the relapse, 10 achieved a long control of the disease, remaining free from RCC at a median interval of 21 months (IQR, 14-70 months) from recurrence (see Supplemental Table 1 in the online version).

Discussion

The present study provided an insight on issue of the prognostic role of PSMs after PN, relying on a cohort with the longest follow-up reported until now (median time, 8 years). Moreover, the population has homogeneous features in terms of surgical management and, most of all, pathologic assessments, because all patients were treated at 1 institution with only 2 expert uropathologists involved. Within our experience, a PSM was detected approximately in 6% of PNs for RCC; that is one-half of the range reported by the literature (0%-15%).[20]

Table 2 Univariate and Multivariable Cox Regression Models for Progression-free Survival After Partial Nephrectomy

	Univariate		Multivariable	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Tumor diameter, cm	1.340 (1.145-1.567)	<.001	1.269 (1.065-1.511)	<.001
Pathologic stage		.001		<.001
pT1a	Referent		Referent	
pT1b	0.935 (0.325-2.686)	.9	0.680 (0.265-1.742)	.42
pT2	2.114 (0.286-15.621)	.47	1.922 (0.347-13.129)	.19
pT3a	6.213 (2.541-15.193)	<.001	5.734 (2.356-13.958)	<.001
High grading	5.399 (1.653-17.632)	.005	5.346 (1.629-17.550)	.006
Histologic subtype[a]	0.842 (0.557-1.273)	.41		
Necrosis	1.042 (0.249-4.360)	.955		
Microvascular invasion	2.005 (0.274-14.666)	.493		
PSMs	3.608 (1.499-8.683)	.004	3.127 (1.272-7.688)	.013

Abbreviations: CI = Confidence interval; OR = odds ratio; PSMs = positive surgical margins.
[a]Clear-cell renal carcinoma versus other histologic subtypes.

The first finding is that the clinical and pathologic features of the cases with and without PSMs were overlapping, indicating that this phenomenon is poorly predictable on the basis of the features of the patient or the tumor, but probably relies on drawbacks of surgical dissection. Splitting the cohort on 2 periods with the same number of procedures, before and after 2005, an increase in the incidence of PSMs was observed, reasonably because of the expansion of the indications for PN.[21] Our data showed an increased risk of recurrence of RCC in the presence of PSMs, both at distant sites and, even more, as relapses in the operated kidney. This involves that the follow-up schedule after PSMs should include both abdominal and extra-abdominal— definitely chest—imaging examinations. In addition, the higher number of local recurrences after PSMs confirms that a new tumor could grow when malignant cells are left on the resection bed, as recently shown by a study that reviewed the pathologic findings at salvage nephrectomy for a relapse after PN.[22] It must therefore be noted that any effort to achieve the complete removal of the tumor at the time of PN should be done. Of note, the median time of recurrence in our cohort was approximately 3 years, but occurred within a maximum of 8 years, suggesting that the follow-up in the case of PSMs might be prolonged. Finally, we found that in case of recurrences suitable for surgical treatment, a significant number of cases achieved long-term control of the disease: this corroborates the utility of controls after PN in order to allow an early diagnosis of recurrence.

The complete removal of the tumor is an obvious primary goal of oncologic surgery, but differently from other fields in which PSMs have a definite prognostic role and, in turn, specific management[23,24]; only a little is known about the real harm related to PSMs after PN. International guidelines often neglect this issue[3] or broadly suggest an "intense surveillance," without providing further details.[2] The results from existing studies on the prognostic role of PSMs are conflicting. Furthermore, considering that RCC, especially when poorly aggressive, as in a consistent number of the cases undergoing PN, could progress at a long distance,[15] the majority of studies are based on a potentially insufficient follow-up time.[20] Khalifeh et al,[25] in a large retrospective multicenter series of patients who underwent robot-assisted PN at a median time of 13 months, showed that PSMs were associated with a higher risk of local recurrence and metastasis with a hazard ratio of 18.4 ($P < .01$) and 78.0 ($P = .02$), respectively. Bansal et al,[26] in a large population study with a median follow-up of 15 months, reported that PSMs were associated with a higher risk of progression. Shah et al[13] reported on a multicentric cohort with a median follow-up time of 33 months and concluded that PSMs were predictive of recurrence-free survival, but only for high-risk tumors (high grading, pT3). Shum et al,[27] in a large matched comparison analysis based on the National Cancer Database, found a significant worse overall survival in the PSM group (hazard ratio, 1.393; $P = .001$).

On the other hand, the results from several other studies undermined the prognostic significance of PSMs. In a large multicenter study[28] with a median follow-up time of 37 months, PSMs were associated with a higher risk of local recurrence but not with impaired cancer-specific survival at 5 years. Kang et al,[29] in a nationwide study on a homogenous cohort of pT1 clear cell RCC, largely low-grade, followed for a median time of 32 months, reported no differences in PFS.

As highlighted above, there is no consensus on the oncologic impact of surgical margins. It must be underlined that most studies are multicentric and therefore suffer from a significant bias related to the variability of margins assessment and lack of central review of specimens. Second, the longest follow-up times so far reported are very close to the median value of the latency we observed, having the advantage of a cohort followed for a significantly longer time: it could be hypothesized that a certain number of events of recurrence were missed without a prolonged control. Finally, multicentric studies cannot adequately report data on resection technique that could influence the risk of PSMs. Wang et al[30] analyzed 117 tumors removed by simple enucleation or standard PN and found that the first had a higher rate of PSMs (17% vs. 0%). Takagi et al[31] instead reported that the 2 resection techniques lead to similar PSMs. Only with the diffuse application of a systematic nomenclature, as suggested by the Surface-Intermediate-Base score,[32] a proper comparison could be done.

Our study has several limitations to be declared, starting from the retrospective design. The exclusion of the patients still without a minimal follow-up of 5 years may have led to unexpected selection biases. Even if only 2 expert uro-pathologists were involved, a slide review could have added some information, such as the extent of margin involvement in the case of PSMs. The utility of frozen sections to protect from PSMs could not have been estimated because this data was not separately recorded.

Conclusion

A PSM is an independent predictor of PFS in patients submitted to PN for RCC owing to a higher rate of local relapses of disease and distant metastasis. Until conclusive evidence is able to reveal the best management of patients with PSMs, a tailored intense and prolonged follow-up is mandatory to allow early diagnosis of relapse and its surgical resection.

Clinical Practice Points

- The role of surgical margin status after PN for RCC is still debated and no strong conclusions are available.
- In our study, with a long-term follow-up, we managed to demonstrate the negative prognostic role of PSMs in predicting disease recurrence.
- These findings suggest an intense follow-up in patients with PSMs after conservative surgery for kidney tumors in consideration of the increased risk of disease recurrence.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2018.08.004.

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Supplemental Table 1 Features of Patients With Disease Recurrence After PN for RCC

Patient No.	Site of Recurrence	Time to Recurrence, mo	Primary Tumor Features	Treatment of Recurrence
1	Operated kidney + surgical incision	11	ccRCC G3 pT3a	Surgery (RN)
2	Operated kidney	23	ccRCC G3 pT1a	Surgery (RN)
3	Operated kidney	40	ccRCC G4 pT1a	Surgery (RN)
4	Operated kidney	96	pRCC pT1b	Surgery (RN)
5	Operated kidney	18	ccRCC G4 pT3a	Surgery (RN)
6	Operated kidney	13	ccRCC G3 pT1a	Surgery (RN)
7	Operated kidney + operated renal fossa	37	ccRCC G4 (sarcomatoid features) pT3a	Best supportive care
8	Operated kidney	34	ccRCC G2 pT1a	Surgery (RN)
9	Operated kidney	42	ccRCC G3 pT1a	Surgery (RN)
10	Operated kidney	49	ccRCC G3 pT1a	Surgery (RN)
11	Operated kidney + operated renal fossa	51	ccRCC G3-4 pT1b	Surgery (RN)
12	Operated kidney	34	pRCC pT1a	Surgery (RN)
13	Operated kidney + Lung	50	ccRCC G3 pT1b	Medical therapy
14	Operated kidney	74	ccRCC G2 pT1a	Surgery (RN)
15	Operated kidney	9	ccRCC G3 pT1b	Medical therapy
16	Operated kidney	101	chRCC pT1a	Surgery (RN)
17	Operated kidney	50	ccRCC G3 pT1a	Surgery (partial nephrectomy)
18	Operated kidney	96	ccRCC G2 pT1b	Surgery (RN)
19	Operated kidney	52	pRCC pT1a	Surgery (RN)
20	Operated kidney	50	ccRCC G2 pT1a	Surgery (partial nephrectomy)
21	Operated kidney	116	ccRCC G3 pT1a	Surgery (RN)
22	Pancreas	45	ccRCC G3 pT1a	Surgery (metastasectomy)
23	Lung	50	pRCC	Surgery (metastasectomy)
24	Liver	29	ccRCC G3 pT1b	Surgery (metastasectomy)
25	Lung	48	ccRCC G2 pT1a	Medical therapy
26	Lung	32	ccRCC G3/4 pT1b	Medical therapy
27	Bones	12	ccRCC G4 pT3a	Best supportive care
28	Lung	65	ccRCC G3 pT1a	Surgery (metastasectomy)
29	Lung	83	pRCC	Medical therapy
30	Bones	36	ccRCC G2 pT1a	Medical therapy
31	Lung	78	ccRCC G3 pT1b	Medical therapy
32	Brain	8	ccRCC G3 pT1a	Medical therapy
33	Contralateral adrenal gland	101	ccRCC G2 pT1a	Surgery (metastasectomy)
34	Pancreas	35	ccRCC G2 pT1a	Surgery (metastasectomy)
35	Bones	10	pRCC G3 pT1b	Best supportive care
36	Lung	47	ccRCC G2 pT1a	Surgery (metastasectomy)

Abbreviations: ccRCC = Clear-cell renal cell carcinoma; pRCC = papillary renal cell carcinoma; PSM = positive surgical margin; RCC = renal cell carcinoma; RN = radical nephrectomy.