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Positive surgical margins in nephron-sparing surgery: risk factors and therapeutic consequences

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Abstract

The increased use of nephron-sparing surgery to treat localized renal cell carcinoma (RCC) lends weight to the question of the value of microscopically positive surgical margins (PSM) in cases with a tumor bed macroscopically free of residual tumor. The aim of this article is to highlight the data available on risk factors for PSM, their clinical relevance, and possible therapeutic consequences. For this purpose, publications on the incidence and relevance of PSM after partial nephrectomy from the last 15 years were examined and evaluated. We summarize that PSM are generally rare, regardless of the surgical procedure, and are seen more often in connection with an imperative indication for nephron-sparing surgery as well as a central tumor location. Most studies describe that PSM lead to a moderate increase in the rate of local relapses, but no study has thus far been able to demonstrate an association with shorter tumor-specific overall survival. Intraoperative frozen section analysis had no positive influence on the risk of definite PSM in most trials. Therefore, we conclude that PSM should definitely be avoided. However, in cases with a macroscopically tumor-free intraoperative resection bed, they should lead to close surveillance of the affected kidney and not to immediate (re)intervention.

Keywords: Renal cell carcinoma, Positive surgical margins, Therapeutic relevance, R1, Prognosis, Survival review

Introduction

In recent years, organ-sparing surgery for renal tumors in terms of partial nephrectomy or tumor enucleation has replaced radical nephrectomy as the standard procedure for treating locally confined renal cell carcinoma (RCC) [1-8]. This change of therapy is based primarily on findings indicating that organ-sparing surgery offers the potential for better preservation of renal function and a lower risk of cardiovascular sequelae [9-15]. Oncological outcomes appear to be equivalent [3,16-20], and perioperative morbidity seems to be only minimally higher for nephron-sparing interventions [3,21,22]. Just like radical nephrectomy, partial nephrectomy should always aim at complete tumor resection. The width of the normal tissue margin or safety margin around the tumor appears to be of no relevance here [1,23,24], but the increased frequency of partial nephrectomies and tumor enucleations has shown that a limited percentage of surgical specimens (between 0 and 7%) have tumor cells in the margin (positive surgical margins, PSM) in the final histopathologic evaluation (Figure 1) [25-27].

However, no prospective and/or randomized study has yet been performed to investigate the prognostic significance of histopathologically positive but intraoperative macroscopically tumor-free surgical margins in predicting the risk of local relapse, metachronous metastases, and tumor-specific survival; only one nonsystematic review has been published thus far [25]. Moreover, most studies had a follow-up of less than five years. This article gives a brief review of currently available data on risk factors for PSM and their potential clinical relevance.

Review

Risk factors for positive surgical margins: surgical technique

According to various studies, the incidence of PSM at final pathology is between 0 and 7% for open surgery [28-37], 1 to 4% for laparoscopic interventions [32-34,38-46], and 4 to 6% [47-49] for robot-assisted surgery. Thus, with appropriate experience and careful patient selection with respect to the optimal surgical approach, PSM rates do not

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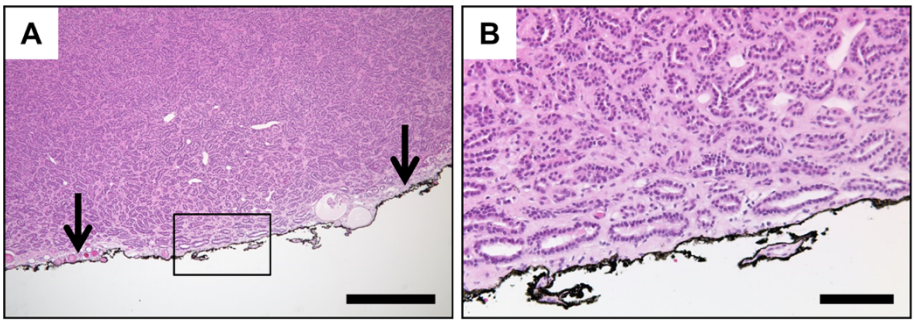

Figure 1 Representative microphotographs of positive surgical margin (PSM) in final histopathologic examination. A, overview shows densely packed papillary and tubular structures closely approaching the inked surgical margin (arrows). **B**, higher magnification of the marked region in **A** confirms neoplastic tubules reaching the inked surgical margin. Staining: hematoxylin-eosin; scale bar in **A**: 500 μm; scale bar in **B**: 100 μm.

appear to differ significantly between surgical procedures [32-34,38,49,50].

Data from smaller studies suggest that enucleation along the plane of the tumor pseudocapsule may be superior to classic partial nephrectomy with regard to the incidence of PSM. Verze *et al.* [51] retrospectively compared pathological results in cT1 RCC patients after partial nephrectomy (n = 309) and tumor enucleation (n = 226). PSM rates were 6.7% and 1.3% (P = 0.01). Multivariate analysis also revealed a nearly five times higher risk of PSM after classic partial nephrectomy (P = 0.04). Minervini *et al.* [52] compared pathological results as well as oncological outcomes in RCC patients after partial nephrectomy (n = 982) and tumor enucleation (n = 537) at 16 medical centers. With a median follow-up of approximately four and a half years, the five-year progression-free survival (88.9 versus 91.4%) and tumor-specific survival (93.9 versus 94.3%) did not differ significantly between the two groups, although here too the PSM rate was higher after classic partial nephrectomy (3.4 versus 0.2%).

Indication

Patients with an imperative indication for nephron-sparing surgery (such as preexisting renal insufficiency, or a functional or anatomical single kidney) have a higher incidence of larger and more unfavorably located tumors than the total patient population. This explains why an imperative indication could be identified as a risk factor for PSM in nearly all studies, at least by univariate analysis. PSM rates of 9 to 28% are described here [5,53-55]. Using multivariate analysis, Bensalah *et al.* [56] also identified an imperative indication (in addition to tumor location) as an independent risk factor for PSM at final pathology (hazard ratio (HR) 14.3, 95% confidence interval (CI) 1.6 to 21.2; P = 0.02).

Tumor-specific risk factors

According to a study by Kwon *et al.* [29] in 770 patients who underwent open surgery, the PSM rate appears to be unrelated to the histopathological subtype and possibly also the differentiation of RCC. PSM were seen in 33 out of 423 (8%) of all patients with tumors of high malignant potential, and in 24 out of 347 (7%) patients with well-differentiated tumors. In contrast to these findings, Bensalah *et al.* [56] reported a higher incidence of PSM in patients with poorly differentiated carcinomas.

It is still controversial whether tumor size has an impact on the PSM rate. While various research groups were unable to demonstrate a correlation [28,43], others found higher PSM rates mainly in smaller RCC [57,58]. Using uni- and multivariate analysis, Yossepowitch *et al.* [57], for example, showed that small tumors are associated more often with PSM but less often with local relapses. It can only be speculated why PSM have been found more often in smaller renal tumors. Possible explanations include the more frequent lack of a pseudocapsule as well as technical inadvertencies during surgical resection or specimen preparation [25]. On the other hand, according to Peycelon *et al.* [5] the PSM rate in very large tumors (more than 7 cm) seems to be rising again. Ani *et al.* [59] have also recently published a study showing a higher PSM rate in patients with larger tumors or a more advanced pathological stage.

It cannot yet be conclusively clarified whether tumor location within the kidney can influence the PSM rate, since none of the published studies included a reproducible nephrometry scoring system. However, available data suggest that PSM is observed more frequently after resection of centrally located tumors [46,56]. Bensalah *et al.* [56] evaluated 111 patients with and 664 patients without PSM and found positive margins in 26% of all centrally located tumors, but only in 9.1% of all peripherally located tumors (P < 0.001).

Role of intraoperative frozen section analysis

Intraoperative frozen section analysis (FSA) to ensure tumor-free surgical margins is performed frequently and may reduce the rate of PSM, at least in some patient subgroups in laparoscopic surgery (clear cell/papillary subtypes, upper/mid-pole tumors, exophytic/endophytic tumors, pT1a/pT1 tumors, and tumors with histologic differentiation (Fuhrman) grades 1 to 2 and 2 tumors) [60]. However, in the same study, it has also been shown that there is no impact of FSA on patient outcomes except an improved recurrence-free survival in patients with pT1 or exophytic renal cell carcinoma upon laparoscopic surgery, and no effect on tumor recurrence after open surgery. Accordingly, several other studies confirmed that in contrast to individual macroscopic assessment of the tumor bed by the surgeon, intraoperative FSA seems to contribute no decisive information and fails to predict final margin status in cases with a macroscopically tumor-free resection bed [25,61-65]. Palermo *et al*. proposed quick-staining cytology as an alternative to FSA in a recent publication and showed a good level of agreement with final histologic examination ($\kappa = 0.751$; $P < 0.0001$) [62].

Impact of positive surgical margins on local relapses and tumor-specific survival

It has not yet been conclusively clarified whether PSM increase the risk of local relapses after partial nephrectomy, even though the majority of studies suggest that this is probably the case [5,29,35,56,66]. An overview of published survival analyses is provided in Table 1. Bernhard *et al*. [35] found 26 (3.2%) local relapses in a group of 809 partially nephrectomized patients during a median follow-up of 27 months. In the univariate analysis, the following correlated with local relapse: advanced tumor stage (pT3a), a tumor size greater than 4 cm, imperative indication, bilateral tumors, poor differentiation (Fuhrman histologic differentiation grade of more than 2), and PSM. Bilateral tumors (HR 6.3), tumor size greater than 4 cm (HR 4.6), and especially PSM (HR 11.5) also proved to be independent predictors of ipsilateral relapse. Khalifeh *et al*. [66] even described an 18.4 times higher risk of tumor relapse in 943 patients with a PSM rate of 2.2% after robot-assisted surgery. Kwon *et al*. [29] showed that, in their patient population (n = 770 with 57 (7%) cases of PSM), local relapses only occurred in PSM cases of high-grade malignant tumors.

Bensalah *et al*. [56] evaluated 111 patients with PSM from various medical centers and established a correlation between PSM and tumor relapse. Time to progression was also shorter in the PSM group (21.4 versus 24.7 months). However, when performing a subsequent matched-pair analysis (n = 101 patients with and n = 102 without PSM), the authors no longer found a significant difference in relapse-free survival ($P = 0.11$) or tumor-specific overall survival ($P = 0.4$). Using multivariate analysis, an imperative indication for partial renal resection (HR 14.3; 95% CI 1.6 to 21.2) and a central tumor location (HR 1.2; 95% CI 1.06 to 1.8) proved to be independent risk factors for tumor relapse, but not PSM at final pathology [56].

Table 1 Published hazard ratios (HR) for positive surgical margins in nephron-sparing surgery

Reference number	Number of cases	HR (recurrence)	HR (OS)	HR (CSS)
[5]	PSM: 22	Not reported	Not reported	Not significant
	NSM: 100			
[68]	PSM: 14	Not reported	Not reported	3.45 (95% CI: 1.79-6.67)
	NSM: 1787			
[67]	PSM: 13	Not reported	Not reported	2.08 (95% CI: 0.84-5.17)
	NSM: 155			
[59]	PSM: 71	Not reported	1.1 (95% CI: 0.66-1.94)	Not significant
	NSM: 587			
[66]	PSM: 21	18.4 (95% CI: 2.27-110.8)	Not reported	Not reported
	NSM: 922			
[57]	PSM: 77	1 (95% CI: 0.23-4.3)	Not reported	Not reported
	NSM: 1313			
[35]	PSM: 12	11.5 (95% CI: 4.66-45.1)	Not reported	Not reported
	NSM: 768			
[56]	PSM: 101	Not significant	Not significant	Not significant
	NSM: 102			

CI, confidence interval; CSS, cancer-specific survival; HR, hazard ratio; NSM, negative surgical margins; OS, overall survival; PSM, positive surgical margins.

In another large study published by Yossepowitch *et al.* [57], 77 out of 1344 (5.7%) patients had PSM; the median follow-up was 3.4 years. In that study too, the risk of local relapse did not differ between patients with or without PSM: five-year rates for freedom from local relapse were 98% and 97%, respectively ($P = 0.97$). Multivariate analysis revealed that, unlike tumor size, PSM was not a risk factor for local relapse (HR 1.0; 95% CI 0.23 to 4.3) or metachronous metastases (HR 1.6; 95% CI 0.6 to 4.1).

A study by Marszalek *et al.* [33] with a median follow-up of 70.7 months showed that, in contrast to tumor size and differentiation, the factor PSM does not predict RCC relapse or overall survival.

In a large study recently published by Ani *et al.* [59], 71 of 664 (10.7%) Canadian patients analyzed retrospectively showed PSM (follow-up of 7.9 years). In that study, the tumor-specific five-year survival rate was 90.9% for patients with PSM and 91.9% for those without PSM ($P = 0.58$). Multivariate analysis also failed to identify PSM status as an independent predictor of cancer-specific survival (HR 1.1; 95% CI 0.66 to 1.94). Thus, microscopic PSM does not appear to significantly influence tumor-specific survival [5,25,33,41,56,57,67]. It has to be noted that in 2002, Frank *et al.* reported a HR of 3.45 (95% CI: 1.79 to 6.67) for cancer-specific survival in patients with PSM; however, one limitation of that study was the small number of PSM cases (n = 14) compared to total cohort size (n = 1801) [68].

Conclusions

PSM should definitely be avoided even if a certain safety margin is no longer required in nephron-sparing surgery for renal tumors [25,35]. However, PSM are apparently associated only with an\slightly increased risk of local relapse [33] and are seen especially in RCC that are large [5], poorly differentiated [29,56], and/or more centrally located [25,56]. On the other hand, no definite impact on tumor-specific overall survival has as yet been demonstrated [5,25,33,41,56,57]. Moreover, a number of studies have already shown that the renal remnant contained a residual tumor in only 0 to 39% of patients with PSM who underwent prophylactic secondary nephrectomy [25,41,56,58,69,70]. Consequently, a surveillance strategy rather than a reoperation (repeat resection, completion nephrectomy, or a minimally invasive ablation technique) is now recommended for patients with PSM at final pathology [25,69].

Abbreviations

CI: confidence interval; CSS: cancer-specific survival; FSA: frozen section analysis; HR: hazard ratio; NSM: negative surgical margins; OS: overall survival; PSM: positive surgical margins; RCC: renal cell carcinoma; (p)T: (pathological) tumor stage.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JS and AJS participated in the design of this review. JS, SS and AJS reviewed literature on PSM risk factors, impact of PSM on local relapses and overall survival. KS reviewed literature on pathologic PSM risk factors and the role of intraoperative frozen section analysis. All authors read and approved the final manuscript.

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