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KIDNEY DISEASES (G CIANCIO, SECTION EDITOR)

Surgical Margins in Nephron-Sparing Surgery for Renal Cell Carcinoma

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Abstract The oncologic impact of positive surgical margins after nephron-sparing surgery is controversial. Herein, we discuss current data surrounding surgical margins in the operative management of renal cell carcinoma. The prevalence, risk factors, outcomes, and subsequent management of positive surgical margins will be reviewed. Literature suggests that the prevalence of positive surgical margins following kidney surgery varies by practice setting, tumor characteristics, and operation type. For patients undergoing nephron-sparing surgery, it is not necessary to remove a margin of healthy tissue. Tumor enucleation may be appropriate and is associated with comparable outcomes. Reflexive intraoperative frozen section use does not provide beneficial information and many patients with positive margins can be monitored closely with serial imaging. The impact of positive surgical margins on recurrence and survival remains conflicting. Though every effort must be performed to obtain negative margins, a positive surgical margin appears to have a marginal impact on recurrence and survival.

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Introduction

Renal cancers, particularly small renal masses (SRM), are increasing in incidence, especially among female and younger patients [1]. For many patients with kidney cancer, surgical removal of their tumor represents the best opportunity for cure. However, the operative management of kidney cancer patients has evolved significantly since the days of Robson's radical nephrectomy (RN). Notably, in the USA, the rising incidence of SRM has paralleled the broad adoption of nephron-sparing and minimally invasive approaches for kidney surgery. Furthermore, based on survival benefits of cytoreductive nephrectomy prior to targeted or immunotherapy, patients are continuing to undergo major resections of locally advanced and metastatic renal cell carcinoma (RCC).

As the paradigm shifts for the management of renal cancer patients, there is greater concern regarding positive surgical margins (PSM) following resection of RCC. With nephron-sparing surgery (NSS), there is an increased likelihood of leaving residual cancer in the remaining kidney. Both the surgical trifecta reported by Hung et al. and the MIC reporting system used in Europe incorporate PSM as a quality metric for patients treated with partial nephrectomy (PN) [2–4]. Furthermore, the unique propensity of RCC for venous invasion places patients at risk of residual disease at venous or caval margins.

In this review, we will discuss the prevalence of PSM across different tumor stages and types of operations. Then, we will review outcomes associated with PSM and the current debate on strategies aimed at minimizing the risk of PSM

during NSS. Finally, we will discuss the management for patients with residual disease following excision of their renal tumors.

Epidemiology of RCC and Contemporary Surgical Management

The incidence of SRMs has been increasing over the past 20 years, likely related to the rising utilization of cross-sectional imaging and subsequent incidental diagnoses of renal tumors [5]. In parallel with these trends, the landscape of surgery for these tumors has shifted away from open radical extirpation towards minimally invasive and often nephron-sparing procedures, frequently utilizing laparoscopic or robotic assistance. However, in the background of the increasing incidence and treatment of SRMs, there are still many patients who present with locally advanced or metastatic RCC. Accordingly, performance of RN with caval thrombectomy has persisted for patients with clinical T3b renal tumors; nearly 1600 patients treated with this procedure were captured in the National Cancer Database (NCDB) from 2008 through 2009 [6].

Defining Appropriate Surgical Margin Width in NSS

A distance of 10 mm has historically been accepted as an appropriate surgical margin during nephron-sparing resections [7]. Recently, this practice has been challenged with reports of unchanged local cancer recurrence outcomes with smaller surgical margins. In fact, data from a number of studies suggest that surgical margin width is not independently predictive of cancer progression, although the goal of complete tumor resection should still remain paramount [8–13].

Efforts to define appropriate renal surgical margin parameters for minimizing the risk of PSM may also be benefited by analysis of recurrences reported in cases of negative surgical margins (NSM) at the time of NSS [14, 15]. A German study of 126 patients with NSM after NSS noted that all of the nine patients who experienced oncologic recurrence had resection margins <1 mm, while 0/49 patients with surgical resection margin >1 mm developed recurrence. Based on this data, the researchers ultimately concluded that surgical resection margin <1 mm led to an increased risk of recurrence, but did not impact overall survival (OS) or cancer-specific survival (CSS) [16]. There are a number of possible explanations for oncologic recurrence in the setting of NSM. These include the growth of a new primary tumor, as well as undetected malignancy at the edge of resection of the pathologic specimen (false NSM). Alternatively, there may be small nests of malignant tissue resting outside of the perceived tumor boundaries defined at the time of surgery. This latter finding is highlighted by the work of Chen et al., who described focal areas of malignancy extending up to 3 mm outside the tumor pseudocapsule in 39% of T1b renal tumors [17]. Overall, these results may indicate that excess surgical margin width is likely less important than the focus on removing all discernible tumor at the time of surgery.

PSM Following Surgery for RCC

For any patient undergoing surgery for RCC, the risk of PSM is tied to both the nature of the tumor itself as well as the surgical approach. For instance, patients with SRMs treated with NSS are inherently at higher risk of PSM compared to those who undergo RN. Furthermore, non-extirpative procedures like cryoablation and radiofrequency ablation place patients at risk for harboring residual tumor in the treatment bed, as ablated tissue remains in situ rather than being extracted. In this section, we will review the individualized risk of PSM based on a variety of factors, including type of operation and surgical approach.

Risk of PSM After Extirpative NSS

Since NSS has gained traction as an appropriate surgical treatment for patients with small renal tumors, the incidence and implications of PSM have come into greater focus. Herein, we will review the reported rates of PSM with their associated risk factors.

Depending on the practice setting, patient population, and surgical approach, reports from the past 4 years describe the prevalence of PSM after NSS to be as low as 0.1% (at a high-volume tertiary center with a world-renowned surgeon) to as high as 10.7% within a population-based cancer registry in Canada (see Table 1) [3, 4, 13, 15, 18, 19••, 20, 21••, 22–25, 26••, 27]. Data from cancer registries can provide a "real-world" snapshot of surgical outcomes across a diverse array of practice settings and patient populations. Ani et al. evaluated the prevalence of PSM among patients captured by the Ontario Cancer Registry from 1995 to 2004. Overall, final pathology demonstrated PSM in 10.7% of 664 patients for whom pathology reports were available. Notably, 16% of the entire cohort had renal tumors >4 cm, and analysis showed that higher tumor stage was associated with an increased risk for PSM [18]. Another cohort of 6038 patients who underwent NSS between 2003 and 2006 was catalogued by the NCDB and found to have 5.3% prevalence of PSM [26••]. More recently, Tabayoyong et al. showed that among 11,587 patients with a T1a renal mass treated with PN, the prevalence of PSM was 7.0% [24].

With a continued shift towards minimally invasive approaches for many cancer operations, understanding the

Table 1 Incidence of positive surgical margins after nephron-sparing surgery (2013–present)

Reference	Publication year	Study type	Study inclusion period	# of patients	Surgical approach	Tumor stage	PSM	Study commentary
Kang et al.	2016	Multiple center, retrospective	1999–2011	1831	OPN/LPN/RPN	T1	31 (1.7%)	Risk of PSM is not associated with any perioperative factors for pT1 disease, including tumor size and location. No significant difference in RFS in patients with PSM compared to those with NSM (recurrence rate 2.1% for NSM and 3.2% for PSM, $p = 0.492$)
Maurice et al.	2016	Population-based	2003–2006	6038	PN	T1-T3a	302 (5.3%)	Uses NCDB. Higher T stage, comorbidity (CCI) and age are associated with increased PSM. Decreased 5-year OS with PSM (91%) vs NSM (94%) for CCI <1 (p 0.0027), no CSS reported
Shah et al.	2016	Multiple center, Retrospective	2006–2013	1240	OPN/LPN/RPN	T1-T2	97 (7.8%)	PSM correlated with increased risk of tumor recurrence in high-risk disease (pT2-3a or Fuhrman grades III-IV)—45% at 5 years ($p < 0.001$)—but not low-risk disease (pT1 or Fuhrman grades I-II)
Antic T and Taxy JB	2015	Multiple center, retrospective	2006–2012	339	RPN	T1	22 (6.5%)	Increasing proportion of PSM with increasing tumor complexity. No correlation between oncologic recurrence and PSM
Tabayoyong et al.	2015	Population-based (NCDB)	2010–2011	11,587	OPN/LPN/RPN	T1a	Overall: 806/11,587 (7%) OPN: 4.9% LPN: 8.1% RPN: 8.7%	Study population: OPN (44%), LPN (14%), RPN (42%). LPN and RPN had higher adjusted risk of PSM when compared to OPN (OR 1.81 vs. 1.79, respectively). Also, increased risk of PSM at academic centers
Lista et al.	2015	Multiple center, prospective	2006–2012	339	RPN	cT1	22 (6.5%)	Describes MIC Criteria in 339 RPN patients
Minervini et al.	2015	Single center, prospective	2010–2013	130	ERASE/ LTE	T1a-T2a	LTE: 1.8% vs. ERASE: 2.2% ($p = 0.45$)	Compared endoscopic robot-assisted simple enucleation and laparoscopic simple enucleation: subgroup analysis for cT1a renal tumors ($n = 101$). Showed comparable PSM rates using ERASE with less warm ischemia time, estimated blood loss and hospital length of stay. No difference in PSM with LTE vs ERASE ($p = 0.45$)
Satkunasivam et al.	2015	Single center	2009–2013	179	RPN	T1-T4	2 (1.1%)	Describes experience with robotic unclamped minimal-margin partial nephrectomy (group 3) vs superselective clamping (group 1—less experienced surgeon vs group 2—more experienced surgeon) with low rates of PSM ($n = 0$ in group 3)
Longo et al.	2014	Multiple center, respective	2009–2011	396	PN(OPN/LPN)/TE	T1	TE: 1.4% vs PN 6.9% ($p = 0.02$)	Compares PN to TE for T1 tumors, showed 4.7 fold decreased risk of PSM with TE compared to PN
Ani et al.	2013	Population-based	1995–2004	664	OPN/LPN	T1-T2	71 (10.7%)	PSM is more common with higher tumor stage, larger tumors, and in academic centers. Five-year DSS and OS survival rates for PSM (91.9 and 88.6%) vs NSM (90.9 and 84.4%), PSM is not an independent predictor of mortality on multivariate analysis
Hillyer et al.	2013	Multiple center, retrospective	2007–2012	26	RPN	T1	1 (3.8%)	Study population: 26 solitary kidney patients who underwent RPN; 1/26 with PSM at time of surgery also developed recurrence within 1 year of surgery
Khalifeh et al. (1)	2013	Single center, retrospective	2002–2012	492	LPN/RPN	T1-T2	LPN: 13 (5.6%) RPN: 8 (2.9%)	Study population: RPN = 261 vs LPN = 231. Lower rates of PSM associated with robotic approach

Table 1 (continued)

Reference	Publication year	Study type	Study inclusion period	# of patients	Surgical approach	Tumor stage	PSM	Study commentary
Khalifeh et al. (2)	2013	Multiple center, prospective	2007–2012	943	RPN	T1-T2	For malignant disease: 21 (2.8%)	Significantly higher risk of tumor recurrence and metastasis with PSM (18.4-fold higher HR for tumor recurrence when adjusted for tumor size and pathologic stage). Local recurrence seen in 2/21 with PSM vs 7/922 with NSM. PSM with lower 3-year cancer-free survival (47.0 vs 98.3%, $p < 0.001$). Metastatic disease detected in 2/21 with PSM vs 2/922 with NSM. PSM with lower 3-year metastasis-free survival (63.0 vs 99.5%, $p < 0.001$). Tumor stage ≥pT2 carries a 3.7-fold higher HR for tumor recurrence and 10.7 higher HR for metastasis
Porpiglia et al.	2013	Single center, prospective	2001–2012	206	LPN	T1-T2	6 (2.6%)	PSM not correlated with learning curve or tumor complexity

PN partial nephrectomy, *OPN* open partial nephrectomy, *LPN* laparoscopic partial nephrectomy, *RPN* robotic partial nephrectomy, *TE* tumor enucleation, *LTE* laparoscopic tumor enucleation, *ERASE* endoscopic robot-assisted simple enucleation, *PSM* positive surgical margins, *NSM* negative surgical margins, *RFS* recurrence-free survival, *OS* overall survival, *DSS* disease-specific survival, *HR* hazard ratio, *CCI* Charlson comorbidity index

impact of laparoscopic and robotic-assisted laparoscopic techniques for PN is also critical. In the largest population-level assessment to date, the prevalence of PSM among patients with T1a renal tumors varied significantly based on surgical approach. Specifically, PSMs were more common among patients treated with robotic-assisted (8.7%) and pure laparoscopic PN (8.2%), compared to open PN (4.9%, $p < 0.001$) [24]. Additional review of the literature also supports different rates of PSM with open (0–7%), laparoscopic (1–4%), and robotic PN (4–6%) cases [28]. Among patients treated with minimally invasive surgery, other data from a recent single-center study has reported decreased prevalence of PSM associated with robotic-assisted laparoscopic PN (2.9%) compared to those treated with pure laparoscopic PN (5.6%) [25]. Collectively, these findings represent a change from data reported by previous institutional studies that showed no significant difference in PSM prevalence based on surgical approach among patients treated with PN [29, 30••, 31, 32].

In addition to surgical approach, a number of other factors have been shown to influence the likelihood of PSM in NSS. These include higher rates of PSM in masses closely approximating the renal hilum and those in a more central location within the renal parenchyma [33, 34]. Such tumor characteristics plausibly increase the difficulty of complete renal mass extirpation using a nephron-sparing surgical approach. For truly central masses lying directly on arborizing vasculature, the distance between the tumor and the main segmental vessels of the kidney may be far less than 1 mm. Ani et al. also showed an increased likelihood of PSM with higher tumor stage (including perinephric fat involvement) as well as with larger masses [18]. Berdjis et al. found a correlation with disease progression after NSS and tumor size in a study of 121 patients with localized RCC [12]. Still other studies show that there is no correlation with tumor size and location with PSM in pT1 renal masses [19••, 35, 36]. Yossepowitch et al., of note, reported that smaller tumor size was actually associated with higher rates of PSM compared to larger tumors [37]. Others have also supported this finding, citing that smaller renal masses may present more difficulty with adequate assessment of tumor extent and have less well-defined tumor border delineation leading to higher rates of PSM [38, 39]. Finally, additional data suggests an increased risk of PSM with surgeries performed for imperative indications (possibly associated with less desirable tumor characteristics, positions, and size parameters than in surgeries performed on a more elective basis) and a correlation with increasing PSM and less surgeon operative experience [33, 39–41].

Risk of PSM After Tumor Enucleation

In the advent of excisional nephron-sparing surgical approaches, alternative techniques for managing localized renal masses have also been developed. Tumor enucleation (TE)

involves the cleavage of the natural tissue plane that often develops adjacent to the pseudocapsule of renal tumors as they grow. Removal of tumors with this approach appears to provide similar rates of PSM and oncologic outcomes as traditional NSS with PN that incorporates a larger rim of benign tissue as a margin.

Several studies have examined the histopathologic features of the renal tumor pseudocapsule, a thin rim of tissue (typically less than 2.5 mm wide) that develops at the periphery of many renal masses [42–44]. Microscopically, this tissue often exhibits interstitial fibrosis (with associated collagen deposition, glomerulo- and arteriosclerosis) while demonstrating evidence of tumor infiltration in 43% (53/119) of cases according to a recent analysis by Azhar and colleagues [44]. Minervini et al. showed that, even in such cases of pseudocapsular tumor infiltration, the associated rind of inflammatory tissue existing at the border of the normal renal parenchyma prevented significant outward tumor extension thus allowing for achievement NSM in all patients ($n = 90$) undergoing TE in their cohort [43]. Consistent with these findings, another study reported comparable progression-free survival and CSS with a low, yet statistically significant decrease in rates of PSM with TE compared to PN (0.2 vs 3.4%, respectively; $p < 0.0001$). Findings from this work were confirmed in a second analysis in 2014 [45, 46].

In terms of oncologic outcomes with TE, Carini et al. showed no PSM and acceptable CSS (5 year, 96.7% vs 10 year, 94.7%) for 232 patients with pT1a renal tumors treated with TE [47]. In a separate series of renal tumors 4–7 cm in size, the same group reported 5-year CSS with TE for pT1a, pT1b, and pT3a tumors to be 95.7, 83.3, and 58.3% [48]. More recently, the Endoscopic Robot-assisted Simple Enucleation (ERASE) trial has shown safety and efficacy in performing robot-assisted tumor enucleation for cT1a renal tumors, again with no significant difference in rates of PSM compared to traditional laparoscopic TE for cT1a renal tumors (2.2 vs 1.8%, $p = 0.45$) [27].

Despite the lack of randomized control prospective studies to evaluate the comparative efficacy of TE as a nephron-sparing surgical alternative to PN, results of multiple smaller prospective and retrospective series indicate that the rates of oncologic recurrence, CSS, and PSM may be acceptably similar. The demonstrated effectiveness of TE for management of RCC again highlights the concept that surgical margin width can be minimal while still achieving good oncologic control rates.

Risk of PSM During Operation for Advanced Kidney Cancer Patients

Patients who have large, more advanced renal tumors are at risk of having venous involvement, either limited to the renal vein or into the inferior vena cava (IVC). Thus, these venous margins are a potential site for PSM, either related to invasive tumor incorporated into the venous wall or as a free thrombus within the vessel lumen (see Fig. 1). Positive venous margins are common following surgical removal of renal masses of clinical stage T3 or greater, and selected studies have reported positive venous margins in 18–32% of these cases [49–51]. Some of these reported positive margins may be artifacts of specimen processing in pathology.

Risk of Oncologic Progression with PSM After Surgical Resection of RCC

The goal of NSS remains to achieve sustainable oncologic control through complete tumor excision while minimizing the removal adjacent uninvolved renal tissue. Efforts to define the ideal amount of tissue to achieve this balance have lead to debate regarding the oncologic risk of residual tumor at the surgical margin after renal-sparing resection. This section seeks to address the recent data regarding PSM for RCC and the risk of local and metastatic tumor progression. Even in recent literature, controversy still exists surrounding the association of PSM after NSS and future cancer progression.

A number of studies to date have shown no definitive correlation between PSM and tumor progression after surgery. In 2015, Antic and Taxy analyzed 406 RCC patients who underwent PN, finding that, of the 61 patients who had PSM, only 5 exhibited local recurrence after resection compared to 6 patients who developed postoperative local recurrence with NSM [15]. Similarly, researchers at Memorial Sloan Kettering examined 777 PN patients, noting that of the 75 patients (7.5%) who had PSM, only 2 (4%) developed local recurrence compared to 4 (0.5%) of the 713 patients with NSM [14]. Bensalah and colleagues also did not detect significant differences between patients with PSM and NSM in 5-year CSS (81 vs 88%, $p = 0.70$) or recurrence-free survival (79 vs 92%, $p = 0.113$) after match-paired analysis [19••, 33]. Additionally, population-based analysis of data from 71 institutions using the Ontario Cancer Registry found that there was no statistical difference in CSS and OS at 5 years in patients with PSM versus NSM (CSS: 90.9 vs 91.9% and OS: 84.6 vs 88.6%, respectively; $p = 0.58$) [18]. One possible explanation for this lack of malignant potential with PSMs includes a low cancer progression rate associated with low-grade primary tumor pathology. Additionally, destruction of tumor cells due to coagulation, mechanical stress, or induced ischemic insult during NSS may limit the survival and propagation of malignant cells at the resection boundary [38].

More recently, several studies have challenged this view on the oncologic potential of PSM after RCC resection. Using the NCDB, Maurice et al. recently showed that, among a large 6038 patient cohort with pathological T1-T3 nonmetastatic disease, there was a significant decrease in 5-year OS in

patients with PSM in both unadjusted (89 vs 92%, $p = 0.002$) and matched Charlson comorbidity index (CCI) <1 (91 vs 94%, $p = 0.027$) patient populations [26••]. Interestingly, this correlation was not found to be statistically significant in study populations with PSM who also had CCI ≥1 [26••]. Also of note, due to limitations in the NCDB reporting data, there was no CSS calculations conducted in this study. Along those lines, Bernard and colleagues similarly found that PSM was associated with a significant increased risk of local tumor recurrence (hazard ratio 11.5) with nearly one third of reported patients showing local recurrence (mean follow-up of 23.2 months) [52].

It is important to note that data from multiple studies have suggested that there may be an association between risk of cancer progression and recurrence with PSM in patients who have higher-grade initial tumor pathology. For instance, a retrospective review of 1240 patients who underwent PN showed an increased risk of tumor recurrence in high-risk disease (pT2-pT3 or Fuhrman grade III-IV), but not low-risk disease (pT1 or Fuhrman grade I-II) [21••]. Indeed, in the setting of low-risk primary malignancy, residual tumor detected as a PSM after operative resection likely exhibits the same baseline pathology and low progressive rate as the previously excised low-grade lesion [10, 21••, 53]. A 2007 study by Kwon et al. also supported this notion, finding that high grade RCC with PSM experienced higher rates of local oncologic recurrence, although tumor histology did not necessarily contribute to higher rates of PSM at time of resection [14]. Conversely, in one of the few available studies in a population exhibiting homogenous pathology, Kang et al. showed no statistical difference in rates of recurrence with both PSM and NSM in pT1 RCC (3.2 vs 2.1%, $p = 0.492$) at median follow-up of 32.5 months [19••]. Others have shown a correlation between oncologic recurrence and PSM without noting association with tumor pathology. Khalifeh et al. performed a multi-institutional assessment of 943 RPN, 21 of which had PSM. This data ultimately showed a lower cancer-free recurrence rate (47.0 vs 98.3%, $p < 0.001$) and metastasis-free survival rate (63.0 vs 99.5%, $p < 0.001$) in patients with PSM when compared to those with NSM, regardless of pathologic stage of the resected renal tumor [20].

To date, additional prospective data is needed in order to accurately determine the oncologic risk of PSM after NSS. Also, controlling future studies for patient populations with similar pathologic tumor staging would allow for more robust, less conflicting conclusions to be ascertained as to the impact of PSM after NSS for high-risk versus low-risk disease. Certainly, an operative surgeon should consistently strive for achieving NSM during RCC operations as this portends the best opportunity for complete tumor control. However, in cases where NSM becomes difficult to achieve, there still remains controversy surrounding the future oncologic potential of the remaining tumor tissue at the edge of the resection bed.

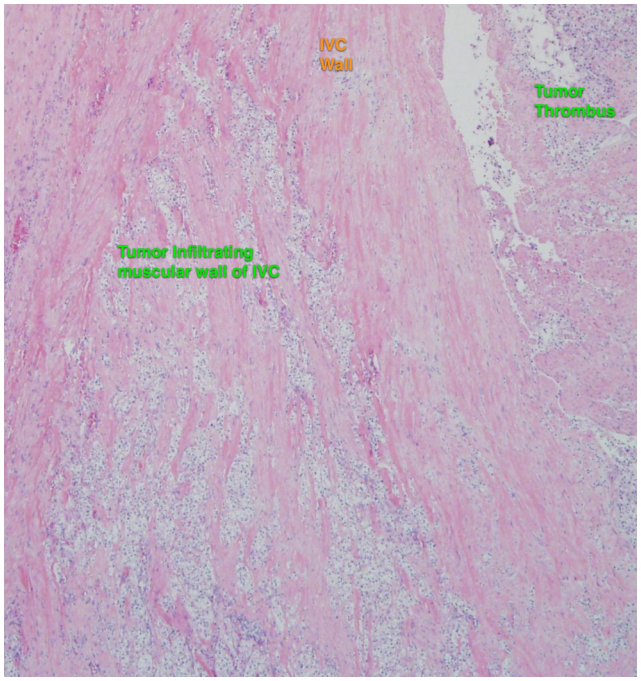

Fig. 1 Histopathology of positive venous margins in advanced renal cancer. The above image depicts the final pathology slide obtained from a patient with advanced renal cancer after surgical resection. This demonstrates the microscopic features of two possible sources for positive venous margins after renal tumor resection—the infiltration of tumor cells into the vascular wall and the tumor thrombus itself. *IVC* = inferior vena cava

Intraoperative Techniques to Minimize Risk of PSM from Kidney Cancer Surgery

In the following section, we will discuss different techniques for minimizing the risk of PSM in addition to the management of PSM after initial NSS has been performed.

Utility of Intraoperative Frozen Section During NSS

The use of intraoperative frozen section (FS) during NSS has been a frequently studied topic. FS is typically employed when there is a concern for incomplete tumor resection at the time of surgery, helping to assess the need for additional tissue excision or possible conversion to RN if appropriate tumor control cannot be achieved through a nephron-sparing approach. In a recent survey of 197 members from the Society of Urologic Oncology and Endourological Society, use of FS was reported by up to 69% of respondents for open and 58% of respondents for laparoscopic PN [54].

A number of studies have reported that surgeon assessment of tumor borders carries comparable ability to prevent PSM as the reflexive use of FS biopsy at time of surgical resection [55, 56]. Additionally, FS provides only a limited representation of tissue from the resection plane and can be distorted by coagulation or mechanical tissue damage created during surgery. Both of these considerations may contribute to the overall inconsistency of this test to predict true positive tumor pathology [57]. In assessing the utility of FS, Dudevandi et al. examined 301 patients who underwent NSS. FS detected PSM in two patients that had no malignancy noted on final pathology (after completion RN) and an additional four specimens were found to have RCC on final pathology which was not detected with intraoperative FS [55]. Another 2013 study examined 433 PN cases reporting that overall FS use contributed to decreased overall PSM compared to no FS use (4.3 vs 17.7%, $p < 0.01$) and use of >1 FS specimen per case showed additional significant decrease in PSM (0.9 vs 6.3%, $p = 0.36$). However, despite its reduction in PSM rates, this data did not show any association with FS use and improved recurrence-free survival [58•]. Similarly, despite its frequent use, multiple other studies have also shown that pathologically positive FS at time of renal mass resection does not significantly influence future oncologic recurrence rates [18, 56, 59, 60]. Based on this data regarding the reliability of FS testing, most experts support restricting the reflexive use of intraoperative FS and pursuing immediate local re-excision of any resection bed tissue showing concern for grossly positive intraoperative tumor margins (or pursuing completion nephrectomy if this is not feasible) [38].

Other Techniques for Reducing Risk of PSM at the Time of Renal Tumor Resection

Several techniques have been developed to help facilitate complete tumor resection with NSS, thus mitigating the risk of PSM. First, close inspection of the tumor (including size, level of adjacent tissue or vascular involvement, proximity to anatomic landmarks such as the hilar vessels or renal collecting system) on both preoperative imaging and at time of surgery is imperative in helping to ascertain tumor margins. As an adjunctive modality, multiple researchers describe the utility of intraoperative ultrasound (US) to more clearly delineate tumor boundaries for use in planning resection planes [39, 61–63]. Gill et al. and others have also highlighted the use of super selective segmental vessel hilar clamping to help differentiate between tumor and normal renal parenchyma by assessing differential blood flow [64–67]. Research to develop further innovation in this area is currently ongoing.

It is also important for surgeons to remember that while renal parenchymal preservation is a worthy goal, RN still remains an appropriate modality, especially for larger (>4 cm) or central tumors and in the context of a normal contralateral kidney.

In further analyzing methods to minimize PSM in the setting of advanced kidney cancer, it should be noted that there is a significant degree of variability in the way that renal tumor thrombus is pathologically assessed. Some pathologists will reflexively report any tumor thrombus as a positive margin, even if it was visually completely removed and the tumor thrombus was not "touching" a solid organ (only the bloodstream). One method that the senior author uses is to extract the thrombus from the IVC and then resect small amounts of the IVC, sending those specimens as "final" margins. It is important to remember, however, that there is a subset of patients who may have tumor growing directly through the intima of the venous wall, and will thus have microscopically PSM in the actual wall of the vena cava (pT3c disease) that confers a poor surgical prognosis.

The more common occurrence for many surgeons, however, is the reporting of a positive margin for renal vein thrombus. This occurs when the surgeon uses an endovascular stapler to transect the renal vein. The vein then retracts and becomes essentially a covering immediately on the renal vein thrombus. Depending on how this is processed, if a knife is used to cut off the staple line, sometimes the very edge of the renal vein thrombus can be transected as well. This often ends up on the same histologic slide as the true vein margin, and will thus be called "positive" leading to consternation for surgeon and patient alike. One method that obviates this problem is to very precisely make a venotomy in the renal vein at the staple line, let the blood out and then inspect the thrombus. It should have rounded tip. If it does not, likely it was transected and the proximal renal vein or cava should be inspected for remaining thrombus with consideration given to re-resection of this margin. If the thrombus does have a rounded tip, the staple line can be excised and sent off as a final margin.

Management of Kidney Cancer Patients with PSM

Several studies suggest that in cases where PSM persist after attempt at complete surgical resection, it is reasonable to pursue ongoing close surveillance with a combination of imaging and laboratory evaluation [67, 68]. Such recommendations are based on low overall risk of local and metastatic progression and the lack of consensus surrounding the oncologic potential associated with PSM found at the time of initial surgery. Others have suggested a management approach that involves risk stratification based on tumor pathology and stage in the setting of PSM, given the data showing higher differential risk of cancer progression with certain primary tumor pathology [21••]. Specifically, noting tumor tissue variants consistent with higher malignant potential (i.e., papillary RCC type 2, clear cell RCC, sarcomatoid pathology) versus those with lower malignant potential (i.e., papillary RCC type 1,

Table 2 Management of positive surgical margin after nephron-sparing surgery

Reference	Year of publication	Study type	Study inclusion period	# of patients	Surgical approach	Tumor stage	PSM	Study commentary
Sundaram et al.	2011	Single center, retrospective	2004–2010	29	Completion RN/ Repeat resection of margin	pT1a-pT3a	*	* Included only patients with PSM (29/29,100%). 2/21 patients after re-resection of PSM were found to have residual tumor vs 0/8 patients after completion RN. Average decrease in GFR was 4 vs 25 mL/min/1.73 m^2 for re-resection and completion RN, respectively
Lopez-Costea et al.	2010	Single center	1995–2003	137	OPN	pT1a-pT3a	11 (8.0%)	2/11 underwent completion nephrectomy (one for bleeding, one as elective), 9 patients followed with CT q6 months × 2 years q1 year × 5 years, then alternating q1 year CT/Ultrasound thereafter. No local or metastatic disease at median follow-up of 80.5 months
Raz et al.	2010	Single center, retrospective	1995–2005	114	OPN	T1a-T1b	17/114 (15%)	9/17 patients with PSM proceeded with completion nephrectomy (5 immediate, 4 subsequent surgery). No remaining tumor was seen in subsequent nephrectomy specimen and no difference was seen in cancer recurrence or CSS between completion nephrectomy and active surveillance group (no RCC-attributable mortality events at mean follow-up 71 months)
Desai et al.	2008	Single center, retrospective	2000–2007	80	LPN	T1a	5 (6.3%)	Discusses surveillance of PSM after RCC resections; no recurrence in 5 PSM patients at mean follow-up of 56.4 months (range 20–80 months)

RN radical nephrectomy, *OPN* open partial nephrectomy, *LPN* laparoscopic partial nephrectomy, *PSM* positive surgical margin, *CSS* cancer-specific survival, *RCC* renal cell carcinoma

chromophobe, oncocytoma) may help identify patients with more aggressive cancerous tissue within a PSM and direct the need for closer follow-up [14, 68].

Need for treatment of identified local tumor recurrence is assessed on an individual basis with options including local re-resection at site of previous tumor excision, ablative modalities, or completion RN. However, active surveillance continues to be supported as a reasonable approach in asymptomatic, low-risk lesions with minimal interval change on follow-up imaging (especially given the known risk of CKD and cardiovascular morbidity associated with progression to RN) [19••, 37, 56, 68–70]. Importantly, Lopez-Costea et al. cited no evidence of recurrence in nine patients with PSM (ranging from pT1 to pT3 disease) undergoing active surveillance over 80.5 months median follow-up [68]. Similarly, Raz et al. reported no difference in cancer recurrence or CSS in eight patients with PSM managed with active surveillance compared to nine patients with PSM who underwent completion nephrectomy at mean follow-up of 71 months. Also of interest, out of these nine patients who underwent completion nephrectomy (five were performed at the time of the initial surgery and four were performed in delayed fashion), no residual tumor was found in any of the four delayed nephrectomy group specimen versus two of five with residual cancer in the immediate completion nephrectomy group [38]. Finally, Sundaram et al. examined 29 patients with PSM after NSS, showing that only 2/21 patients who underwent re-resection of the margin site and 0/8 patients who underwent completion RN showed residual tumor in the subsequent specimen [70]. Based on these results, many experts recommend judicious use of completion nephrectomy in the setting of PSM after NSS, instead supporting pursuit of active surveillance due to the low rate of progression and lack of definitive cancer-specific mortality in those managed with active surveillance compared to those who undergo further treatment [38, 67]. See Table 2 for additional details on studies pertaining to the management of PSM after NSS [38, 67, 68, 70]. Risk stratifying patients based on their initial pathology may be beneficial in terms of constructing appropriate timing of follow-up monitoring; however, more randomized prospective analyses are needed to better direct these management recommendations.

Conclusion

PSM have a low incidence in NSS for RCC, varying between 0.1 and 10.7% in the most recent literature. Variations in the rates of PSM with different surgical approaches to NSS have been reported, but rates across techniques are comparably low. Factors such as tumor size, location, and imperative indications for surgery all have been shown to affect the rate of PSM. However, controversy still exists surrounding the risk of oncologic progression and effect on cancer-specific mortality in the setting of PSM after NSS. Ultimately, additional work is needed to help better risk stratify patients in terms of oncologic progression and management based on tumor staging and primary histopathology.

Compliance with Ethical Standards

Conflict of Interest Dean D. Laganosky, Christopher P. Filson, and Viraj A. Master each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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