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Importance of surgical margins in the management of renal cell carcinoma

John S Lam, Jonathan Bergman, Alberto Breda and Peter G Schulam*

SUMMARY

Surgical resection remains the standard treatment for clinically localized renal cell carcinoma. Pathological features of the surgical specimen, including the margin status, play an important part in determining the patient's prognosis. Negative surgical margins have traditionally been sought to maximize the efficacy of treatment. Initial concerns that partial nephrectomy might have high local recurrence rates compared with radical nephrectomy have now been minimized as a result of technological advances and refinements in surgical technique. Current concerns in relation to partial nephrectomy include the width of parenchymal tissue that should be removed to avoid positive surgical margins, effects of positive margins on recurrence-free survival, and the use of frozen-section analysis to determine margin status. Size of the surgical margin in partial nephrectomy does not seem to affect the risk of local tumor recurrence, and not all positive surgical margins lead to recurrent disease. Intraoperative frozen-section analysis is not definitive and its value in guiding the surgical management of renal tumors remains to be defined. Laparoscopic partial nephrectomy is emerging as an attractive approach for selected renal masses. Intraoperative use of ultrasound, cold-scissor parenchymal transection, embolization, and hilar clamping to achieve a bloodless operative field with clear visibility, may minimize the risk of positive margins during partial nephrectomy.

KEYWORDS kidney cancer, laparoscopy, partial nephrectomy, radical nephrectomy, surgical margin

REVIEW CRITERIA

The data for this Review were obtained by scanning the PubMed database for articles published between 1968 and 2007. The search terms used were "kidney cancer", "laparoscopy", "partial nephrectomy", "radical nephrectomy", and "surgical margin". All papers identified were English-language, full-text papers. The reference lists of identified articles were also searched for further papers.

CME

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Identify historical parameters for referral to radical nephrectomy vs partial nephrectomy for renal cell carcinoma (RCC).
2 Compare techniques of partial nephrectomy for RCC.
3 List management options for patients with RCC and positive surgical margins following partial nephrectomy.
4 Specify interventions that can reduce the risk for positive surgical margins following partial nephrectomy for RCC.

Competing interests

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INTRODUCTION

There are an estimated 200,000 new diagnoses of renal cell carcinoma (RCC) and over 100,000 deaths from RCC each year in North America, Europe and Australia.[1] The gold-standard treatment for renal tumors is radical or partial nephrectomy; however, approximately one-third of patients who undergo surgical resection for clinically localized RCC will develop tumor recurrence.[2] The indications for nephron-sparing surgery—once reserved for patients with solitary kidneys, bilateral renal tumors, or renal insufficiency—have been expanded to allow elective partial nephrectomy for selected patients with a normal contralateral kidney.

The rationale for expanding the indications for nephron-sparing surgery includes an increase in the life expectancy of the general population, along with an increase in incidental diagnoses of RCC in younger patients. These features have led to increased concern about the long-term risks of renal insufficiency or contralateral tumor recurrence in patients who undergo radical nephrectomy. The generally suggested indication for elective partial nephrectomy is a small renal mass, usually less than 4 cm, located peripherally and easily amenable to resection.[3] However, there are emerging data that partial nephrectomy can be performed in patients with anatomically amenable tumors larger than 4 cm, provided that an adequate surgical margin can be safely obtained.[4,5] There is concern that patients who undergo partial nephrectomy might subsequently develop ipsilateral renal recurrence, which can be attributed to multifocal renal tumors, *de novo* development of a second primary tumor, or a positive surgical margin. Furthermore, patients with positive surgical margins at partial nephrectomy have previously been reported to have shorter cancer-specific survival times compared with those with negative margins.[6] This Review will focus on the importance of surgical margin status after surgical resection and address technical considerations that minimize the risk of positive surgical margins.

Table 1 Positive margin rates in selected open and laparoscopic partial-nephrectomy series for cancer.

Series	Number of patients	Tumor size (mean [range] cm)	Number of positive margins (%)
Open partial nephrectomy			
Gill *et al*. (2007)[21]	858	3.3 (0.13–9)	10 (1)
Kwon *et al*. (2007)[39]	770	2.6[a] (2.2–3.5)	57 (7.4)
Patard *et al*. (2007)[16]	542	3.4 ± 2.1[b]	8 (1.5)
Porpiglia *et al*. (2005)[19]	30	3.14[a] (1.3–4.8)	1 (3.3)
Thompson *et al*. (2005)[66]	480	3.6 ± 2.2[b]	4 (0.8)
Gill *et al*. (2003)[17]	100	3.3 (3–4)	0 (0)
Sutherland *et al*. (2002)[22]	44	3.22 (1.3–10)	3 (6.8)
Lee *et al*. (2000)[67]	79	2.5 (0.9–4)	1 (1.3)
Laparoscopic partial nephrectomy			
Gill *et al*. (2007)[21]	556	2.6 (0.4–8)	12 (1.6)
Breda *et al*. (2007)[40]	808	2.7 (2–4)	21 (2.4)
Permpongkosol *et al*. (2006)[43]	511	2.8 ± 0.9[b]	9 (1.8)
Porpiglia *et al*. (2005)[19]	34	3.2[a] (1.8–4.1)	1 (2.9)
Venkatesh *et al*. (2005)[41]	123	2.6 (1–9)	3 (2.5)
Gill *et al*. (2003)[17]	100	2.8 (2–4)	3 (3)

[a]Median tumor size. [b]Mean tumor size ± 1 SD.

LAPAROSCOPIC VERSUS OPEN NEPHRECTOMY

Open radical nephrectomy (ORN) for renal tumors was first described in 1969 by Robson *et al*.[7] Surgical results for ORN were better than the results for simple nephrectomy in previously published studies of renal tumors: ORN had a 52% 5-year survival for all pathological stages, and a 66% 5-year survival in patients with nonmetastatic RCC confined to the kidney parenchyma, whereas simple nephrectomy had overall 5-year survival rates of 39–48%.[7] In 2004, a study reported 5-year survival rates after ORN of 75–95% for patients with organ-confined disease, 65–80% for tumors with perinephric fat or adrenal involvement, 40–60% for patients with vena cava thrombus, 10–20% for those with lymph-node involvement, and 0–5% for patients with metastatic disease.[8] Laparoscopic radical nephrectomy (LRN) was first introduced in 1991 by Clayman *et al*.[9] and this procedure can result in similar oncological outcomes to those of ORN.[10,11]

Since Wells[12] first reported the feasibility of partial nephrectomy in 1884 the application of this technique has been expanded, and in current clinical practice includes selected patients with a normal contralateral kidney. Tumors less than 4 cm in size can be safely treated with open partial nephrectomy (OPN), which has 10-year cancer-specific survival rates similar to those of radical nephrectomy.[13–15] Emerging data now indicate that OPN can be performed in patients with anatomically amenable tumors of over 4 cm in median size, provided that an adequate surgical margin can be safely obtained (Table 1).[4,5,16] Laparoscopic partial nephrectomy (LPN) has become a technically feasible alternative to OPN with similar surgical efficacy as measured by intermediate oncological outcomes and positive surgical margin rates (Table 1).[17–20]

Gill *et al*.[17] compared the perioperative outcomes of 100 consecutive patients treated with LPN and a cohort of 100 consecutive patients treated with OPN, for a sporadic single renal tumor of 7 cm or less. Margin status was compared between the two groups; there

were three positive margins in the LPN group compared with none in the OPN group. A multicenter study published in 2007 compared early postoperative outcomes in 1,800 consecutive patients who underwent either OPN or LPN to treat a single renal tumor of 7 cm or less in size.[21] Positive surgical margin rates for cancer were 1.6% for LPN and 1.0% for OPN. Of the 12 LPN and 10 OPN patients who had a positive surgical margin, 1 underwent prophylactic LRN 2 months later without delayed recurrence, whereas 1 patient with bilateral synchronous tumors who had OPN for a 2 cm tumor (histopathology showed a stage T1a papillary RCC) experienced local and distant recurrence, underwent radical nephrectomy for multiple large tumors, and ultimately died from this cancer. The other patients treated with OPN or LPN who had a cancer-positive surgical margin did not have any recurrence during follow-up (median 1.9 years, range 0.1–5.6 years). The 3-year cancer-specific survival for patients with a single RCC tumor of clinical stage T1N0M0 was 99.3% after LPN and 99.2% after OPN, respectively.

Lane *et al.*[20] reported the outcomes of 56 patients who were followed up for a minimum of 5 years after LPN. The final surgical margin was positive for cancer in one patient. During follow-up (median 5.7 years, range 5.0–6.9 years), there were no distant recurrences and local recurrence was detected in only one patient (2.7%). Allaf *et al.*[18] reported the outcomes of 48 patients who underwent LPN for clinically localized RCC. Intraoperative frozen-section biopsies showed negative margins in all patients. Final surgical margins were positive in one patient (2.1%). During follow-up (mean 37.7 months, range 22–84 months), one patient with von Hippel–Lindau disease experienced a local recurrence 18 months after surgery, and elected to be managed by observation.

SURGICAL MARGINS

Radical nephrectomy

Visually negative surgical margins have traditionally been subjected to histopathological analysis in the attempt to maximize cancer control (i.e. to minimize the risk of spread or recurrence of cancer). Positive margins in specimens from radical nephrectomy are not common, with reported rates of up to 6%.[16–19,22–24] A positive surgical margin after radical nephrectomy may show that all the tumor cells were not removed, which increases the patient's risk of recurrent disease at a later date. Any doubtful area of the specimen must be marked with ink. If the margins are positive, their anatomic location and whether there is extension into adjacent structures must be described. If there is renal-vein invasion, the status of the cut edge of the renal vein or the vena cava must be indicated. However, high-powered, prospective, randomized studies to identify the predictors of positive surgical margins after ORN remain to be conducted.

Partial nephrectomy

Concerns about the use of partial nephrectomy were raised after local recurrence rates of up to 10% were reported in the early 1990s.[25–28] These concerns have now disappeared, however, after refinement of the surgical technique reduced local recurrence rates after partial nephrectomy to 0–6%, which is similar to the recurrence rate after radical nephrectomy.[3,13,29,30] Traditionally, partial nephrectomy has required the removal of a 1 cm margin of healthy tissue surrounding a resected tumor—the standard technique to ensure a cancer-negative surgical margin and, therefore, to decrease the risk of local recurrence.[31,32] With partial nephrectomy, adherence to this dictum can be quite a challenge. Several studies, however, indicate that any negative margin (even less than 1 mm) is adequate for cancer control as long as the tumor is completely excised (Table 2).[22,33–37] Lerner *et al.*[38] described tumor enucleation with intraoperative, frozen-section-guided sharp dissection and *in situ* partial nephrectomy. The local recurrence rate in that study was similar to that of the aforementioned 1 cm-margin technique. The question of what is an appropriate width for surgical margins has become a controversial topic. Piper *et al.*[33] reviewed 67 patients who had a partial nephrectomy to determine the optimum surgical margin; of seven patients with a positive surgical margin, one died of metastatic RCC, five remained alive with systemic recurrence, and five had no evidence of disease during follow-up (mean 29 months). Piper and colleagues concluded that positive surgical margins did not indicate as poor a prognosis as expected compared with negative surgical margins.

Open partial nephrectomy

Sutherland *et al.*[22] reported on a series of 44 patients treated with OPN for RCC. Surgical margins were positive in three individuals

Table 2 Partial-nephrectomy series that assessed the size of surgical margins.

Series	Number of patients	Tumor size (mean [range] cm)	Negative margin size (mean [range] mm)	Number of local recurrences	Follow-up (mean [range] months)
Timsit *et al*. (2006)[36]	61	3.2 (1.2–5)	2 (0–5)	0 (0)	72.5 (46–95)
Berdjis *et al*. (2006)[37]	121	3.2 (0.7–9.9)	5.6 (1–23)	3[a] (2.5)	49.3 (12–113)
Porpiglia *et al*. (2005)[19]	29 (open) 33 (laparoscopic)	3.14 (1.3–4.8) 3.2 (1.8–4.1)	2 (0–3) 2.08 (0–6)	1[a] (3.4) 0 (0)	50 (30–72) 16 (2–35)
Sutherland *et al*. (2002)[22]	41	3.22 (1.3–10)	2.5 (0.5–7)	1[a] (2.4)	49[b] (8–153)
Piper *et al*. (2001)[33]	60	3 (0.9–11)	4.5 (1–12)	1 (1.7)	60 (5–124)

[a]Local recurrence occurred at a site distant from the original lesion. [b]Median follow-up.

(6.8%). Patients with a negative surgical margin had a mean parenchymal margin of 2 mm. There were no patients with negative surgical margins and local recurrence at the 4-year follow-up, whereas one of the three patients with a positive surgical margin had local and metastatic recurrence. Sutherland and colleagues' data suggest that although ensuring that the surgical bed is free of residual tumor is essential, the size of the parenchymal margin does not affect survival. Li *et al.*[35] reported the results of step-sectioning the peritumoral tissue from 82 radical nephrectomy cancer specimens at 3 mm intervals. This study sought to determine the presence of tumor multicentricity. The maximum distance between the tumor pseudocapsule and tumor was found to be 0.5 mm, which suggested that a surgical margin of 1–2 mm was adequate.

Timsit *et al.*[36] prospectively assessed the status of surgical margins and margin width in 61 consecutive patients who underwent OPN. No surgical margins were positive, and no patient developed metastatic or locoregional relapse during follow-up. The mean peritumoral margin was 7 mm (range 4–10 mm) for the cortex, and 2 mm (range 0–5 mm) for the deepest part of the resection. The surgeons' assessments showed 51 complete (i.e. a continuous ring of healthy tissue surrounding the lesion) and 10 incomplete (i.e. tumor abutted the intact enucleation capsule) margins, whereas frozen-section and histologic analysis showed 53 complete and 8 incomplete margins. There was no association between peritumoral margin width and risk of recurrence, even for tumors that abutted the hilum where 'incomplete' margins are inevitable. Furthermore, there was very good concordance between surgeons' assessments and histologic assessments of margin status. However, Timsit and colleagues concluded that frozen-section analysis is still mandatory if there is any doubt about the margin status.

Kwon *et al.*[39] assessed patients with positive surgical margins after OPN. Of 770 patients who underwent OPN, 57 (7%) had a positive surgical margin on final pathologic analysis, despite negative margins reported on frozen-section analysis. Interestingly, 6 of 63 patients (10%) with multifocal disease had a positive margin. In the 57 patients with positive surgical margins, 24 tumors were characterized as having low malignant potential (benign tumors, papillary RCC type I, chromophobe RCC) whereas 33 tumors were classified as having high malignant potential (clear-cell RCC, papillary type II RCC, collecting-duct RCC, and tumors with sarcomatoid differentiation). The only independent predictor of positive surgical margins was an imperative (rather than elective) indication for partial nephrectomy. During follow-up (median 22 months, range 7–45 months), 2 out of 57 patients with positive surgical margins had a local recurrence (4%), compared with 4 of 713 patients with a negative surgical margin (0.5%). Patients with a tumor of low malignant potential and a positive surgical margin did not experience local disease recurrence, despite the positive margin. Interestingly, the presence of a positive surgical margin did not affect metastatic progression. This study, as well as others,[22,33] demonstrates that not all positive surgical margins lead to recurrent disease, but further therapy or careful surveillance for these patients might still be warranted because of their increased risk of local recurrence (Table 3). Nevertheless, studies with extended follow-up might reveal late recurrences in such patients.[2]

Table 3 Outcomes after a positive surgical margin in partial-nephrectomy series.

Series	Number of patients	Number of local recurrences	Number of distant metastases	Length of follow-up ([range] months)
Kwon *et al*. (2007)[39]	57	2 (3.5)	2 (3.5)	22[a] (7–45)
Permpongkosol *et al*. (2006)[43]	9[b]	0 (0)	1 (11.1)	10[c], 32[d] (6–76)
Sutherland *et al*. (2002)[22]	3	1 (33.3)	1 (33.3)	29, 39, 62[e]
Piper *et al*. (2001)[33]	7	0 (0)	2 (28.6)	5[f], 9[f], 29[d] (8–44)

[a]Median follow-up. [b]Two patients underwent secondary completion radical nephrectomy and no residual disease was identified in either specimen. [c]One patient with von Hippel–Lindau disease died of metastatic renal cell carcinoma (RCC) 10 months after surgery. [d]Mean follow-up. [e]No evidence of disease at 39 and 62 months, while multiple local and metastatic recurrences developed in 1 patient at 29 months. [f]One patient was alive with ipsilateral adrenal recurrence at 5 months and 1 patient died of metastatic RCC at 9 months.

Laparoscopic partial nephrectomy

Porpiglia *et al*.[19] compared the status of the peritumoral parenchyma after OPN and LPN for RCC. There was no significant difference in the rate of positive margins between patients who had OPN or LPN (3.3% versus 2.9%), respectively. Porpiglia and colleagues measured surgical margins at the minimum-width and maximum-width points of the section. The mean minimum surgical margin was 2.00 mm in the OPN group and 2.08 mm in the LPN group ($P = 0.75$), whereas the mean maximum surgical margin was 4.56 mm in the OPN group and 5.2 mm in the LPN group ($P = 0.09$). The difference between minimum and maximum margin thickness was significantly smaller in the OPN group compared with the LPN group (2.56 mm versus 3.16 mm, $P = 0.04$). The OPN group included one patient with a local recurrence that was treated with radical nephrectomy, whereas the LPN group did not report any recurrences.

In 2007, Breda *et al*.[40] reported the practice patterns and pathological outcomes in patients after LPN from 17 multinational centers. A total of 855 patients who underwent LPN were assessed, and an overall positive margin rate of 2.4% was reported, which was comparable to that reported in contemporary LPN series[20,23,41] as well as OPN series.[17,19,21,22] Of the 21 patients with positive surgical margins, 14 underwent immediate radical nephrectomy on the basis of frozen-section analysis findings, and the other 7 were followed up expectantly. Importantly, the mean tumor sizes in previous studies of LPN have been small (2.6–3.3 cm),[17,19,21,22,33,41] which might indicate a potential effect of tumor size in the attainment of negative surgical margins. Frank *et al*.[42] compared the outcomes of patients with central and peripheral tumors treated with LPN. Central tumors were defined as tumors that extended centrally into the kidney and were in direct contact with or invading into the pelvicaliceal system and/or renal sinus on preoperative three-dimensional CT. Lesions that had no contact with the pelvicaliceal system were classified as peripheral. After LPN, the positive margin rate was similar for central and peripheral tumors.[42]

Permpongkosol *et al*.[43] assessed the outcomes of 511 patients who underwent LPN for a renal tumor, 9 of whom had a positive surgical margin on final pathology (1.8%). Two patients underwent secondary completion radical nephrectomy after LPN, and no residual disease was identified in either specimen. Seven patients with positive margins chose to be managed with surveillance: one patient who had von Hippel–Lindau disease died of metastatic RCC in the pancreas 10 months after LPN, and the other six remained free of disease during follow-up (mean 32 months, range 6–76 months). The researchers concluded that a positive margin after LPN does not necessarily indicate the presence of residual disease, but they advised that such patients should be vigilantly monitored.

TREATMENT OPTIONS FOR PATIENTS WITH POSITIVE SURGICAL MARGINS

Radiation therapy has been used to treat patients without metastasis after nephrectomy when surgical margins are positive for tumor involvement, or if there is known residual tumor after surgery. However, there has been no proven benefit for the use of local irradiation in these settings. Initial results with adjuvant radiation seemed favorable in terms of decreased local recurrence rates,[44] but other randomized studies with long-term follow-up[45,46] of adjuvant radiation

compared with observation after nephrectomy for locally advanced RCC did not show differences in survival. Adjuvant radiotherapy might also considerably increase morbidity for these patients as a result of radiation-induced damage to abdominal organs.

Local recurrence of RCC in the renal fossa might result from an incomplete resection of the primary tumor or from persistence of tumor in the regional lymph nodes. The proportion of patients who develop local recurrence is 1–14%.[2] Local disease recurrence is usually associated with a poor prognosis, but surgical resection, particularly in the case of a solitary, local, recurrent tumor, can be associated with long-term survival. Itano *et al.*[47] reported that aggressive surgical resection of recurrent disease significantly improved survival when compared with medical therapy (radiation, chemotherapy, or immunotherapy): the 5-year survival rates for surgical resection and medical therapy were 51% and 18%, respectively. Other studies have reported long-term survival rates ranging from 40% to 62% after surgical management of local recurrence.[48–50] Tanguay *et al.*[51] reported the outcomes of 16 patients with a local renal-fossa recurrence, 15 of whom were managed with complete surgical resection. At a median follow-up of 23.5 months, 12 patients were still alive. By contrast, one study showed that combined intraoperative radiation and surgery resulted in improved long-term survival compared with surgery alone.[52]

Consensus has yet to be reached on what intervention is appropriate after positive surgical margins. Positive surgical margins must be addressed with the understanding that residual disease might not be present, despite the positive findings on pathological analysis. Positive margins could be caused by inadvertent capsulotomy during specimen extraction, which highlights the need to reconstruct the specimen before its submission to the pathologist. Positive margins could also be caused by artifacts of specimen processing. Even if cancer cells were initially present at the tumor margin, they are usually destroyed during hemostatic maneuvers (such as coagulation) or during bolstering maneuvers with mesh, which lead to inflammatory and immunological reactions that might destroy tumor cells. In addition, most small renal tumors grow slowly and are more likely to be of low malignant potential.[53] Treatment options for patients with positive margins after partial nephrectomy include active surveillance, repeat partial nephrectomy, percutaneous ablation, or radical nephrectomy. There are limited data on guiding patients' decision-making in this situation.

Partial nephrectomy versus tumor enucleation

The excision of a 1 cm margin of 'normal-looking' renal parenchyma around the tumor is considered the standard surgical technique in partial nephrectomy to avoid the risk of local recurrence.[39,40] Nevertheless, whether or not it is necessary to excise a rim of healthy parenchyma to avoid the risk of positive surgical margins and local recurrence is becoming a matter of controversy. Reports published in the past few years concluded that the width of resection margins did not correlate with disease progression and that, if the tumor is completely excised, the margin size is irrelevant and not correlated with disease progression.[22,33–35] RCC tends to compress the normal parenchyma and so forms a pseudocapsule around the tumor, which allows the surgeon precise and easy intraoperative tumor location as well as surgical removal and possibly tumor enucleation. Carini *et al.*[54] have shown favorable cancer-specific survival rates after tumor enucleation for pathological stage T1a RCC, similar to those of partial nephrectomy. Their study of 232 patients showed 10-year cancer-specific and progression-free survival rates of 95% and 94%, respectively. Of the 2% who had a local recurrence, none occurred at the level of the enucleation bed. Furthermore, Carini and colleagues also assessed enucleation for RCC tumors of 4–7 cm in greatest diameter and found 5-year and 8-year cancer-specific survival rates to be 85% and 82%, respectively.[55] Overall, 10 (14.9%) patients had progressive disease, of whom 3 (4.5%) had local recurrence alone or local recurrence associated with distant metastases.

ROLE OF FROZEN-SECTION ANALYSIS AFTER PARTIAL NEPHRECTOMY

There are various techniques for intraoperative histopathological analysis. Previous studies have reported taking sections of the inked margins of the excised tumor itself[19] or multiple random biopsies of the resection bed.[18] Several studies, however, have found discordance between frozen-section and final pathology.[39,40,56,57] Kubinski *et al.*[56] assessed the use of routine, intraoperative, frozen-section analysis to ensure

negative surgical margins in 76 patients who underwent OPN. A single margin was interpreted as positive for cancer in one patient (1.3%), which prompted a deeper resection; however, the final histopathologic finding was interpreted as angiomyolipoma rather than cancer. One local recurrence (1.9%) arose in the resection bed 19 months after surgery, despite both the intraoperative frozen-section margins and final pathologic margins being negative. In addition, one patient developed pulmonary metastases that represented the only metastatic recurrence, as well as the only cancer-associated death (1.9%) in this series. A study of intraoperative, frozen-section analysis in 301 patients who underwent OPN found that the results of frozen-section analyses had minimal clinical significance.[57] Positive margins were found on frozen-section analysis in two patients who subsequently underwent radical nephrectomy, but no residual tumor was present in the final pathology of the radical nephrectomy specimens. Furthermore, final pathology revealed four positive surgical margins in samples in which the frozen-section analyses had negative findings. Kwon *et al.*[51] reported a 7% positive surgical margin rate on final pathology despite their use of frozen-section analysis to confirm the margin status during partial nephrectomy in 770 patients who underwent OPN. Breda *et al.*[40] also found that the results of intraoperative frozen-section analysis did not correlate well with the final pathology in 855 patients who underwent LPN. These discrepancies between intraoperative frozen-section pathology and final pathology could be caused by numerous factors including technical reasons, such as missing the remaining tumor during random biopsy, limited availability of special stains and comparative studies, freezing and drying artifacts, and/or pathologist error.[58] Normal constituents of renal parenchyma can also be misinterpreted as neoplasm, and neoplastic tubules of low-grade RCC can be misinterpreted as thickly cut, crushed, benign tubules.[59] These studies show that intraoperative frozen-section analysis is not definitive and raises questions about its value in guiding the intraoperative management of patients with RCC. Further studies that aim to examine the use of frozen-section analysis in partial nephrectomy are needed to determine whether careful macroscopic examination of the tumor bed can yield reliable data on tumor infiltration. Whether or not these data can reliably be used to guide the intraoperative management of patients must also be investigated.

MINIMIZING THE RISK OF POSITIVE MARGINS DURING PARTIAL NEPHRECTOMY

Intraoperative ultrasound

Although preoperative radiologic examination can show the probable extent of the tumor mass, intraoperative ultrasonography can accurately define the size and depth of the mass, as well as show its associations with adjacent structures (e.g. the renal sinus, collecting system, and vasculature). Intraoperative ultrasonography also helps to distinguish and characterize adjacent cysts that can mimic the renal mass of interest and, in masses with little exophytic component, ultrasonography is critical to determine the proper orientation of the resection. Polascik *et al.*[60] assessed 100 kidneys in patients who were undergoing surgery for presumed renal cancer. Eight patients were considered candidates for partial nephrectomy, but underwent radical nephrectomy after intraoperative ultrasonography and this showed the presence of extensive tumor. Similarly, three patients with a suspected malignancy were spared nephrectomy after intraoperative ultrasonography and frozen-section analysis showed benign multilocular cysts. Ultrasonographic assessment helped to ensure that all surgical margins were negative in patients who underwent partial nephrectomy. Laparoscopic ultrasonography has been used to expedite tumor identification and was particularly useful in patients with a large amount of perinephric fat.[61,62] Laparoscopic ultrasonography has also been useful to determine an adequate margin of parenchymal transection: Nguyen *et al.*[63] developed a technique wherein ultrasound-confirmed needle localization of the deep tumor margin before resection of the mass during LPN helped to ensure that surgical margins were negative.

Hilar clamping

Adequate hilar clamping reliably achieves a bloodless operative field and decreases kidney turgor. This procedure offers excellent visualization, which allows for precise resection with adequate margins during tumor excision, identification of any collecting-system involvement, watertight suturing of the calyceal entry, and renal parenchymal reconstruction. Lack of hilar control results in increased blood loss and prolonged operative times.[61,62] However, hilar

clamping results in warm ischemia, which can affect recovery of renal function. Occasionally, small, shallow, completely exophytic tumors can be managed without hilar clamping.

Embolization

Gallucci *et al.*[64] described a method to reduce the risk of bleeding during LPN, which consisted of superselective embolization of tumor vessels. This technique means that LPN can be performed without any regional vascular control or clamping. Embolization results in a definite boundary between the healthy and necrotic parenchyma, with a clear view of the cleavage plane. As such, intraoperative ultrasonography and other techniques to delineate the extent of the tumor are unnecessary. A depth of up to 5 mm of healthy parenchyma around the tumor (under radiologic visualization) can be made necrotic. LPN is also now being used to treat large, complex and infiltrating tumors in appropriately selected patients. Nonetheless, central tumors present a substantial technical challenge to treat laparoscopically because of the need for complex reconstruction; selective arterial embolization before LPN might be useful in the management of such tumors.[42]

Cold scissors

Cold-scissor parenchymal transection most closely resembles the open technique for resection of a renal mass;[61] this technique expedites tumor excision without the tissue charring associated with energy-based tools.[65] Without charring, visual confirmation of the plane of parenchymal transection to ensure an adequate tissue margin is possible. Furthermore, sharp excision provides an unaltered specimen that is straightforward to assess pathologically. If there is doubt as to whether LPN can be done safely—that is, in such a way as to ensure that surgical margins are negative—OPN should be done instead.

CONCLUSIONS

Positive surgical margins after radical nephrectomy for clinically localized RCC are rare. There has been no proven benefit for the use of additional treatments in this setting. Surgical resection of recurrence in the renal fossa might benefit a few patients. The size of the surgical margin in partial nephrectomy does not seem to affect the risk of local tumor recurrence, and any margin (even less than 1 mm) is adequate as long as the cancer is completely excised. Intraoperative frozen-section analysis is not definitive and its value in guiding the patient's intraoperative management remains to be defined. However, we recommend site-directed frozen-section analysis of the partial nephrectomy specimen if there is suspicion of a positive margin during gross inspection of the specimen. In addition, not all positive surgical margins on final pathology lead to recurrent disease and, therefore, might not require immediate management.

The risk of positive margins during partial nephrectomy can be minimized with the use of intraoperative ultrasound (which defines the size and depth of the mass and its relationship to adjacent structures), cold-scissor parenchymal transection (which avoids tissue charring, and so improves visualization), and hilar clamping or embolization (which provide a bloodless operative field that improves visibility). Experience with LPN continues to grow; nevertheless, it remains a technically advanced procedure that requires the complete laparoscopic skill-set applied in a time-sensitive environment.

KEY POINTS

- Positive surgical margins after radical nephrectomy for clinically localized renal cell carcinoma are rare, and there has been no proven benefit for the use of additional treatments in this setting
- Size of surgical margin in partial nephrectomy does not seem to affect the risk of local tumor recurrence
- Any surgical margin (even less than 1 mm) is adequate as long as there is complete excision of the tumor
- Intraoperative frozen-section analysis is not definitive and its value in guiding intraoperative management remains to be defined; site-directed frozen-section analysis of the partial nephrectomy specimen is recommended if there is suspicion of a positive margin on gross inspection of the specimen
- Not all positive surgical margins on final pathology lead to recurrent disease and, therefore, may not require immediate management
- Risk of positive margins during partial nephrectomy can be minimized with the use of intraoperative ultrasound, cold-scissor parenchymal transection, and hilar clamping or embolization

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