Is there a benefit to frozen section analysis at the time of partial nephrectomy?

Steven N. Sterious, MD,[1] Jay Simhan, MD,[1] Marc C. Smaldone, MD,[1] Kevin J. Tsai, MD,[1] Daniel Canter, MD,[2] Edward Wameedh, MD,[3] Tianyu Li, MD,[4] James Helstrom, MD,[5] Rosalia Viterbo, MD,[1] David Y. T. Chen, MD,[1] Richard E. Greenberg, MD,[1] Alexander Kutikov, MD,[1] Tahseen Al-Saleem, MD,[3] Robert G. Uzzo, MD

[1]Division of Urologic Oncology, Department of Surgical Oncology, Fox Chase Cancer Center, Temple University School of Medicine, Philadelphia, Pennsylvania, USA

[2]Department of Urology, Emory University School of Medicine, Winship Cancer Institute, Atlanta, Georgia, USA

[3]Department of Pathology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA

[4]Department of Biostatistics, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA

[5]Department of Anesthesiology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA

STERIOUS SN, SIMHAN J, SMALDONE MC, TSAI KJ, CANTER D, WARMEEDH E, LI T, HELSTROM J, VITERBO R, CHEN DYT, GREENBERG RE, KUTIKOV A, AL-SALEEM T, UZZO RG. Is there a benefit to frozen section analysis at the time of partial nephrectomy? *Can J Urol* 2013;20(3):6778-6784.

Introduction: *The utility of frozen section performance during partial nephrectomy (PN) is controversial. We assessed the predictive value of frozen sections on final margin status for patients undergoing PN for localized renal tumors.*
Materials and methods: *We queried our prospectively maintained kidney cancer database for patients undergoing PN with localized renal tumors from 2005-2011. Patients were stratified based on the receipt of frozen section analysis into 'frozen' and 'no frozen' groups. Groups were compared using ANOVA, Chi-square, and Wilcoxon's tests.*
Results: *A total of 537 patients (mean age 58.1 years ± 12.0 years, 64.2% male) underwent PN (mean tumor size 3.7 cm ± 2.0 cm; mean Nephrometry score 7.5 ± 1.8) from 2005-2011. Comparing tumor characteristics between patients undergoing frozen sections (83.1%) and those who did not (16.9%), no differences in histology, Fuhrman grade, pathologic stage, or Nephrometry Score were observed between groups. Final margins were positive in 10 patients (11.0%) in the 'no frozen' group compared to 20 patients (4.5%) in the 'frozen' section group (p = 0.01) but in patients with a documented malignancy on final pathology, final margins were positive in 5.5% and 2.9% respectively (p = 0.16). Four patients (0.7%) had local recurrences, all of whom had negative frozen and final pathologic margins. There was no correlation between positive surgical margins and local recurrence (p = 1.0) at a median follow up of 21 months (IQR = 9-31months).*
Conclusions: *In our institutional cohort, frozen section analysis failed to impact final margin status in patients with documented renal cell carcinoma. Given the oncologic uncertainty of positive surgical margins, further prospective evaluation is necessary to determine the clinical utility of frozen section analysis.*

Key Words: frozen section, partial nephrectomy

Accepted for publication April 2013

Acknowledgement
All authors deny any financial and/or conflict of interest with the presented subject matter. This publication was supported in part by grant number P30 CA006927 from the National Cancer Institute. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. Additional funds were provided by Fox Chase Cancer Center via institutional support of the Kidney Cancer Keystone Program.

Address correspondence to Dr. Robert G. Uzzo, Department of Surgery, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111 USA

Introduction

Kidney cancer is the sixth most common malignancy with an incidence of 64,770 in the United States alone.[1] For patients presenting with clinically localized renal cell carcinoma (RCC), the gold standard treatment is surgical excision through either radical nephrectomy (RN) or nephron sparing surgery (NSS).[2] Compared to RN, partial nephrectomy (PN) provides equivalent oncologic outcomes with added benefits of decreased rates of renal insufficiency, cardiovascular morbidity, and overall mortality.[3-5]

Although the earliest descriptions of PN described the importance of achieving a 1 cm margin of healthy, noncancerous tissue,[6] more recent studies have demonstrated no increase in the rates of cancer recurrence as long as negative margins alone are achieved.[7-9] With various methodologies being employed to achieve nephron preservation, including tumor enucleation,[10,11] sharp dissection,[5] and a combination of both,[10] wide ranging recommendations on the utility of frozen section analysis of pathologic margins pervade the renal oncologic literature.[11-13] As such, the practice of obtaining frozen section analysis as well as the management of a positive margin found on frozen section during PN remains controversial.[7,11-13] Guidelines that assist urologists in the proper utilization of intraoperative frozen sections are lacking, thus resulting in considerable variation in current practice patterns. In this study, our objective was to evaluate the impact of intraoperative frozen section performance on final margin status in patients undergoing PN for localized renal tumors.

Materials and methods

We reviewed our IRB approved, prospectively maintained institutional kidney cancer database for all patients undergoing PN for clinically localized renal tumors from 2005-2011. All patients in this study underwent either open (OPN) or robotic (RPN) partial nephrectomy. Surgical technique and approach were at the discretion of the primary surgeon. No patient in this study underwent pure laparoscopic partial nephrectomy. Robotic nephron sparing techniques were adopted at our institution prior to the beginning of the study period. Demographic, clinical, and pathologic data analyzed included patient age, procedure type, gender status, race, tumor histology, tumor grade, pathologic stage, frozen margin status, Nephrometry score (NS), and final margin status. The NS, a quantitative reproducible measure of tumor anatomic complexity (www.nephrometry.com), was calculated based on preoperative imaging and recorded for each renal mass at the time of surgery.[14]

Patients were stratified based on the receipt of frozen section analysis at the time of PN into 'frozen' and 'no frozen' section groups. All patients underwent analysis of final margins by experienced uropathologists. For patients in the frozen section group, pathologic specimens were taken from the base at the point deemed closest to the tumor by the operative surgeon. In these patients, margin status was assessed both by intraoperative frozen section as well as final pathology.

TABLE 1. **Demographic and tumor characteristics of patients undergoing partial nephrectomy**

n (%)	All patients 537	Frozen 446 (83.1)	No frozen 91 (16.9)	p value
Age				
Mean ± SD		57.9 ± 11.9	58.9 ± 11.0	0.68
Median (range)		59.0 (21.0-83.0)	60.0 (25.0-83.0)	
Gender, n (%)				0.54
Male	345 (64.2)	284 (63.7)	61 (67.0)	
Female	192 (35.8)	162 (36.3)	30 (33.0)	
Race, n (%)				
Caucasian	457 (85.1)	384 (86.1)	73 (80.2)	0.34
Afr. Am	60 (11.2)	46 (10.3)	14 (15.4)	
Other	20 (3.7)	16 (3.6)	4 (4.4)	
Size				
Mean ± SD (cm)		3.6 ± 2.0	4.0 ± 2.1	0.13
Median (range)		3.0 (0.5-15.0)	3.5 (1.0-10.0)	
NS				
Mean ± SD		7.5 ± 1.8	7.5 ± 2.1	0.86
Median (range)		8.0 (4.0-11.0)	7.0 (4.0-12.0)	
Procedure type, n (%)				
Open	259 (48.2)	228 (51.1)	31 (34.1)	0.003
Robotic	278 (51.7)	218 (48.9)	60 (65.9)	

Afr. Am = African American; NS = Nephrometry score

TABLE 2. **Pathologic characteristics of partial nephrectomy specimens**

n (%)	All patients (n = 537)	Frozen (n = 446)	No frozen (n = 91)	p value
Histology combined				0.89
Histologic type-malignant, n (%)				
Clear cell	300 (55.9)	250 (56.1)	50 (54.9)	
Papillary	92 (17.1)	76 (17.0)	16 (17.6)	
Chromophobe	34 (6.3)	30 (6.7)	4 (4.4)	
Sarcomatoid	2 (0.4)	2 (0.5)	0	
Mixed histology	5 (0.9)	4 (0.9)	1 (0.1)	
Non-RCC malignancy	7 (1.3)	7 (1.6)	0	
Unspecified RCC	2 (0.4)	1 (0.2)	1 (1.1)	
Histologic type-benign, n (%)				
Oncocytoma	53 (9.9)	42 (9.4)	11 (12.0)	
Angiomyolipoma	29 (5.4)	23 (5.2)	6 (6.6)	
Other benign	13 (2.4)	11 (2.5)	2 (2.2)	
Fuhrman grade, n (%)				0.55
1	27 (9.2)	22 (8.5)	5 (10.0)	
2	165 (55.3)	148 (57.1)	17 (34.0)	
3	97 (33.1)	85 (32.8)	12 (24.0)	
4	4 (1.4)	4 (1.5)	0	
Unknown	7 (2.3)	0	14 (28.0)	
Pathologic stage, n (%)				0.69
T0	88 (16.4)	73 (16.4)	15 (16.5)	
T1	392 (73.0)	328 (73.5)	64 (70.3)	
T2	28 (5.2)	21 (4.7)	7 (7.7)	
T3	29 (5.4)	24 (5.4)	5 (5.5)	

RCC = renal cell carcinoma

Patients with a negative intraoperative frozen section but positive margin on final pathologic analysis were considered to have a positive final margin. Those patients with positive margins on intraoperative frozen section underwent immediate re-resection. Such patients with no evidence of malignancy on immediate re-resection were considered to have a final negative margin. Positive margin rates for both groups were compared in order to determine the predictive accuracy of frozen section analysis during PN. Demographic, clinical, and pathologic data between groups were compared using ANOVA, Chi-square tests, and Wilcoxon's tests. All analyses were performed using SAS statistical software (ver. 9.2) with a p value of < 0.05 considered statistically significant.

Results

Five hundred thirty-seven patients (mean age 58.1 years ± 11.7 years, 63.7% male) underwent PN (48.2% OPN) for enhancing renal masses (mean tumor size 3.7 cm ± 2.0 cm; mean NS 7.5 ± 1.8, Table 1). Four hundred forty-six patients (83.1%) underwent frozen section at the time of PN while 91 patients were managed without frozen section analysis (16.9%). Of those managed without frozen sections, 65.9% underwent robotic partial nephrectomy. No significant differences in demographic characteristics, including age ($p = 0.68$), gender ($p = 0.54$), and race ($p = 0.34$) were observed when comparing patients undergoing frozen section analysis at the time of surgery to those managed expectantly. Groups were similar with respect to mean total NS (7.5 ± 1.8 versus 7.5±2.1, $p = 0.86$) as well as tumor size (3.6 cm ± 2.0 cm versus 4.0 cm ± 2.1 cm, $p = 0.13$) while patients undergoing RPN were less likely to undergo frozen section (21.5% versus 11.9% $p = 0.003$) at the time of surgery compared to OPN patients. Compared to OPN patients, RPN patients were more likely to have a low complexity NS (43.8% versus 13.2%, $p < 0.0001$) and smaller tumor size

(3.1 cm ± 1.6 cm versus 4.3 cm ± 2.2 cm, $p < 0.0001$). Further, RPN patients were less likely to have frozen section analysis amongst intermediate NS patients ($p = 0.009$) when compared with OPN patients.

A comparison of pathologic characteristics revealed equivalent groups with respect to histology ($p = 0.89$), Fuhrman grade ($p = 0.55$), and pathologic stage ($p = 0.69$), Table 2. A majority of patients with malignant tumors had clear cell pathology (55.9%) followed by papillary (17.1%) and chromophobe (6.3%) RCC, Table 2. Overall final margin status was positive in 10 patients (11.0%) in the 'no frozen' group compared to 20 patients (4.5%) in the 'frozen' group ($p = 0.01$), but this include 12 patients with benign pathology. When restricted to patients with a documented malignancy on final pathology, final margin status was positive in 5.5% (n = 5) and 2.9% (n = 13) in the 'no frozen' and 'frozen' section groups, respectively ($p = 0.16$). In correlating frozen section pathology to overall final permanent margin status, the negative predictive value (NPV) and positive predictive value (PPV) were 98% and 24% while the sensitivity and specificity of frozen section analysis were 36% and 91%, respectively.

During the study period, four patients (0.7%) died of metastatic renal cancer while 19 patients (3.5%) were found to have disease recurrence currently managed with tyrosine kinase therapy (n = 11, 2.0%) and active surveillance (n = 4, 0.7%). Four patients (0.7%) were diagnosed with local recurrences at the tumor resection bed diagnosed at a median of 33 months (IQR: 28-54 months) following surgery. All local recurrence patients had negative frozen sections at the time of PN with negative final pathologic margins and are currently managed under active surveillance. There was no correlation between positive margin status and local recurrence ($p = 1.0$) with a median follow up of 21 months (IQR = 9-31 months).

Discussion

Large clinical series have suggested that NSS results in equivalent cancer specific survival when compared to RN,[2,5,15] as well as decreased risks of chronic renal disease[16] and cardiovascular morbidity.[17] As such, PN is now being preferentially performed for renal masses of increasing size and complexity.[18] The assessment of surgical margins, a commonly utilized measure to determine adequate tumor extirpation, has been implicated by some as an important prognostic factor for cancer control after surgery. Although the exact effect of positive surgical margins (PSM) on disease specific survival has yet to be defined,[7,12,19,20] we demonstrate that intraoperative frozen section analysis has limited clinical utility in predicting local recurrences in patients undergoing PN.

While some investigators have advocated for routine frozen section analysis at the time of partial nephrectomy,[7,11,21] others have demonstrated that obtaining intraoperative frozen sections has limited clinical impact.[12,13,22] In an effort to delineate the utility of intraoperative frozen section, Kubinski et al retrospectively evaluated 78 patients who underwent PN and noted one positive frozen margin (1.3%) consisting of angiomyolipoma rather than RCC. The authors concluded that obtaining frozen sections had limited clinical utility when excision was performed with an attention to maintaining grossly normal renal parenchyma. Similarly, in a series of 301 patients undergoing partial nephrectomy, Duvdevani et al reported a 1.3% false negative rate suggesting limited clinical utility with routine frozen section.[12] Our analysis reflected a false negative rate of 1.6% (n = 7), which included 4 (0.9%) patients with malignant RCC that continue to demonstrate no evidence of cancer recurrence to date.

While false negative results are uncommon, other studies have suggested obtaining frozen sections utilized in concert with a macroscopic evaluation of the resection bed in operative decision-making during complex PN. In an analysis of 61 consecutive OPN, Timsit et al evaluated surgical margins macroscopically and compared their findings prospectively with frozen section examination.[11] The study investigators, reporting a PPV of 80% and a NPV of 100%, demonstrated the important relationship between a surgeon's macroscopic evaluation and frozen section analysis in helping ensure a final negative margin.[11] In our analysis of 537 PN specimens, we observed similar rates of positive margins as described previously in the literature[7,12,19,20] ('frozen' group 4.5% versus 'no frozen' group 11.0%, $p = 0.01$). While no differences in tumor anatomic or pathologic characteristics were demonstrated when comparing patients undergoing frozen section to those who did not, it is possible that suspicion of benign disease on preoperative imaging may have negatively influenced the decision to proceed with a frozen section during the procedure. Supporting this explanation, a significant difference in final margin status between groups was not demonstrated in patients with malignancies documented on final pathology.

Lack of standardization for proper frozen section techniques and indications has led to variation in the practice of obtaining frozen sections intraoperatively. Surgeon preference differs in obtaining frozen sections leading some surgeons to perform tumor

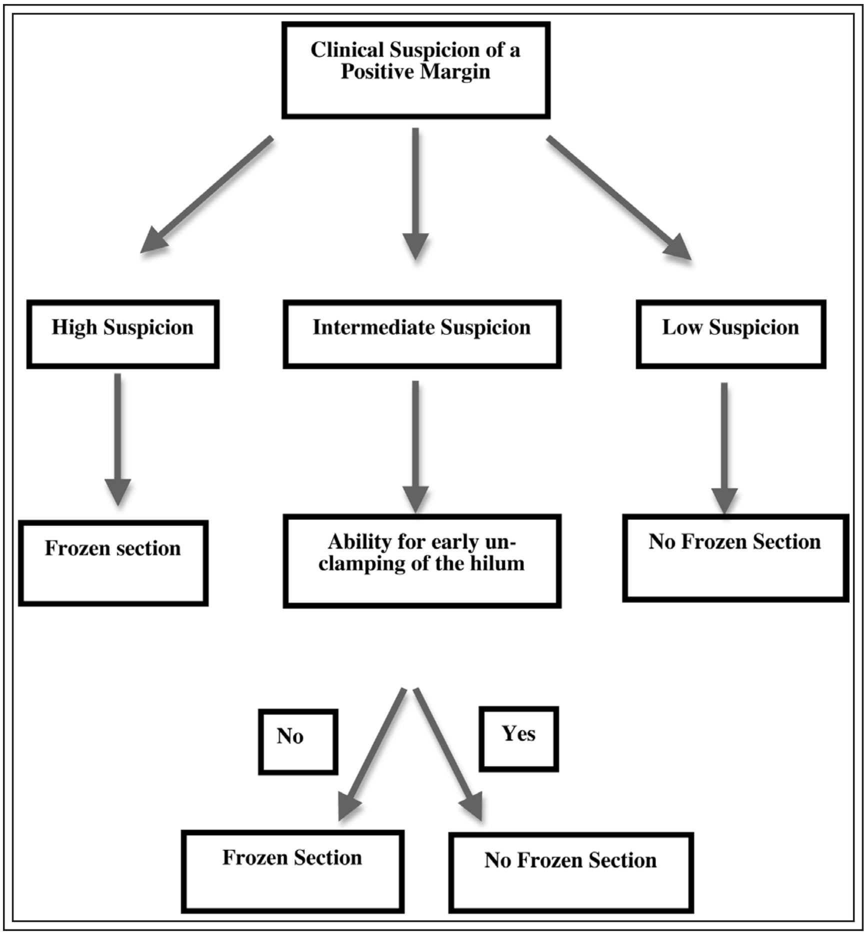

Figure 1. Algorithm for indications of frozen section analysis based on clinical suspicion of a positive margin at the time of partial nephrectomy.

bed biopsies (TBB), gross intraoperative consultation by the pathologist with or without frozen sections, gross inspection of the partial nephrectomy specimen by the surgeon with or without frozen sections, or a combination of these approaches.[11,12,20] Using a combined approach has proven to have better sensitivity and specificity than any one technique alone.[11,12,20] TBB has the poorest sensitivity yet it is the most common in practice. There are no guidelines as to the appropriate indication to obtain frozen sections or how to manage positive surgical margins. Further research stratifying patients by tumor complexity or by minimally invasive versus open approach will clarify a more defined role in select patient populations.

At our institution, we have developed an algorithm that may aide in the decision-making process for indications of frozen section analysis at the time of PN, Figure 1. As such, three factors should be integrated into the decision-making process: the surgeon's clinical suspicion for a positive margin at the time of tumor resection, the ability to unclamp the hilum early, and the time necessary for pathology review of the frozen margin during hilar clamping. Unpublished data from our institution have revealed that frozen section analysis is obtained from our pathologists on average 26.8 ± 7.8 minutes after a margin is sent for review. Furthermore, we have noted variability in the time necessary for frozen section review according to the time of day with the 3-5PM timeframe being the quickest turnaround for frozen section intraoperative results (n = 68, 24.3 minutes ± 6.5 minutes). In cases where frozen sections are reviewed in a delayed fashion, renorrhaphy is often completed prior to the availability of results, thus rendering valuable information useless from a clinical standpoint.

In our algorithm, the surgeon's clinical suspicion drives the indication for frozen section, a finding that has been demonstrated previously.[11] Although cases with high clinical suspicion of a positive margin warrant frozen section performance, instances of low clinical suspicion often render performance of frozen sections as unnecessary. However, if clinical suspicion is intermediate and the ability for early unclamping of the hilum is not possible due to intraoperative factors such as bleeding or complexity of renorrhaphy necessary, then a frozen section could be obtained to further guide operative strategy. In intermediate cases that present an opportunity for low ischemia time, frozen section performance should be avoided as our institutional data has demonstrated a notable time necessary for pathology review of frozen margin status.

The significance of PSMs as a predictor of oncologic outcomes is controversial. Although several studies correlate PSM with shorter cancer-specific survival with increased local recurrence rates,[6,23] others have found no correlation between PSM and disease recurrence.[24-27] In a retrospective review of 809 NSS procedures performed at eight academic institutions, Bernhard et al found 26 ipsilateral recurrences (3.2%), and correlated PSM as a predictor of local recurrences on multivariate analysis ($p < 0.01$). Alternatively, Yossepowitch et al reviewed 1390 PN and found no association between PSM on final pathology for local disease recurrence or metastatic progression when compared to negative surgical margins.[24] Similarly, we found no correlation between local recurrence rates and positive margin status ($p = 1.0$). All four of our local recurrences were in the resection bed and should be considered a true local recurrence. Local recurrences not observed in the resection bed could be synchronous or metachronous metastasis suggesting multifocal disease rather than disease persistence. If one looks at the active surveillance literature, approximately 25% of renal masses on active surveillance exhibited zero growth kinetics according to a recent pooled analysis.[28] Conceivably, even if present, the malignant potential of a PSM may be of an indolent nature taking years to demonstrate any biologic effect or manifest clinical relevance complicating the importance of PSM. It is worthwhile to note that our data demonstrated a difference in final positive margin status by procedure type (RPN 7.6% versus OPN 3.5%, $p = 0.04$), and that patients undergoing RPN were less likely to undergo frozen section analysis (RPN 21.5% versus OPN 11.9% $p = 0.003$). While one could assume that reluctance to perform frozen section during a minimally invasive procedure may have contributed to an increased positive margin rate, this was almost certainly also influenced by our institutional learning curve with the adoption of a new surgical technique. Further, when comparing final margin status in patients with a documented malignancy, no differences between surgical groups was noted (RPN, n = 12, 5.5% versus OPN, n = 6, 2.7%, $p = 0.14$). The clinical significance of this finding is uncertain given the controversial oncologic outcomes with PSM. As per our algorithm, the clinical suspicion for a positive margin may have been low in the RPN cohort due to a high proportion of patients undergoing PN with low complexity NS tumors (43.8% versus 13.2%, $p < 0.0001$) as well as smaller tumor sizes (3.1 cm ± 1.6 cm versus 4.3 cm ± 2.2 cm, $p < 0.0001$) when compared to the OPN cohort.

Limitations of this study include biases inherent to its retrospective methodology. Additionally, variations in surgical technique among the different surgeons at our institution imply the possibility of sampling bias. Furthermore, this study was conducted at a single tertiary care center with experienced uropathologists, which limits the generalizability to community practices. In order to reduce selection bias and more accurately assess the efficacy of frozen section margins, prospective evaluation would be required.

In summary, our institutional cohort of patients undergoing PN for localized RCC demonstrates that performance of frozen section analysis yields limited clinical utility for patients undergoing PN. Frozen section performance was not predictive of final margin status and additionally revealed only limited clinical information in regards to local recurrence. Unfortunately the complexities of frozen section analysis and its clinical applicability are difficult to interpret as it pertains to PSM and local recurrences. PSM may have an unclear biological significance due to growth kinetics as well as difficulties interpreting multifocal recurrence rather then true persistence of disease. Additional prospective studies are needed to evaluate the role of frozen section analysis at the time of partial nephrectomy.

Conclusions

In this large single-institution, retrospective cohort of patients with localized renal tumors, frozen section performance demonstrated limited clinical utility in predicting final pathologic margins as well as local tumor recurrences in patients undergoing partial nephrectomy. Lack of standardization of frozen section techniques as well as indications may be contributing factors. Also, the unclear biological significance of PSM as well as the differences in multifocal recurrences versus disease persistence has complicated interpretation with regards to local recurrences and oncologic efficacy. Further prospective studies are warranted to appropriately delineate the role of frozen section analysis at the time of partial nephrectomy. ☐

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62(1):10-29.
2. Campbell SC, Novick AC, Belldegrun A et al. Guideline for management of the clinical T1 renal mass. *J Urol* 2009;182(4): 1271-1279.
3. Huang WC, Elkin EB, Levey AS et al. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? *J Urol* 2009;181(1):55-61.
4. Thompson RH, Boorjian SA, Lohse CM et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol* 2008;179(2):468-471.
5. Uzzo RG, Novick AC. Nephron sparing surgery for renal tumors: indications, techniques and outcomes. *J Urol* 2001;166(1):6-18.

6. Vermooten V. Indications for conservative surgery in certain renal tumors: a study based on the growth pattern of the cell carcinoma. *J Urol* 1950;64(2):200-208.
7. Lam JS, Bergman J, Breda A, Schulam PG. Importance of surgical margins in the management of renal cell carcinoma. *Nat Clin Pract Urol* 2008;5(6):308-317.
8. Piper NY, Bishoff JT, Magee C et al. Is a 1-CM margin necessary during nephron-sparing surgery for renal cell carcinoma? *Urology* 2001;58(6):849-852.
9. Schlichter A, Wunderlich H, Junker K et al. Where are the limits of elective nephron- sparing surgery in renal cell carcinoma? *Eur Urol* 2000;37(5):517-520.
10. Minervini A, Ficarra V, Rocco F et al. Simple enucleation is equivalent to traditional partial nephrectomy for renal cell carcinoma: results of a nonrandomized, retrospective, comparative study. *J Urol* 2011;185(5):1604-1610.
11. Timsit MO, Bazin JP, Thiounn N et al. Prospective study of safety margins in partial nephrectomy: intraoperative assessment and contribution of frozen section analysis. *Urology* 2006;67(5): 923-926.
12. Duvdevani M, Laufer M, Kastin A et al. Is frozen section analysis in nephron sparing surgery necessary? A clinicopathological study of 301 cases. *J Urol* 2005;173(2):385-387.
13. Kubinski DJ, Clark PE, Assimos DG, Hall MC. Utility of frozen section analysis of resection margins during partial nephrectomy. *Urology* 2004;64(1):31-34.
14. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. *J Urol* 2009;182(3):844-853.
15. Thompson RH, Siddiqui S, Lohse CM et al. Partial versus radical nephrectomy for 4 to 7 cm renal cortical tumors. *J Urol* 2009;182(6): 2601-2606.
16. Huang WC, Levey AS, Serio AM et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006;7(9):735-740.
17. Weight CJ, Larson BT, Fergany AF et al. Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. *J Urol* 2010;183(4):1317-1323.
18. Touijer K, Jacqmin D, Kavoussi LR et al. The expanding role of partial nephrectomy: a critical analysis of indications, results, and complications. *Eur Urol* 2010;57(2):214-222.
19. Marszalek M, Carini M, Chlosta P et al. Positive surgical margins after nephron-sparing surgery. *Eur Urol* 2012;61(4):757-763.
20. Hagemann IS, Lewis JS Jr. A retrospective comparison of 2 methods of intraoperative margin evaluation during partial nephrectomy. *J Urol* 2009;181(2):500-505.
21. Breda A, Stepanian SV, Liao J et al. Positive margins in laparoscopic partial nephrectomy in 855 cases: a multi-institutional survey from the United States and Europe. *J Urol* 2007;178(1): 47-50.
22. Kwon EO, Carver BS, Snyder ME, Russo P. Impact of positive surgical margins in patients undergoing partial nephrectomy for renal cortical tumours. *BJU Int* 2007;99(2):286-299.
23. Bernhard JC, Pantuck AJ, Wallerand et al. Predictive factors for ipsilateral recurrence after nephron-sparing surgery in renal cell carcinoma. *Eur Urol* 2010;57(6):1080-1086.
24. Yossepowitch O, Thompson RH, Leibovich BC et al. Positive surgical margins at partial nephrectomy: predictors and oncological outcomes. *J Urol* 2008;179(6):2158-2163.
25. Lopez-Costea MA, Fumado L, Lorente D et al. Positive margins after nephron-sparing surgery for renal cell carcinoma: long-term follow-up of patients on active surveillance. *BJU Int* 2010;106(5):645-648.
26. Permpongkosol S, Colombo JR Jr, Gill IS, Kavoussi LR. Positive surgical parenchymal margin after laparoscopic partial nephrectomy for renal cell carcinoma: oncological outcomes. *J Urol* 2006;176(6 Pt 1): 2401-2404.
27. Minervini A, Serni S, Tuccio A et al. Local recurrence after tumour enucleation for renal cell carcinoma with no ablation of the tumour bed: results of a prospective single-centre study. *BJU Int* 2011;107(9):1394-1349.
28. Smaldone MC, Kutikov A, Egleston BL et al. Small renal masses progressing to metastasis under active surveillance. *Cancer* 2012; 118(4):997-1006.