Determination of the Safe Surgical Margin for T1b Renal Cell Carcinoma

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Purpose: To determine the rational surgical margin for pathological T1b renal cell carcinoma (RCC).

Materials and Methods: This retrospective study included surveys of 60 patients with T1bN0M0 RCC who underwent radical nephrectomy (RN, n = 40) or partial nephrectomy (PN, n = 20) between October 2008 and December 2014 at the Sun Yat-sen Memorial Hospital affiliated with Zhongshan University. Specimens were collected from 6 sites at the tumour periphery for RN and PN, and at suspected sites on the tumour surface for PN in addition. The histological subtype, pathological grade, surgical margin, pseudocapsule completeness, distribution of satellite foci, and largest distance between the extra-pseudocapsule lesion and primary tumour (DEP) were evaluated. This paper will analyse the relationships between these factors.

Results: The positive surgical margin rate was 10% in patients undergoing PN. The study found no significant relationships between the incidence of satellite foci and tumour diameter, Fuhrman grade, or histological subtype (all $P > 0.05$). However, male sex, positive surgical margins, and an incomplete pseudocapsule were associated with the incidence of satellite foci ($P < 0.05$). Cases with satellite foci tended to show positive surgical margins. The DEP was <1.0 mm for all tumours, but there were no significant relationships between the DEP and the tumour diameter, pathological grade, or histological subtype ($P > 0.05$).

Conclusion: In T1b RCC, a 1-mm surgical margin would be sufficient to attain integrated resection of the primary tumour and its cancerous tissue beyond the pseudocapsule. PN was insufficient to prevent a positive surgical margin, most likely due to the presence of satellite foci.

Keywords: renal cell carcinoma; partial nephrectomy; distance of extra-pseudocapsule lesion; satellite tumours; safe surgical margin

INTRODUCTION

Presently, for T1a renal cell carcinoma (RCC) (< 4 cm in diameter), partial nephrectomy (PN) is recommended by the experts' consensus. However, PN is increasingly being used for resection of T1b RCC tumours (diameter, 4–7 cm). In the 2010 National Comprehensive Cancer Network Kidney Cancer guidelines, PN and radical nephrectomy (RN) were suggested as standard surgical procedures for T1b RCC,[1] although the application of PN for T1b RCC remains controversial.

The greatest concern for applying PN is the possibility of residual tumours. Chen et al.[2] compared T1a and T1b RCC patients who underwent PN, and found that the pseudocapsule incompleteness rates and the incidence rates of lesions beyond the pseudocapsule were significantly higher in patients with T1b RCC, suggesting that PN is not very efficacious for eradication of T1b RCC. Another concern is that PN is associated with operative complications, such as renal parenchyma damage and intrarenal arteries and collecting system lesion, which can cause urinary leak and bleeding[3] .PN also carries the postoperative risk of positive surgical margins. Currently, there is no consensus[4–7] on whether positive surgical margins are a risk factor for RCC recurrence. Similarly, there is no consensus on the rational management for patients with positive surgical margins after PN.[8] Therefore, in order to avoid a positive surgical margin, it is imperative to excise all cancerous tissues completely during PN.

As the practice of PN evolved and minimal invasive techniques were developed to maintain long-term renal function, the traditional surgical margin width was reduced from 1 cm to 0.5 cm for small local RCC tumours. In 2008, the Chinese Diagnosis and Treatment of Urological Disease Guide recommended a 0.5–1-cm surgical margin.[9] As early as 2003, Li et al.[10] proposed that a 0.5-cm surgical margin was sufficient to eradicate lesions beyond the pseudocapsule in T1a RCC tumours. However, other studies have suggested that there were no relationships between surgical margin width and RCC progression, recurrence, or survival rates.[11–12] Therefore, it is likely that a histologically confirmed tumour-free margin of resection, irrespective of margin width, is sufficient to achieve complete local excision of RCC. However, during PN, surgeons attempt to persist the normal renal parenchyma surrounding the tumour, which tends to make the surgical margin larger than desirable. To achieve a clear surgical margin, imaging modalities such as computed tomography and magnetic resonance imaging are used to locate the tumour and surrounding cancerous tissues. In addition, ultrasonography is used to locate suspected satellite foci

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<div align="center">Table 1: Tumour-associated characteristics</div>

	T1b	RN	PN
Pseudocapsule (n, %)			
Complete	25 (41.7)	16 (64.0)	9 (36.0)
Non-infiltrating	6 (10)		
Infiltrating	19 (37.1)		
Incomplete	35 (58.3)	24 (68.6)	11 (31.4)
No tumour invasion	16 (26.6)		
Tumour invasion	13 (21.7)		
No pseudocapsule	6 (10)		
Margin status (n, %)a			
Positive			2 (10)
Negative			18 (90.0)
Satellite foci (n, %)			
Positive	17 (28.3)	13 (76.5)	4 (23.5)
Negative	43 (71.7)	27 (62.8)	16 (37.2)

Abbreviations: RN, radical nephrectomy; PN, partial nephrectomy
a Margin status was evaluated in patients who underwent PN alone.

during PN,[12] but the risk of a positive surgical margin also depends on the surgeon's perioperative predictions of pseudocapsule completeness and normal renal parenchyma capsule completeness around the tumour, which could result in widening margin during the surgery.[13] Previous studies on the safe surgical margin for PN have mostly considered T1a RCC, but this may not translate well to T1b RCC.[14-15] This retrospective study aims to evaluate the rational margin for PN of T1b RCC tumours based on clinicopathological tumour features such as tumour size, pseudocapsule morphology, tumour histology, and the incidence of satellite foci.

PATIENTS AND METHODS

Study population
In this retrospective study, we analyzed the data from patients with histological confirmed T1b RCC who underwent PN or RN (all operations were laparoscopic by two surgeons) at the Sun Yat-sen Memorial Hospital affiliated with Zhongshan University between October 2008 and December 2014. After reviewing the patients' medical records, we reviewed the patients' medical records and identified 469 patients who met the following

criteria: the presence of a single primary renal tumour; the absence of metastasis, as determined by preoperative computed tomography (CT) or magnetic resonance imaging (MRI); and common histological RCC subtypes such as clear-cell, papillary-cell, and chromophobe-cell carcinomas. Finally, we analyzed the data from 60 patients, 40 of whom underwent RN and 20 of whom underwent PN.

Histopathological analysis
In order to determine the maximum tumour diameter, we fixed the 60 excised tumour tissues in 10% formalin and cut along the coronal plane of the kidney. For each tumour specimen, 6 circular specimens from the tumour surface measuring $1.4 \times 1.4 \times 0.4$ cm3 were collected. These specimens were obtained from the centre of tumour and consisted of the primary tumour, tumour margins, and the normal renal parenchyma surrounding the primary tumour (**Figure 1**). During the study period, the surgical margin apart from the tumour in PN was at least 0.5cm. For the 20 PN-excised tumours, suspected sites (without surrounding of normal renal parenchyma by naked eye) at the surgical margin were sampled to determine the surgical margin status. A total of 398

<div align="center">Table 2. Frequency distribution of DEP</div>

DEP(mm)	T1b	percentage%	Accumulative percentage %
0	16	55.2	55.2
0.01-0.50	7	24.1	79.3
0.51-1.00	6	20.7	100.0

*when pseudocapsule existed and was incomplete

Table 3: Frequency of DEP according to tumour diameter, Fuhrman grade, and histological subtype

	DEP		*P* value
	N	X ± SD	
Tumour diameter (cm)[a]			
4.1–5.0	7	0.61 ± 0.17	-
5.1–6.0	3	0.37 ± 0.24	.015
6.1–7.0	3	0.18 ± 0.11	.006
Fuhrman grade [a]			.070
High differentiation	7	0.58 ± 0.15	
Moderate differentiation	4	0.24 ± 0.15	
Low differentiation	2	0.43 ± 0.47	
Histological type [a]			NA
Clear-cell	13	0.45 ± 0.25	
Papillary-cell	0	0	
Chromophobe-cell	0	0	

Abbreviations: DEP, distance of the extra-pseudocapsule lesion; SD, standard deviation; NA, non-applicable
a Analysis of variance (ANOVA)

specimens were paraffin-embedded, sectioned, and subjected to haematoxylin and eosin staining. Slides were evaluated using a light microscope with a camera attachment. All the specimens were examined by one dedicated pathologist.

Tumour characteristics
Characteristic tumour features are shown in Figure 2. A complete pseudocapsule was defined as being present when all tumour samples from the same patient had a
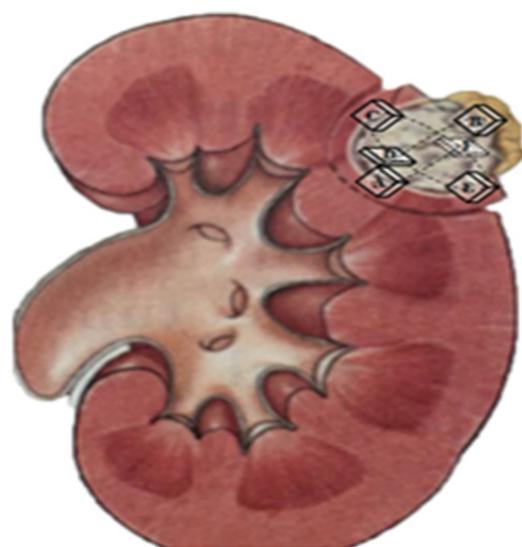

Figure 1. Diagrammatic representation of tumour sampling regions
The tumour edge close to the pelvis (A), the tumour edge close to the renal parenchyma and medulla (C, D, E, and F), and the tumour edge close to the renal capsule (B).

pseudocapsule that continuously separated the tumour from the normal renal parenchyma. Incomplete pseudocapsules was defined where is was found with : no tumour invasion (**Figure 2A**), with tumour invasion beyond the pseudocapsule (**Figure 2B**), or as a complete absence of pseudocapsule (**Figure 2C**). The distance of the extra-pseudocapsule lesion (DEP) was defined as the maximal distance from the outermost margin of the primary tumour to the outermost layer of the pseudocapsule, as measured to a precision of 0.01 mm (**Figure 2D**). The DEP was defined as 0 mm when incomplete pseudocapsule had no tumour invasion. The status of the surgical margin was described as positive if tumour cells were present, and was described as negative if they were not. Satellite foci were defined as small distinct focal points of tumour cells outside the pseudocapsule and departed from the primary tumour (**Figure 2E**).[16-17]

Outcome assessment
SPSS®, version 19.0 (IBM, Armonk, NY, USA) and Excel® 2010 (Microsoft, Redmond, WA, USA) were used for all statistical analysis. Differences between the RN and PN groups were evaluated using Student's t-test or the Chi-square test. Differences among factors possibly affecting DEP were evaluated using the analysis of variance (ANOVA). Relationships between variables were evaluated using a Pearson's correlation test. The two-sided alpha level of 0.05 and a *P*-value of < 0.05 were considered statistically significant.

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

Histopathological Tumour-associated Characteristics

Table 4: Factors associated with the incidence of satellite foci

Variable	Satellite foci		*P* value
	Negative	**Positive**	
Sex [a]			
Male	29 (64.4)	16 (35.6)	.032
Female	14 (93.3)	1 (6.7)	
Tumour diameter (cm) [a]			
4.1–5.0	21 (80.8)	5 (19.2)	.385
5.1–6.0	14 (63.6)	8 (36.4)	
6.1–7.0	8 (66.7)	4 (33.3)	
Fuhrman grade [a]			
High differentiation	28 (77.8)	8 (22.2)	.433
Moderate differentiation	12 (63.2)	7 (36.8)	
Low differentiation	3 (60.0)	2 (40.0)	
Margin status [a]			
Negative	16 (88.9)	2 (11.1)	.003
Positive	0 (0.0)	2 (100.0)	
Histological subtype [a]			
Clear-cell	35 (71.4)	14 (28.6)	.988
Papillary-cell	5 (71.4)	2 (28.6)	
Chromophobe-cell	3 (75.0)	1 (25.0)	
Pseudocapsule [a]			
Complete	22 (88.0)	3 (12.0)	.018
Incomplete	21 (60.0)	14 (40.0)	

[a] Chi-square test

The pseudocapsule morphologies, margin statuses, and existence of satellite foci are shown in **Table 1**, both for the overall patient cohort and groups according to the surgical procedure. There was no significant difference in rates of pseudocapsule completeness according to surgical modality. The majority of patients did not have satellite foci.In the PN group, the majority of patients had negative surgical margins.

Factors Affecting the DEP
Distribution of DEP was shown in **Table 2**. DEP varied significantly as tumour diameter increased. This appeared to indicate an association between increasing tumour size and decreasing DEP which failed to achieve statistical significance. In addition, there were no significant correlations between DEP and pathological grade. All cases of RCC infiltrating beyond the pseudocapsule into normal parenchyma were clear-cell carcinomas (**Table 3**).

Factors Associated with the Incidence of Satellite Foci
We evaluated the relationship between clinicopathological parameters and the incidence of satellite foci (**Table 4**). In 17 cases of positive satellite foci, the distances between the primary tumour and the satellite focus ranged from 0.5 mm to 5.2 mm. The presence of satellite foci was not associated with tumour diameter, Fuhrman grade, or histological subtype ($P > 0.05$), but was associated with sex and pseudocapsule completeness ($P < 0.05$). Male patients and patients with an incomplete pseudocapsule were more likely to have satellite foci.

DISCUSSION
Numerous clinical studies have indicated that PN and RN have comparable effective local control and disease-specific survival rates in patients with T1b RCC. [18–19] The major concern for the application of PN is the risk of incomplete tumour excision because of tumour extension beyond the pseudocapsule or the presence of satellite foci, which are difficult to detect both by using imaging modalities. In addition, discrepancies concerning the appropriate surgical margin width have been a cause for concern. [20–21]

The traditional tumour excision margin of 5–10 mm was applied. However, without a reference point, it was impossible to excise the thick parenchyma that surrounds the primary tumour evenly, because the bottom of the margin was usually thinner than the rest of the margin. [24] In addition, thicker surgical margins are difficult to achieve by laparoscopic PN within 20–30 min of hot ischemia, which can lead to an increased risk of complications.

All DEPs in the present study were well within the traditional surgical margin width. Based on the DEP, a 1-mm surgical margin would be sufficient to attain
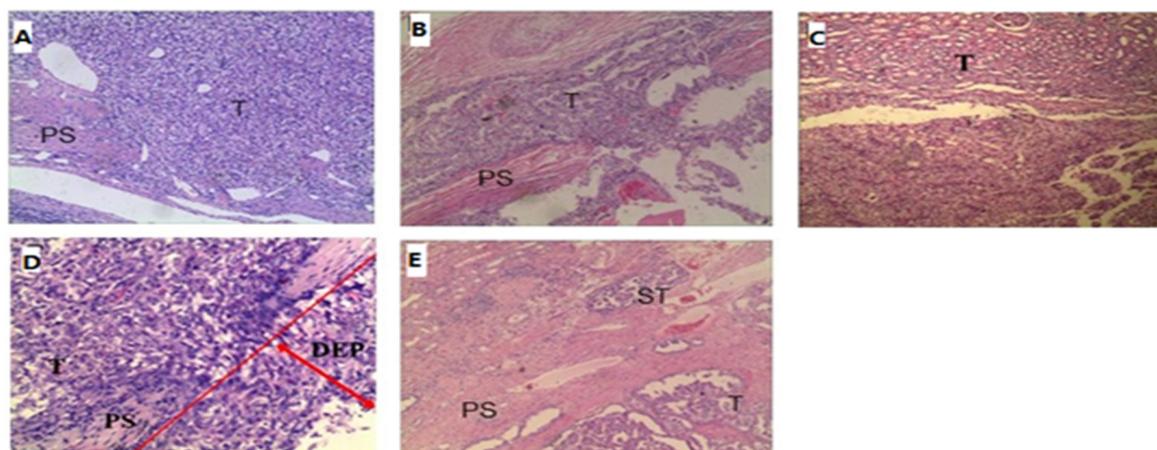
Figure 2. Histological tumour features
(A) Incomplete pseudocapsule with no tumour invasion
(B) Incomplete pseudocapsule with tumour invasion
(C) Incomplete pseudocapsule with a complete absence of tumour capsule
(D) The DEP
(E) Satellite foci
PS, pseudocapsule; T, tumour; ST, satellite foci; DEP, distance of the extra-pseudocapsule lesion

integrated resection of the primary tumour and its cancerous tissue beyond the pseudocapsule. However, this margin was not sufficient for two patients who did show positive surgical margins, most likely because those patients had satellite foci. This suggests that, although PN with a surgical margin <1 mm might be useful for preventing positive surgical margins by removing residual tumour, it might not be sufficient for preventing positive margins caused by satellite foci.

In the present study, the incidence rate of satellite foci was 28.3%, In this study, the satellite foci incidence rate was higher than the positive surgical margin rate of 10.0%. A similar finding was reported in a previous study of local RCC after PN; the satellite foci incidence rate was 15.7% and the positive surgical margin rate was 0.0–7.0%.[11,22] It is likely that some correlation exists between satellite foci and positive surgical margin. In 17 cases, the distance between satellite foci and the primary tumour was 0.5–5.2 mm. However, because the measured distance was limited by pathological sampling, only those foci in proximity to the tumour could be observed. This may result in false negative findings. In 32 cases of multicentric foci, Li et al.[11] found that 23 cases were < 8 mm from the primary tumour, but 9 cases were about 30 mm (range:15–60 mm) . Loran et al. indicated that the distance between multicentric foci and the primary tumour was more than 20mm.[25] Taken together, these results suggest that the traditional surgical margin width of 5–10 mm would not be sufficient to remove satellite foci. Local recurrence after PN is more likely attributable to satellite foci, rather than (in any substantial sense) residual tumour caused by incomplete removal of the primary tumour. Some researches show positive surgical margins have been shown to increase the recurrence risk after PN, but did not affect the survival of patients. However, others proved positive surgical margins did not affect local recurrence or metastases risks after PN.[22] There are a number of factors that may explain why having a positive surgical margin did not appear to affect clinical efficacy in these studies.[23] As mentioned above, because either ectomy does not completely clear up the satellite foci, it makes no obvious difference to overall survival no matter whether the surgical margin is positive or negative.

In general, a narrow surgical margin width is recommended in T1a RCC, but we do not advocate tumour enucleation for T1b RCC. In the present study, the incomplete pseudocapsule rate in patients with T1b RCC was much higher than that reported for T1a RCC.[2] Even if the pseudocapsule was complete, tumour invasion of the pseudocapsule was prevalent(76%). Besides, there is a risk of disrupting the pseudocapsule during tumour enucleation, which could lead to tumour dissemination. Both Minervini et al.[26] and Ficarra et al.[21] demonstrated that cancer cells could be separated from the surgical margin by a thin layer of chronically inflamed tissues. However, some sites with incomplete pseudocapsule did not show an inflammatory layer enveloped (**Figure 2B**). These results may narrow applications of tumour enucleation, especially for highly malignant T1b RCC or tumours with an incomplete pseudocapsule.

There were some limitations in this study: 1) to meet the inclusion of this study and to match paired groups demand, it can only recruit 60 patients in all, the number of patients is relatively small; 2) Although the presence of satellite foci and their exact location could be better evaluated in a radical nephrectomy specimen rather than a partial specimen, more and more patients choose to use partial nephrectomy. So there is great significance to explore the relationship between satellite foci and surgical margin in partial nephrectomy; 3) The follow-up is not long enough to study the long term prognosis.

CONCLUSIONS

In T1b RCC, a 1-mm surgical margin was sufficient to excise the primary tumour and its residual tissue beyond the pseudocapsule. However, the presence of sat-

ellite foci might cause a positive surgical margin. The incidence of satellite foci was associated with male sex and an incomplete pseudocapsule in patients who underwent laparoscopic PN. Therefore, we conclude that laparoscopic PN is not sufficient to remove satellite foci in patients with T1b RCC.

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CONFLICT OF INTEREST

The authors report no conflict on interests.

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