

Scoring the Positive Margin Status in Partial Nephrectomy

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Abstract

Objective

A clear resection margin is one of the trifecta outcomes in partial nephrectomy. We proposed a positive surgical margin scoring system and implemented it in our cases to assess its effect on the oncological outcomes.

Methods

Retrospective review of prospectively collected multi-center data was performed for all the partial nephrectomy (PN) procedures performed between April 2009 and August 2019. Demographic data, RENAL nephrometry score, peri-operative data and margin status were collected. Positive surgical margin (PSM) cases were given a scoring system of I, II and III for PSM that are <3mm, 3-5mm and >5 mm, respectively. Postoperative, oncological results and adverse events were using Stats Direct. Data analysis was performed using t-test. Comparative data between the two groups was calculated using z-score calculator. *p* values of 0.05 or less were considered statistically significant.

Results

A total of 339 PN procedures were performed for histologically proven renal cancer. Forty four patients had PSM. There were 17, 16 and 11 patients with score I, II and III PSM, respectively. Those with a high RENAL nephrometry score had the highest rate of PSM (n=21) as opposed to the intermediate (n=13) and the low (n=10) score groups. After an average follow up of 38 months (10-132), a total of 21 recurrences were recorded; 14 had clear resection margins, 7 were PSM (PSM-I=1, PSM-II=2, PSM-III=4, respectively).

Conclusion

Overall patients with PSM status have a low chance of recurrent or metastatic disease although those with a wider PSM (III) have a higher chance of recurrent and/or metastatic disease. Tumour grade and pathological T-stage are independent factors for recurrence/metastasis. Larger cohort and longer follow up would be recommended.

Keywords: Laparoscopy, Partial nephrectomy, Positive margin.

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Introduction

There is a growing trend of utilizing nephron-sparing surgery (NSS) as the gold standard treatment for localised renal tumours. One of the goals of NSS is obtaining negative surgical resection margins. Several papers initially described a safe resection margin of 1-2cms. This however has changed recently to include a minimal negative resection margin to be a safe approach¹

Several studies investigated the recurrence rate after partial nephrectomy. They found that the recurrence rate is exceedingly low². Others studied the use of intra operative frozen sections to ensure negative surgical margin status. These sections, however, were found to be unreliable in determining the actual margin status on the main specimen^{3,4,5}.

The authors and other urologists are aware of the extent of positive surgical margins in radical prostatectomy specimens and how studies have shown strong correlation with the biochemical and clinic recurrence⁶. However, this was not explored yet this far for the partial nephrectomy procedures, hence we proposed a PSM scoring system and aimed to categorize the positive margin status and explore its relationship with the oncologic outcome in NSS.

Methods

The records of laparoscopic partial nephrectomy (LPN) patients across two tertiary care centres in Northern Ireland between April 2009 and August 2019 were reviewed. Demographic data, RENAL nephrometry score, peri-operative information and margin status were all collected. Positive margin (PSM) cases were given a scoring system of I (focal margin and/or margin ≤ 3 mm), II (PSM=3-5mm) and III (PSM>5 mm)⁶. RENAL nephrometry and the PSM scoring systems were assessed by two independent clinicians.

Peri-operative complications were recorded and assessed according to Clavien-Dindo scoring system. The follow up frequency of post nephrectomy patients will very much depend on the grade and stage of the tumour.

However, European Association of Urology guidelines provided level 3 evidence to NSS being associated with an increased risk of recurrence for larger (> 7 cm) tumours, or in a PSM status. Hence in our institute, patients with PSM were followed up using six monthly contrast enhanced CT scan for the first two years followed by annual CT for at least 10 years. Postoperative oncological results and adverse events were analysed using Stats Direct. Data analysis for each group was performed using t-test, and for comparative results z-score was used. Statistical significance was considered for *p* values of 0.05 or less.

Results

A total of 359 PN procedures were performed for radiological renal cancer. Of those, 20 patients were initially excluded given the benign histology and another 39 cases were excluded due to lack of sufficient data. Patients' demographics, tumour characteristics and peri-operative complications were listed in tables 1, 2 and 3, respectively. There were 100, 89 and 111 patients with low (0-6), intermediate (7-9) and high Nephrometry score (>9), respectively.

The two groups of surgically clear margins (CM) and PSM were comparable in terms of demographics, peri-operative outcomes, tumour histology and staging (tables 1, 2, 3).

Of the 300 finally identified and analysed patients, we had 44 with PSM. There were 17, 16 and 11 patients with PSM score of I, II and III, respectively. There was no difference in the patient demographics in the two groups (CM vs PSM) as illustrated in table 1. However, higher RENAL nephrometry scores were found in the clear margin group ($p=0.02$), and higher pathological stages in the PSM group ($p=0.02$) as illustrated in table 2.

PSM-I tumours had 4, 3 and 10 patients with low, intermediate and high RENAL nephrometry scoring system, respectively. PSM-II had 2, 4 and 10 cases of low, intermediate and high RENAL nephrometry scoring system, respectively. While those with PSM-III had 2, 4 and 5 cases of low,

intermediate and high RENAL nephrometry scoring system, respectively. Although RENAL scoring is directly proportional to the scoring of PSM (using t-test: $p=0.02$), however, using chi-square calculator, RENAL scoring is not associated with a higher overall PSM ($p=0.76$). The median tumour grade was significantly higher in the PSM group ($p=0.004$).

After an average of follow up of 38 months (10-132), one PSM-III patient elected for a completion nephrectomy, and the subsequent histological analysis showed no residual tumour. A total of 21 recurrences were recorded; 14 had initial clear resection margins, while 7 patients had PSM (PSM-I=1, PSM-II=2 and PSM-III=4, respectively). Although the actual number of recurrences within the clear margin group was higher (14 vs 7), the percentage of recurrence rate was higher in the PSM group ($p<0.0001$) at 5% for the CM and 15% for the PSM group.

On another hand, there was a statistically significant association between tumour pathological stage and recurrences in the clear and PSM groups ($p=0.01$, $p=0.002$, respectively). Similarly, higher tumour grade was associated with higher tumour recurrence in both groups ($p=0.01$) as shown in table 2.

One PSM-III patient (G3pT3a) developed distant metastasis. One patient (clear margins, G2 pT1b) died 7 years later of metastatic disease. Using Kaplan-Meier survival analysis, tumour recurrence did not seem to affect the cancer free survival ($p=0.06$) but it does for the overall survival ($p=0.017$), Figures 1 and 2, respectively.

Discussion

Partial nephrectomy has gained wide acceptance as the gold standard procedure for localized renal tumours with a comparative oncological and better functional outcome compared to radical nephrectomy that is true even for this with high-risk tumours upon final histology⁷. However, with widening the indications of PN and performing more complex ones, this would inevitably be at the expense of attaining the peri-operative

trifecta⁸.

The incidence of PSM in partial nephrectomy has varied widely, ranging from 2 to 10%^{9,10} and managing the postoperative PSM in partial nephrectomy has been controversial.

Those who followed up their PSM patients have shown a latent incidence of recurrent and/or metastatic tumour that could be observed at any time during the studied 10 years of follow up⁸.

In this study we had 12% positive margin cases out of all the 359 partial nephrectomies done. As there was no prior scoring of the PSM in partial nephrectomy, we proposed one and extrapolated the classification from other cancer papers⁶. Out of all cases, 44 patients had a PSM and interestingly though, only 7 patients developed recurrences from this group, and the other 14 recurrences were with negative resection margins. Higher PSM score was associated with higher recurrence rate; 4 of the 7 recurrences occurred in the PSM group that has a score of PSM-III. Whilst the tumour grade did not affect the recurrence in the clear margin group, it did with the PSM group, with higher grade being associated with higher tumour recurrence (The tumour characteristics for the recurrent cases are shown in table 5).

Some of those within the CM group that recurred had a clear margin within 1mm, but the recurrences occurred at the site of the tumour bed, so one can argue about the safety of the minimal clear margin. However, recent evidence supports the minimal margin to be oncologically equal to the traditional wide (0.5-1cm) margin^{11,12}.

One of the clear margin cases showed a breach of the tumour pseudocapsule, but a separate biopsy from the tumour base was clear, hence it was concluded to be with a final clear margin result. Literature is currently disputing the accuracy and importance of obtaining a frozen section from the tumour bed at the time of partial nephrectomy. This may be explained by the technical challenge of obtaining a biopsy from the tumour bed, especially with those that have a wide contact base with the kidney¹³, and a biopsy from one area does not necessarily give the accurate margin clearance¹⁴.

The rate of recurrence in PSM cases in this paper was 15%, which concurs with the current literature¹⁵. Our recurrence rate is less than the current evidence¹⁶ and our average distance of the clear margins from the tumour is 3.4mm (0.3-10mm).

Conclusion

Despite the limited number of recurrences, it is shown that they were not related to the extent (scoring) of the PSM, although those with a wider (>5mm) margin or PSM-III had a higher chance of recurrent and/or metastatic disease. Higher tumour grade and higher pathological stage independently influence recurrence in PSM cases, and this should be used when counseling

patients with PSM. Finally, there is a potential for further collaboration, work and analysis on a larger group of patients to develop a solid scoring system for partial nephrectomy patients with a PSM.

Compliance with Ethical Standards: No conflict of interest to declare.

- Disclosure of potential conflicts of interest: None
- Research involving human participants and/or animals: No ethical issues.
- Informed consent: prospectively obtained and departmentally approved.

Tables

Table 1: Patient demographics

Demographic	CM		PSM		<i>p</i>
Patient number	256		44		
Median Age	58 (IQR 61-75)	0.51	59	(IQR 65-75)	
Male	180	0.9	28		
Female	76		16		
			4		
Single kidney	8	0.8			

CM=clear margin

PSM=positive surgical margin

Table 2: Tumour characteristics

Characteristic	CM	PSM	<i>p</i>
Diameter	26mm (IQR 20-31)	25mm(IQR 18-31)	0.4
Anterior	93	9	0.015
Posterior	153	35	0.9
Low RENAL score	85	16	0.7
Intermediate RENAL score	79	20	0.06
High RENAL score	92	8	0.02
Histology	CM	PSM	<i>p</i>
Renal Cell Carcinoma	199	34	0.9
- Clear Cell	G1 33	6	0.8
	G2 143	24	0.8
	G3 23	4	0.9
- Papillary	39	6	0.78
- Chromophobe	16	4	0.4
- Mucinous tubular and spindle cell	1	0	
- Carcinoid	1	0	

pT stage	CM	PSM	p
T1a	196	29	0.13
T1b	42	9	0.5
T2	6	0	0.3
T3a	12	6	0.02

CM=clear margin

PSM=positive surgical margin

IQR = Interquartile range

pT stage = pathological stage

Table 3: Complications

Complication	Clavien-Dindo Classification	No. of Patients	R.E.N.A.L Nephrometry Score
PSM group			
Atelactasis	1	2	8P, 7A
Bleeding (transfusion)	2	1	9P
Urine leak - conservative	2	1	7P, 6A
Urine leak (Stenting GA)	3b	1	6A
Bleeding (laparotomy)	3b	1	5P
		Total 6	
CM group			
Atelactasis	1	7	
Bleeding		8	
Conservative	2	3	6P,7A,7A
Embolisation	3a	4	8P,9A,6P,10A
Re-operated	3b	1	10A
Urine leak - conservative	2	8	6A,4A,9P,3A,4A,7P,5A,8A
Urine leak (Stenting GA)	3b	4	6A,5A,8A,4P
Port site hernia-theatre	3b	1	4A
		Total 36	

CM = clear margin

PSM = positive surgical margin

A = Anterior

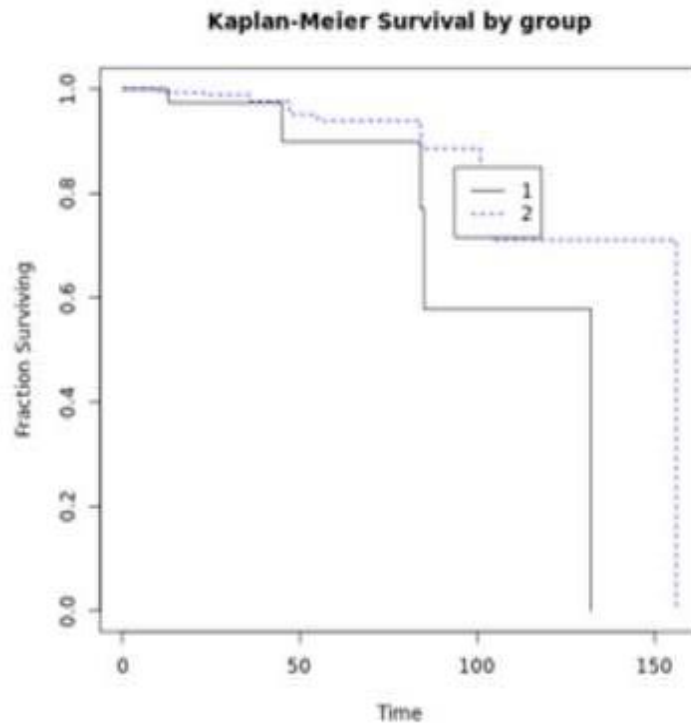
P = Posterior

Table 4: tumour recurrences and their characteristics

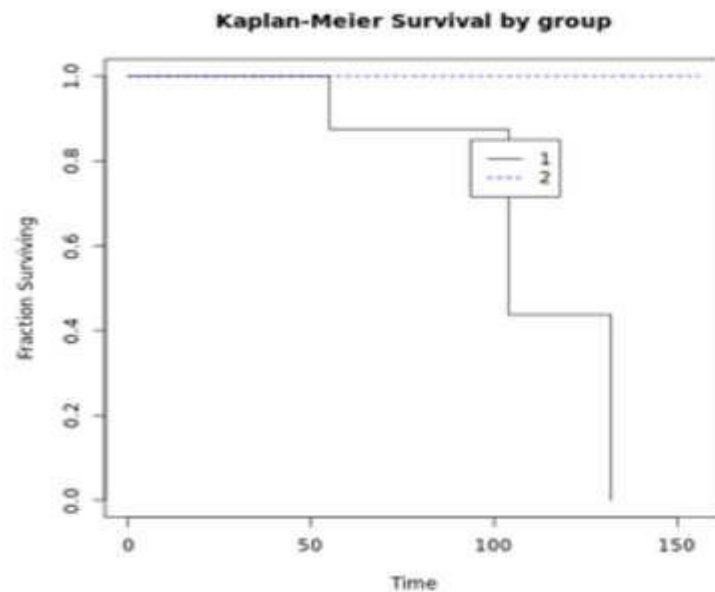
Patients	Margin	RENAL score	Grade	Type	pT stage
1	Clear	7A	2	Clear CC	1a
2	Clear	8A	2	Clear CC	1b
3	Clear	6P	2	Clear CC	1a
4	Clear	7A	2	Clear CC	1a
5	Clear	5A	2	Papillary	3a
6	Clear	4A	2	Clear CC	1a
7	Clear	4A	3	Clear CC	1a
8	Clear	6P	3	Papillary	1b
9	Clear	8A	3	Clear CC	1a
10	Clear	4A	4	Clear CC	3a
11	Clear	7A	3	Clear+Sarcoma	3a
12	Clear	5P	4	Clear CC	2b
13	Clear	7A	2	Clear CC	1a
14	Clear	6P	3	Clear CC	1a
Median		7	2		1a
Patients	Margin	RENAL score	Grade	type	pT stage
15	PSM-1	6A	1	Clear CC	1a
16	PSM-2	9A	3	Papillary	1a
17	PSM-2	7A	2	Oncocytoma	1a
18	PSM-3	5A	3	Papillary	3a
19	PSM-3	7A	3	Clear CC	3a
20	PSM-3	9P	3	Clear CC	1a
21	PSM-3	10A	2	Clear CC	1a
Median		7	3	Papillary	1a

Table 5: differences in tumour characteristics in the two groups

	Grade-1	Grade-2	Grade-3	Grade-4	pT1a	pT1b	pT2a	pT3a
Clear-NR	22	143	77	0	164	57	9	12
Clear-R	0	8	6	0	7	3	1	3
<i>p</i> value	0.2	0.8	0.4		0.17	0.85	0.52	0.01
	Grade-1	Grade-2	Grade-3	Grade-4	pT1a	pT1b	pT2a	pT3a
PSM-NR	4	26	6	1	28	7	0	2
PSM-R	1	2	4	0	2	2	0	3
<i>p</i> value	0.3	0.02	0.008	0.32	0.007	0.28	0.52	0.002

Figures:**Figure 1: Kaplan Meier cancer free survival analysis of the two groups**

Group1: PSM group, Group2: clear margin group

Figure 2: Kaplan Meier overall survival analysis of the two groups**Group1: PSM group****Group2: clear margin group****References**

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نظام تسجيل قيمة الحواف الجراحية الموجبة في عمليات استئصال الكلية الجزئي

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الملخص

الأهداف:

استحداث نظام تسجيل لقياس قيمة الحافة الجراحية على المرضى المصابين بأورام الكلى، والمعالجين جراحياً باستئصال الكلية الجزئي، وتقييم نتائج التطبيق على علاج ومستقبل هذه الأورام.

طرائق الدراسة:

تم إجراء مراجعة رجعية للبيانات من المراكز الجراحية المتعددة، والتي تم دراستها مستقبلياً لعمليات استئصال الكلية الجزئي جميعها، والتي تم إجراؤها بين أبريل (2009)، وأغسطس (2019)، والتي تضمنت البيانات السكانية (الديموغرافية)، ونتيجة قياس الكلى، والبيانات المحيطة بالعملية، وقيمة الحافة الجراحية للحالات قيد التحليل، وأعطيت الحالات التي لديها حافة جراحية موجبة وفق نظام التسجيل الدرجة: (1) و (2) و (3) للحافة البالغة (3) ملم، و (3-5) ملم، وأكثر من (5) ملم على التوالي. وتم أيضاً- تحليل نتائج ما بعد الجراحة، وحالة الأورام والأحداث السلبية -إن وجدت- باستخدام التحليل الإحصائي المباشر، وتم إجراء تحليل البيانات باستخدام اختبار (t) الإحصائي، إضافة إلى حساب البيانات المقارنة بين المجموعتين باستخدام حاسبة قياس مجموع النقاط المحرزة (z-Score)، واعتبرت قيم الاحتمالية البالغة (0.05) أو أقل قيم ذات دلالة إحصائية.

النتائج:

تم إجراء تحليل (339) عملية جراحية لحالات سرطان الكلى المثبت بالفحص النسيجي، حيث كان لدى (44) مريضاً حافة جراحية موجبة، وكان هناك (17) و (16) و (11) مريضاً ضمن الدرجة: (1) و (2) و (3) (على التوالي)، وكان المرضى الذين لديهم درجة عالية في قياس الكلوي (RENAL NEPHROMETRY) أعلى معدل للهامش الجراحي الموجب (21) مريضاً مقارنة بالمجموعة المتوسطة (13) مريضاً، والمجموعة المنخفضة (10) مريضاً، وبعد المتابعة لمعدل مدة (38) شهراً -المدى 10-132 شهراً- تم تسجيل عودة الورم مجدداً لدى (21) مريضاً، من ضمنهم (14) مريضاً كان لديهم قيمة الحافة الجراحية واضحة، و (7) مريضاً كانت لديهم حافة جراحية موجبة: مريض واحد من الدرجة (1) ومريضين من الدرجة (2) وأربعة مريضاً من الدرجة (3).

الاستنتاج:

المرضى المصابون بسرطان الكلى والمعالجين جراحياً باستئصال الكلية الجزئي والذين لديهم حافة جراحية موجبة، لديهم فرصة منخفضة لعودة المرض وظهوره مجدداً، وأولئك الذين لديهم قيم للحافة الجراحية أعلى، لديهم فرصة أكبر للإصابة بالمرض المتكرر وظهوره مجدداً، ودرجة الورم والتصنيف التائي لمرحلة الورم، هي عوامل مستقلة لعودة المرض وانتشاره مجدداً، مع التوصية بمتابعة هؤلاء المرضى لمدة طويلة.

الكلمات الدالة: منظار البطن، استئصال الكلية الجزئي، حافة جراحية موجبة.