

Original Article

Gross intraoperative evaluation (GIE): a reliable method for the evaluation of surgical margins at partial nephrectomy

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Abstract: To determine the efficacy of a new method called by us as “gross intra-operative evaluation (GIE)” for the assessment of surgical margin (SM) status. A total of 26 consecutive patients operated with cT1a-b renal tumors at a single center were included in this study. After the excision, the tumors were uniformly divided into two halves in the longitudinal axis ex vivo. In this way, margins were exposed for GIE for the evaluation of the safety of SMs. Findings of GIE were compared with the permanent section analysis in terms of SM status. Mean patient age, tumor size and margin thickness was 59 (38-79), 3.1 (1.5-6) cm and 3.7 (0.1-12) mm, respectively. In all patients, GIE showed intact margins and none of the patients had positive SM in the final pathological examination. There was no evidence of local recurrence or distant metastasis with a mean follow-up of 25 (4-104) months. All patients are alive. GIE of resected specimen without FS analysis is a safe and effective method for the evaluation of SMs in partial nephrectomy patients.

Keywords: Kidney cancer, nephron sparing surgery, partial nephrectomy, surgical margin, tumor bed biopsy

Introduction

The gold standard for the treatment of T1 stage renal cell carcinoma (RCC) is nephron sparing surgery or partial nephrectomy (PN) [1]. Sometimes nephron loss needs to be minimized because of bilateral involvement or in the setting of a tumor bearing single kidney.

As dictated by oncological teaching, margin-negative resection is an essential goal. Currently, routine approach for the evaluation of the margins is the macroscopic inspection of the undisturbed specimen during surgery followed by tumor bed frozen section biopsies. Given the facts that frozen section of the tumor bed biopsy (TBB) prolongs surgical time, increases ischemia time and cost of operation, safe alternative methods for the improvement of these factors are obviously needed. The requirement of frozen section biopsies during PN for negative surgical margin is a controversial issue and has been recently evaluated by a

few studies. Both of these studies showed that so called gross intraoperative consultation (GIC)/macroscopic assessment with pathologists alone was superior to TBB alone in the determination of surgical margin status, somewhat outdating the practice of TBB [2, 3].

In our prospective study, we similarly present a new method which eliminates frozen section TBB and pertinent time delay. We evaluated surgical margins of open PN specimens macroscopically, without taking TBBs, by intraoperative examination of the tumors divided ex vivo into two halves called by us as “gross intra-operative evaluation (GIE)”. The objective of this study was to determine the efficacy of GIE prospectively by comparing the findings of GIE with the gold standard permanent section analysis in terms of surgical margin status.

Materials and methods

A total of 28 (21 males, 7 females) consecutive patients who had open PN for cT1a-b renal

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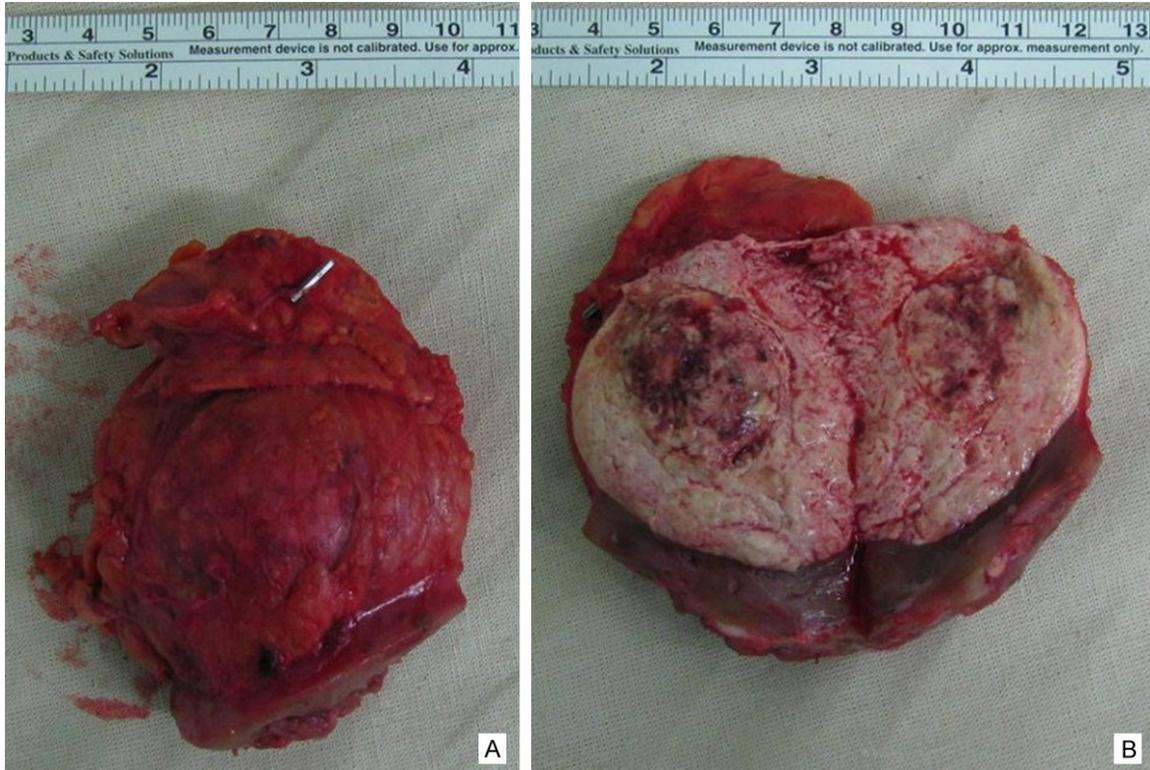


Figure 1. A: Partial nephrectomy specimen surrounded by continuous normal parenchyma. B: The same specimen divided into two halves for gross intraoperative evaluation (GIE).

tumors by the senior author (OD) between 2001 and 2010 were included in this study. Preoperative evaluation protocol includes ultrasonography, computerized tomography (CT) \pm angiography and/or magnetic resonance imaging (MRI) \pm angiography of the abdomen and PA-lateral chest x-rays and routine blood work. All cases were restricted to the kidney with no image detected or incidentally encountered (at surgery) lymph node or metastatic involvement, or any other malignancy. Informed consent was obtained from all patients.

Surgical technique

All patients were operated with retroperitoneal approach. A flank incision was made parallel to the 11th or 12th rib, depending on the tumor location. The renal pedicle was carefully isolated and controlled with vascular clamps before tumor resection. To prevent ischemic renal damage, all patients were hydrated and infused with 16 grams of 20% mannitol a few minutes before arterial occlusion to decrease intracellular swelling. Renal hypothermia was induced by intracorporeal ice slush applied to the sur-

face for 15 minutes. During PN, the normal kidney tissue was excised aiming to leave approximately 3-5 mm of normal kidney parenchyma around tumor tissues, and fatty tissues over the tumors were preserved. Except in two patients, tumors were removed “en block” in one piece. These two patients were excluded because continuous, uninterrupted tumor pseudocapsule is a theoretical and practical pre-requisite for GIE. In other words, interrupted, discontinuous pseudocapsule indicates positive surgical margins at the moment when this was visually recognized. Besides these two patients were not included because surgery was completed as radical nephrectomy in order not to leave tumor behind. The remaining 26 patients were evaluated. Their average age was 59 (38-79). In all of these 26 patients, the tumors were uniformly divided, ex-vivo, by using 20 no. scalpel and different gloves into two halves in the longitudinal axis, from the base (the deepest portion of the tumor) towards the top (outermost part) of the tumor on a separate sterile table (to prevent tumor seeding) immediately following excision of the tumor. In this way, the tumor margins were exposed for GIE for the

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Table 1. Patient characteristics

Number of Patients	26
Age (year); mean (range) median	59 (38-79) 60
Sex (n)	
Male	19
Female	7
Tumor Size (cm); mean (range) median	3.1 (1.5-6.0) 3.0
Tumor Stage (n)	
pT1a	14
pT1b	7
Histological Findings	
Renal Cell Ca	21
Clear cell	17
Papillary cell	3
Sarcomatoid/Indifferentiated	1
Oncocytoma	5
Fuhrman Nuclear Grade (n)	
I	12
II	7
III	1
IV	1
Surgical Margin (mm); mean (range) median	3.7 (0.1-12) 3.0
Positive Surgical Margin	0

safety of surgical margins (**Figure 1**). Because all of the tumors had pseudocapsules, GIE could be easily performed in all patients. Findings of GIE were compared with the gold standard permanent section (final pathology) analysis in terms of surgical margin status.

Histopathology

Histological analysis determined the histological type of tumor, 2002 TNM stage (2010 TNM Staging is not different in terms of T1 tumors), Fuhrman grade, margin thickness, and the status of peritumoral parenchyma for the presence of possible satellite lesions.

Follow-up

Follow-up includes sophisticated imaging (ultrasound, bone scan, CT and/or MRI) and standard evaluation which consists of history and physical examination, urine analysis, antero-posterior/lateral chest x-ray, CBC, serum BUN, creatinine, electrolytes and ferritin level. During the first two years standard evaluation is done every four months, twice a year during the 3rd and 4th years, and once a year thereafter. Sophisticated imaging was done once a year or

when indicated (i.e., new onset bone pain, back pain etc.).

Statistical analysis

Basic statistical calculations (mean, median, range) were performed by commercially available SPSS (Statistical Package for Social Sciences) for Windows13.0 statistical software package. Comparative statistical analysis was not necessary.

Results

Patient characteristics and the margin status are shown in **Table 1** and detailed individual patient data is given in **Table 2**. Of the 26 patients, the tumors were histologically RCC in 21 (80.8%), and oncocytoma in 5 (19.2%) patients. The RCCs were histologically classified as clear cell in 17 (81%), papillary in 3 (14.3%), and sarcomatoid in 1 (4.8%). The Fuhrman grade was grade I in 12 (57.1%), grade II in 7 (33.3%), grade III in 1 (4.8%), and grade IV in 1 (4.8%) patient. The mean tumor size was 3.1 cm (1.5-6 cm). Of the 21 patients with RCC, 14 had TNM stage pT1a (66.7%) and 7 had stage pT1b (33.3%), and of the 5 patients with oncocytoma all were stage pT1a.

In all patients GIE showed intact margins. None of the patients in the final pathological examination had positive surgical margin. The mean and median margin thickness was 3.7 and 3.0 mm respectively. The tumors were resected with a rim of normal looking parenchymal margins of 0.1 to 12 mm.

The mean (range) median duration of follow-up was 25 (4-104) 16.5 months. There was no evidence of local recurrence or distant metastasis during follow-up. All patients are alive.

Discussion

Epidemiological studies showed that there is an increasing incidence of renal cancers [4, 5], largely due to the increase of small renal masses [6]. The mean size of stage I tumors also decreased by the time [6]. These findings may have been a result of improvement in renal imaging and health-care [5, 7, 8]. Consequently, the practice of nephron sparing surgery has increased [9].

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Table 2. Individual patient data

Case	Age (yr)/gender	Hystologic type	Hystologic subtype/grade	Tumor diameter (cm)	Negative margin size (mm)	Follow up (month)/recurrence
1	57/F	RCC	Clear cell/G:I	1.5	0.1	104/No
2	60/F	RCC	Clear cell/G:I	3.5	4.0	60/No
3	53/F	RCC	Clear cell/G:II	2.0	3.0	69/No
4	39/M	Oncocytoma	—	2.3	9.0	49/No
5	64/F	RCC	Clear cell/G:I	2.0	5.0	35/No
6	49/M	RCC	Clear cell/G:I	2.5	6.0	31/No
7	43/F	RCC	Papillary/G:I	2.5	0.1	41/No
8	60/M	RCC	Clear cell/G:II	4.6	7.0	33/No
9	66/F	RCC	Clear cell/G:III	4.0	4.0	29/No
10	79/M	RCC	Sarcomatoid/G:IV	4.3	8.0	17/No
11	60/M	RCC	Clear cell/G:I	3.5	3.0	17/No
12	72/M	Oncocytoma	—	3.5	1.0	23/No
13	54/M	RCC	Clear cell/G:I	1.5	3.0	20/No
14	52/M	RCC	Clear cell/G:II	6.0	2.5	14/No
15	76/M	RCC	Clear cell/G:II	2.0	4.0	8/No
16	61/M	RCC	Papillary/G:II	5.0	8.0	16/No
17	38/M	Oncocytoma	—	3.0	2.0	7/No
18	61/M	RCC	Clear cell/G:II	3.0	2.0	11/No
19	64/M	Oncocytoma	—	5.0	1.0	8/No
20	49/M	RCC	Papillary/G:I	1.8	1.5	12/No
21	59/F	RCC	Clear cell/G:I	4.0	0.1	11/No
22	61/M	RCC	Clear cell/G:II	2.5	6.0	9/No
23	53/M	Oncocytoma	—	2.4	1.0	7/No
24	74/M	RCC	Clear cell/G:I	3.0	1.0	7/No
25	67/M	RCC	Clear cell/G:I	2.0	2.0	7/No
26	58/M	RCC	Clear cell/G:I	4.3	12.0	4/No

The essential principle of renal sparing surgery is tumor resection with negative surgical margins. But there is a critical question in this issue: "What is the role of TBB with frozen section for the evaluation of negative surgical margins in partial nephrectomy?". Almost all renal tumors have pseudocapsules which demarcate tumor tissue clearly from normal renal parenchyma. It has been shown that tumor enucleation techniques that based on tumoral pseudocapsules have low recurrence rates [10, 11]. Consequently, several studies demonstrated the safety of limiting the surgical resection margins down to the border of pseudo capsules. The width of resection margin has been proposed to be unimportant provided that tumor pseudocapsule is intact in macroscopic observation. Recent studies confirmed that the width of resection margins did not correlate with disease progression [12, 13]. Castilla et al evaluated prognostic importance of resection mar-

gin after nephron sparing surgery in their 69 cases with 8.5 years of mean follow up. They categorized the width of the resection margin as 1 mm or less (5 patients), 1.01 to 2 mm (15 patients), 2.01 to 2.5 mm (7 patients) and greater than 2.5 mm (42 patients). They found that if the tumor is completely excised with surrounding margin of normal renal tissue, the width of the resection margin after NSS for RCC did not correlate with long-term disease progression [12]. Similarly, Sutherland et al. evaluated 44 cases of nephron sparing surgery for local recurrence. Their mean and median negative margin size was 0.25 and 0.20 cm, respectively (range 0.05 to 0.7 cm). They found that no patient with negative parenchymal surgical margin after partial nephrectomy for RCC had local recurrence at the resection area at a mean follow up of 49 months [13]. These findings support Carini's long term results of tumor enucleation [10]. Carini et al. evaluated simple

enucleation for the treatment of pT1a RCC in 232 cases. They found none of the patients had positive surgical margins detected at the pathologic examination and they concluded that simple tumor enucleation provides similar rates of progression-free and cancer-specific survival, compared with radical nephrectomy and is not associated with an increased risk of local recurrence [10]. Therefore, we were encouraged to conduct our study by the aforementioned results. In our study, we did not detect any local or distant metastasis with the range of 0.1 to 12 mm surgical margin.

Another question is that whether detection of microscopic positive surgical margin in final pathological examination in an area where tumor looked safe in GIE, portends increased risk for local or distant metastasis. Piper et al found 7 positive surgical margins on permanent section in their 67 patients [14]. Of these 7 patients, one died of metastatic RCC at 9 months, 1 was alive with ipsilateral adrenal tumor at 5 months, and 5 were alive without evidence of disease at mean follow up of 29 months (range 8 to 44). They concluded that patients with positive margins did not correlate with poorer prognosis compared with negative surgical margins [14]. Kwon et al found similar results in their large series of 770 patients [15]. They classified their patients' tumor histology into two groups; (1) low malignant potential group which included oncocytoma, angiomyolipoma, papillary RCC type I (basophilic), chromophobe RCC, and all benign tumors, and (2) high malignant potential group that included conventional RCC, collecting-duct carcinoma, papillary RCC type II (eosinophilic), and those with sarcomatoid differentiation. They found positive surgical margins in 57 of 770 specimens. 33 of 57 positive surgical margins were in high malignant potential group and 24 were in low malignant potential group. The presence of a positive surgical margin did not affect metastatic progression. The 5 year probabilities for freedom from distant metastasis were not significantly different between negative surgical margins and positive surgical margins. Only 2 patients had local recurrence in 57 positive surgical margins and all were in high malignant potential group. Patients with low malignant potentially tumor, despite positive margins, did not experience local disease recurrence [15]. However, we did not detect any microscopic

margin positivity or local recurrence in our 26 patients with mean follow-up of 25 months.

On the other hand, there is an issue of the presence or absence of satellite lesions. There is also no clear evidence that microscopic residual cancer due to satellite lesions which cannot be recognized during GIE results in progressive disease. The reported incidence of multifocality of renal cell carcinoma is 7% to 25% in general and 0% to 5% in tumors \leq 4 cm [16-20]. Zucchi et al. found satellite microlesions in macroscopically healthy peritumoral tissues in only 3 cases of 53 elective pT1a PN patients. These 3 cases were due to papillary adenocarcinoma, oncocytoma and papillary adenoma. None of the 3 patients with microscopic satellite lesions had local recurrence and all are currently disease free at a mean follow-up of 61 months [21]. Similarly, Timsit et al found 4 satellite lesion in their 61 PN patients and none of them had local recurrence or distant disease at a mean follow-up of 72.5 months [3]. Both authors thought that satellite lesions are rare (especially when the tumor is 4 cm or less), most often benign small adenomas (less than 1 cm) and are always low grade [3, 21]. In our study we had 2 patients who had satellite tumors; both were benign papillary adenomas.

Timsit et al had 53 cases with intact pseudocapsule surrounded by continuous renal parenchyma and 8 cases with intact pseudocapsule not surrounded by continuous renal parenchyma. They had no pathologically positive tumor margins in any of these 61 cases; even in 8 cases not surrounded by continuous renal parenchyma [3]. We also had 3 patients who had intact pseudocapsules not surrounded by continuous renal parenchyma during GIE (**Table 2**). As reported above, all of these patients also had negative margins similar to that reported by Timsit et al.

Most of the PN procedures are performed with renal ischemia. An intraoperative frozen section in PN requires approximately 30 minutes while the kidney is kept in ischemia. Prolongation of kidney ischemia time is deleterious to the functional reserve of the organ.

The incidence of acute renal failure is reported in 1.3% to 12.7% of the patients who had PN [22-25]. Renal failure is reportedly caused by reduction of functional parenchyma and by

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intraoperative ischemia [26]. Reported warm ischemia and cold ischemia times are 20 and 70 minutes, respectively [27-33]. Frozen section certainly results in an additional ischemia prolongation compared with single final pathological examination alone, and elimination of this prolongation should improve residual kidney function.

Frozen sections do not always yield correct results. TBB sections have been shown to have very small rate of positive results because they can only sample a little part of all tumor bed resection area. Hagemann et al tried to calculate the TBB areas. They found that mean total biopsied area in their 251 cases was only 0.72 cm², and admitted that this area comprised only a small portion of the resection bed [2]. On the other hand, frozen sections have also been shown to give false positive results. Because of the false positive results many PN procedures have been reported to be converted to unnecessary radical nephrectomy. Duvdevani found only 2 positive surgical margins in frozen section analyses of 301 cases and none translated into residual tumor in the radical nephrectomy specimens [34]. Hageman et al had 15 positive margins in frozen sections of the 120 cases where only 3 were true, but the majority (n=12) were false positives [2].

In our study, we had high sensitivity in GIE. Hageman et al. showed that sensitivity of GIC alone (75%) was much better than TBB alone (25%) examined by permanent section [2]. Duvdevani et al. found that frozen section TBB was positive in only 2 of the 301 (0.7%) PN patients, while an additional 4 patients (1.3%) were found to have positive surgical margins in permanent section [34]. Timsit et al. reported 100% sensitivity of macroscopic assessment of the surgical margins in undisturbed tumors in 61 patients [3]. Here in our prospective study we report a novel method of intraoperative GIE with 100% sensitivity similar to comparable studies. So, it appears that it should be sufficient to visually observe clearly negative surgical margins with intact tumor pseudocapsules by GIE for safe assessment of surgical margins. In other words, surgeon does not have to pay strict attention to provide thick normal parenchymal width for acceptable oncological outcome, provided that pseudocapsule is intact.

In conclusion, frozen section analysis of TBB has important disadvantages regarding kidney

function and it is not reliable enough alone to be confident about the surgical margins. As reported above, GIE of resected PN specimen by eliminating frozen section analysis has high sensitivity and safety for the evaluation of surgical margins.

Disclosure of conflict of interest

None.

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