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ORIGINAL ARTICLE

Tumor enucleation specimens of small renal tumors more frequently have a positive surgical margin than partial nephrectomy specimens, but this is not associated with local tumor recurrence

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Abstract Approaches to nephron-sparing surgeries (NSS) of renal lesions include partial nephrectomy (PN) and tumor enucleation (TE). Our objective was to examine the pathology of the pseudocapsule and status of the surgical margin in small renal masses treated by NSS and to correlate these findings with the surgical and oncological outcomes. All consecutive renal TE and PN specimens obtained during the period between January 2012 and December 2014, of which clinical follow-up was available, were included in this study. Pathologic features and clinical data were reviewed and analyzed. A total of 117 NSS specimens (59 EN, 58 PN) were reviewed. Clear cell renal cell carcinomas and paraganglioma had the thickest pseudocapsules (0.36 mm), while angiomyolipomas did not form a well-defined pseudocapsule. Other tumors were intermediate in their characteristics. The positive margin rate for TE and PN was 17.2 and 0 %, respectively. Compared to PN, TE involved a significantly shorter procedure time, less blood loss, and fewer post-operative complications. None of the patients from either group was found to have a local recurrence after follow-up imaging. Although positive surgical margins were more frequently seen in TE specimens, local tumor recurrence was comparable to PN. Thus, TE is a reasonable choice for pT1 renal tumors, especially for those without a prominent infiltrative growth pattern.

Keywords Small renal tumor · Pseudocapsule · Nephron-sparing surgeries · Surgical margin · Surgical and oncologic outcome

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Introduction

According to the data from the American Cancer Society, in 2015, about 61,560 kidney cancers were expected to occur, leading to more than 14,080 deaths [1]. In the future, with the advent of cross-sectional imaging techniques, more renal tumors are expected to be detected at early stages as small lesions. Conventional treatment by radical nephrectomy places the patient at substantial risk of progression to chronic renal insufficiency and end-stage renal disease. Hence, partial nephrectomy (PN), involving preservation of an uninvolved kidney parenchyma, is a preferred alternative for treatment of small renal masses [2]. It has been argued that PN has a lower risk of renal failure, and its attendant need for dialysis, while providing an equally effective form of local control and an enhanced 5- and 10-year disease-specific survival rate [3–7].

However, due to concerns for local recurrence, the distance between the tumor and the surgical margin of PN specimens is still under debate. A margin of ten millimeters (10 mm) of uninvolved kidney, between the tumor and the surgical margin, has been accepted as the norm for PN [6]. However, Li. et al. argued that the 10 mm margin may be too large and militate against the maintenance of normal renal function [8]. Other studies showed that the local recurrence of kidney tumors is only related to the positivity of the surgical margin and not to the distance from the margin [9–12].

While PN has been widely accepted as the current standard of treatment for T1 renal masses [2], tumor enucleation (TE) partial nephrectomy is under discussion as another form of nephron-sparing surgery (NSS). TE involves a blunt dissection along the natural cleavage plane between the tumor pseudocapsule and normal kidney parenchyma, thereby providing maximal preservation of the uninvolved nephrons.

TE is possible because most renal tumors, in particular these which are small, have well demarcated tumor borders and are enveloped by a peritumoral pseudocapsule, which contains smooth muscle, reticulin, and collagens [13]. Our recently published study, based on an analysis of 178 small renal tumors (≤4.0 cm), (including 86 radical nephrectomy specimens, 62 PN specimens and 30 TE specimens) showed that clear cell renal carcinomas (ccRCC) had the thickest pseudocapsule, while oncocytomas had the thinnest (but with the least infiltrative pattern) [13]. Also, small renal tumors (≤4 cm) rarely showed multi-focality (0–5 %), compared to larger tumors (7–25 %) [14–16]. These findings support the contention that TE is an attractive surgical procedure for the treatment of small renal tumors (Fig. 1a, b). In addition, TE not only allows maximal preservation of uninvolved renal parenchyma but this surgery can also be performed off-clamp in a majority of cases. This latter option protects the residual renal parenchyma from ischemic injury caused by clamping of the hilar renal vessels during partial nephrectomy. However, long-term outcomes of TE have been questioned since it may be associated with surgical margin positivity, with potential tumor recurrence in some cases. Hence, advantages and disadvantages of this procedure are still under discussion [17].

This study aims to analyze histologic features of the renal tumor pseudocapsule, the status of the surgical margin and surgical and oncologic outcome in patients with small renal masses treated with TE and PN at our institution.

Materials and methods

A retrospective cohort study was performed on patients with renal tumors who underwent TE and PN, with post-operative follow-up, at our institution, from January, 2012 to December, 2014. Routine tumor surveillance for local recurrence was done by cross-imaging techniques (CT and MRI). Patients were scheduled for imaging follow-up at 3 and 12 months after NSS, then every 12 months. The study was approved by the Institutional Review Board for the Protection of Human Subjects. Clinical data, including patient demographics, NSS procedure time, intraoperative blood loss, post-operative complications and imaging follow-up for tumor recurrence, were reviewed. The surgical margin of NSS specimens, including the surface of the pseudocapsule and the remnant peritumoral kidney tissue of TE specimens and the renal parenchyma margin of PN specimens, was inked. Renal tumors were serially sectioned every 3–5 mm. To completely evaluate the surgical margin, TE specimen is submitted entirely for histological examination. PN specimen are either submitted entirely (tumor ≤4 cm) or by representative sampling (tumor >4 cm). Overall, an average of 7 samples per specimen were submitted (range 4–15 samples). Particular attention was paid to the interface of the tumor with the surrounding uninvolved renal parenchyma or pseudocapsule. Hematoxylin and eosin stained slides were re-examined microscopically. All kidney tumors included in this study were categorized according to the classification scheme of the International Society of Urological Pathology (ISUP), Vancouver, 2012 [18], including ccRCC, papillary renal cell carcinomas (papRCC), chromophobe renal cell carcinoma (chrRCC), oncocytoma, mucinous tubular spindle cell carcinoma (MTSCC), paraganglioma, and angiomyolipoma (AML). Tumors were staged (pTNM staging) according to the seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual [19]. Renal cell carcinomas (RCCs) were graded according to the ISUP grading system [20]. To investigate the relationship between tumor size and the pseudocapsule, renal tumors were further subcategorized into a ≤4.0 cm group and a >4.0 cm group. Special attention was given to the completeness, thickness of pseudocapsule, extra-pseudocapsular extension (EPE) of the tumor, and margin status. The number and dimension of larger intrapseudocapsule arteries (outer diameter ≥0.2 mm) was recorded. EPE is defined as the complete penetration of tumors through the pseudocapsule with invasion of the surrounding renal parenchyma. The following three conditions were not counted as EPE: (1) intact tumor pseudocapsule; (2) incomplete pseudocapsule but no tumor protrusion into the renal parenchyma; and (3) pseudocapsule with tumor protruding but not penetrating.

The data were analyzed according to the histologic tumor types and sizes. Categorical covariates were assessed using the Student *t* test and two-tailed Fisher's exact test. A p value <0.05 was set for statistical significance. All data was

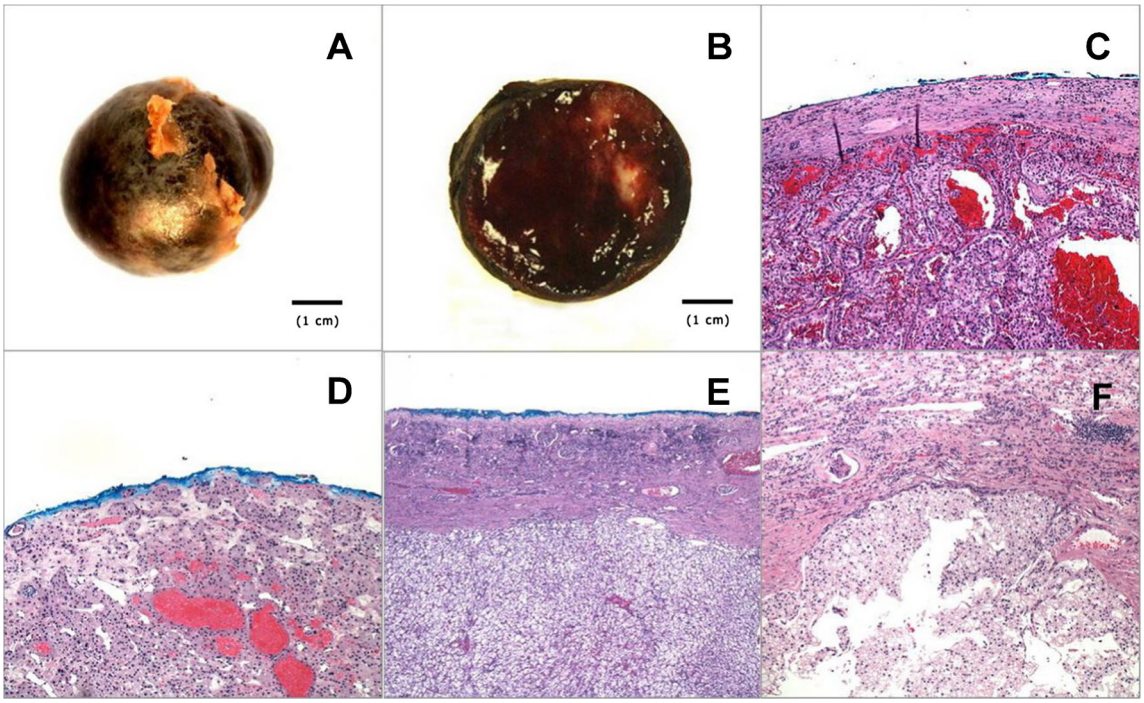

Fig. 1 Gross picture of renal tumor enucleation and histologic features of tumoral pseudocapsule. **a**, **b** Gross picture of enucleation specimen (renal oncocytoma, 4.3 cm, **a**: intact, **b**: cutting surface of the bisected specimen). **c** Enucleation specimen (cc RCC) with intact pseudocapsule and negative resection margin (H&E, ×40). **d** Enucleation specimen (oncocytoma) without well-developed pseudocapsule and focal positive resection margin (H&E, ×40). **e** Enucleation specimen (ccRCC) with a rim of the uninvolved kidney tissue. Focal pseudocapsular tumor penetration, chronic inflammation, and atrophic change of the adjacent kidney are present (H&E, ×20). **f** Partial nephrectomy specimen (ccRCC) with focal extra-pseudocapsular extension (H&E, ×40)

examined using GraphPad QuickCalcs online data analysis tool (GraphPad Software, Inc., La Jolla, CA) and Microsoft Office Excel 2007 (Microsoft Corporate Office Headquarters, Redmond, WA).

Results

A total of 117 NSS specimens as well as intraoperative and post-operative follow-up data were reviewed, including 59 specimens of TE and 58 of PN. Of the 117 cases (including 30 TE specimens and 12 PN specimens), 42 had been included in our previous study [13]. Average patient age at the time of TE was 57.7 years (range 31–80) with a male to female ratio of 1.5:1, while corresponding data for PN patients was 62.1 years (range 24–83) with male to female ratio of 1:1 (Table 1). Average renal lesion size for the TE and PN groups was similar (2.99 vs. 3.01 cm). However, PN specimens were more often large (>4.0 cm) than TE specimens (24 vs. 17 %), but this was not statistically significant ($p = 0.368$) (Table 2). Most RCC from both TE (81 %) and PN (75 %) were staged as pT1a; however, two ccRCC with larger tumor size (6.5 and 4.6 cm, respectively) from the PN group (4 %) were staged as pT3a. The highest pT stage for RCC from the TE procedure was pT1b (18.7 %). High nuclear grade (ISUP grade 3, 4) was more commonly seen in larger RCC (>4.0 cm) than in small RCC (≤4.0 cm) (9/19, 47 % vs. 12/70, 17 %, $p = 0.012$). This feature was also more commonly seen in the PN group rather than in the TE group (34 vs. 13 %, $p = 0.026$) (Table 2). All nine high-grade, large-sized RCCs were ccRCC.

The average minimum distance from the tumor to the surgical margin was 0.27 mm in TE specimens (Fig. 1c-e), compared to 2.84 mm in the PN group ($p < 0.001$). Ten (4 ccRCC, 3 oncocytoma, 2 AML and 1 papRCC) of 58 renal tumors (17 %, excluding 1 cyst) from the TE procedures showed a positive surgical margin (Fig. 1c), while none were seen in 56 renal tumors from the PN group (excluding 2 cysts) ($p < 0.001$). Uninvolved peritumoral kidney parenchyma showed chronic inflammation in 14 and 16 % of TE and PN specimens, respectively. Atrophic and sclerotic changes were seen in 3 % of TE and 5 % of PN specimens (Table 2) (Fig. 1e).

When NSS specimens were categorized by tumor type, the most common renal tumor was ccRCC (59 %), followed by papRCC (16 %), oncocytoma (9 %), AML (7 %), and chrRCC (5 %). One paraganglioma and one MTSCC were seen in the TE and PN groups, respectively (Table 3). CcRCC had the thickest pseudocapsule (mean 0.36 mm, range 0–1.1 mm), while oncocytomas had the thinnest (mean 0.12 mm, range 0–0.17 mm). PapRCC (mean 0.20 mm, range 0–0.38 mm)

Table 1 Comparison of demographic and clinical data between TE and PN patients

Demography and clinic	TE	PN	*p* value
Total patients	59	58	
Mean age (age range)	57.7 years (31–80)	62.1 years (24–83)	0.781
Male/female (ratio)	35:24 (1.46:1)	29:29 (1:1)	0.356
Number of NSS without hilar clamp (percentage)	31 (52.5 %)	0 (0 %)	<0.001
Average clamping time	25 min	25 min	1
NSS procedure time	181 min	241 min	<0.001
Blood loss during NSS	180 ml	280 ml	<0.001
Average hospital stay	1.71 days	2.67 days	<0.001
Patients with post-operative complications (percentage)[a]	7/59 (11.9 %)	15/58 (25.9 %)	0.062
Patients need re-admission of hospital within 1 month (percentage)	0 (0 %)	7 (12.1 %)	0.006
Median follow-up months (range)	22 (11–40) months	19 (8–42) months	
Tumor local recurrence	0	0	

[a] Post-operative complications: Enucleation—elevated Jackson Pratt drain creatinine; atrial fibrillation; non-ST segment elevation myocardial infarction; post-operative hypertension; urinary tract infection; leukocytosis. Partial nephrectomy—acute kidney injury; transfusion (RBC or platelet); fever; prolonged extubation; pseudoaneurysm; atrial fibrillation

and chrRCC (mean 0.19 mm, range 0–0.40 mm) were intermediate. AML only showed focal, poorly developed pseudocapsules. EPE rates were similar among ccRCC (19 %), papRCC (22 %), and chrRCC (17 %) (Fig. 1f). Although a partially absent pseudocapsule is a common feature of oncocytoma, the tumor rarely had an infiltrating growth pattern. Only 10 % of oncocytomas had EPE.

Pseudocapsular arteries, with an outer diameter ≥0.2 cm, were seen in 62/106 (59 %, excluding AML and cysts) specimens, including a total of 240 arteries, with an average arterial density of 2.26/case. The average outer diameter of arteries was 0.30 mm. As expected, AML had the highest number of intratumoral arteries (5.1/specimen), compared to less than 1 in other renal tumors. Vascular compression and prominent subintimal fibrosis contributed to lumen narrowing, with an average diameter of 0.08 mm. Most arteries (228/240) ran parallel to the pseudocapsule, while 12 ran perpendicularly. Intrapseudocapsular veins were largely collapsed or obliterated.

Compared to PN, which routinely requires hilar vessel clamping during the procedure, 53 % (31/59) of TE were performed by off-clamp surgery (Table 1). TE had a shorter procedure time (181 min) and involved a shorter average hospital stay (1.71 days) compared to PN (241 min and 2.67 days, both $p < 0.001$). Blood loss was also significantly less during TE than during PN (180 vs. 280 ml, $p < 0.001$). Post-operative

Table 2 Comparison of demographic and clinical data between TE and PN patients

Pathology		TE	PN	*p* value
Average lesion size		2.99 cm (1–6.0 cm)	3.01 cm (1–6.5 cm)	0.741
Number of lesion	≤4.0 cm	49 (83.1 %)	44 (75.7 %)	0.368
	>4.0 cm	10 (16.9 %)	14 (24.3 %)	0.368
Pathological stage (percentage)[a]	T1a	39 (81.3 %)	36 (75 %)	0.622
	T1b	9 (18.7 %)	10 (20.8 %)	1.000
	T3a	0 (0 %)	2 (4.2 %)	0.495
Nuclear grade (percentage)[b]	Low grade (grade 1, 2)	39 (86.7 %)	29 (65.9 %)	0.026
	High grade (grade 3, 4)	6 (13.3 %)	15 (34.1 %)	0.026
Peritumoral kidney changes	Chronic inflammation	8 (13.6 %)	9 (15.5 %)	0.799
	Atropy/sclerosis	2 (3.4 %)	3 (5.2 %)	0.679
Average margin distance		0.27 mm	2.84 mm	<0.001
Specimen with positive margin[c]		10 (17.2 %)	0 (0 %)	<0.001

[a] Exclude benign lesions

[b] Exclude benign lesions and chrRCC

[c] Exclude cyst

Table 3 Histological features of the pseudocapsule and intratumoral vessels

Tumor categories	Number of specimen		Average thickness of PC (mm)	Average number of intratumoral arteries	Number of specimen with EPE
	TE	PN			
ccRCC	30 (50.8 %)	39 (67.2 %)	0.36	0.38	13 (18.8 %)
papRCC	15 (25.4 %)	4 (6.9 %)	0.20	0	4 (21.1 %)
chrRCC	3 (5.1 %)	3 (5.2 %)	0.19	1.20	1 (16.7 %)
Oncocytoma	6 (10.2 %)	4 (6.9 %)	0.12	0.20	1 (10 %)
AML	3 (5.1 %)	5 (8.6 %)	N/A	5.00	N/A
Paraganglioma	0 (0 %)	1 (1.7 %)	0.36	0	0
MTSCC	1 (1.7 %)	0 (0 %)	0.12	0	0
Cyst	1 (1.7 %)	2 (3.4 %)	N/A	N/A	N/A
Total	59	58			19

N/A not applicable

complications, including cardiovascular instability, infection, and disturbed homeostasis, were seen in 12 % of patients who underwent TE, compared to 26 % of the PN group. None of the TE group of patients was re-admitted to hospital within 1 month of surgery. On the contrary, hospital re-admission occurred in 7 of 58 PN patients (12 %) mainly due to embolization for hematoma and a requirement for transfusion. To date, the median follow-up times of patients who underwent TE and PN are 22 months (range 11–40 months) and 19 months (8–42 months), respectively. There were no local recurrences in either cohort. Neither tumor re-excision nor total nephrectomy was performed on those patients during the period of follow-up.

Discussion

Radical nephrectomy for surgical treatment of renal masses carries a substantial risk of progression to chronic renal insufficiency and end-stage renal disease [21]. In contrast, NSS offers the possibility of preservation of renal function and the avoidance of future renal insufficiency; to this end, both PN and TE have been utilized [22].

PN, which comprises wedge resection with a rim of healthy parenchyma, has been shown to lead to oncologic outcomes that are equal to the results of a total nephrectomy. It has, therefore, been widely accepted as the current standard of treatment for renal masses of <4.0 cm (T1a) [2]; more recently, the use of PN been extended to include some patients with lesions of >4.0 cm (T1b) [23].

Currently, TE, which involves a blunt dissection along the natural cleavage plane between the tumor pseudocapsule and normal kidney parenchyma, is under discussion as a further improvement of NSS. Besides maximally preserving the uninvolved renal parenchyma, TE offers the option of off-clamp surgery. The latter protects the residual renal parenchyma from ischemic injury caused by clamping of the hilar renal vessels, which is necessary during conventional PN. However, while the risk of a positive surgical margin is perceived to be increased in TE, as opposed to PN, there is sparse data comparing the oncologic and surgical outcome of both procedures.

Historically, to decrease the risk of local recurrence and to ensure a cancer-negative surgical margin, a 10-mm margin of normal-appearing parenchyma was recommended for PN [5]. In subsequent studies, smaller surgical margins (such as 4–5 mm) were shown to be equally effective, since they were not associated with an increased local recurrence rate [11, 24].

Several studies subsequently have shown that the width of the resection margin per se appears to be irrelevant since it did not correlate with disease progression in patients with completely excised tumors [9–12].

In the current study, EPE rates were comparable between ccRCC (19 %), papRCC (22 %), and chrRCC (17 %). Overall EPE rates of RCCs in the current study were lower than those seen in our previous study (33.1–44.4 %), which also included radical nephrectomy specimens (13). This may be due to the fact that RCCs with a prominent infiltrative growth pattern are more likely to be removed by radical nephrectomy. The 2016 WHO Classification of Tumors of the Urinary System set a tumor size of 1.5 cm as the new cutoff point between renal papillary adenoma and carcinoma [25]. In our current study, only one of 15 papillary tumors met the updated criteria for papillary renal adenoma, and exclusion of this specimen from the study would not have a significant impact on the conclusions.

According to Minervini et al. [12], high EPE rates correlated with larger tumor size and high nuclear grade. In the current study, high nuclear grade features of RCCs were more commonly seen in larger RCCs (47 %) and PN specimens (34 %) rather than small RCCs (17 %) and TE specimens (13 %).

This finding may be, at least in part, the result of the larger tumor size found in PN group specimens.

The significance of a positive surgical margin is also debated. In one study of 770 PNs, a positive margin was found in 7 % of patients. Four percent of patients with a positive margin subsequently developed local recurrence. However, of the patients with a negative margin, 0.5 % developed local recurrence [26]. The authors concluded that the margin status does not determine recurrence, but that patients with a positive surgical margin may have a higher incidence of local recurrence. Similarly, Yossepowitch et al. reported that a positive surgical margin does not increase long-term risk of local recurrence and/or metastatic progression [27]. Most recently, Antic and Taxy [28] looked for the relationship between a positive resection margin and local recurrence in a large group of patients (406 RCCs) after PN. They concluded that a positive margin in PN seldom correlated with local recurrence while a negative margin does not always protect from recurrence.

Gupta and Boris [17] proposed that TE is a valid approach to sporadic RCC in the new era of maximal nephron preservation. It allows for equivalent oncologic control, enhanced surgical precision and a potential for fewer intraoperative complications, and may obviate the need for warm ischemia and complex renorrhaphy. TE should, therefore, be considered a viable alternative to PN by urologists who are comfortable with this technique. In contrast, Campbell and Zhang [17] considered that the above advantages of TE do not translate into a clinical benefit. They argued that 20 to 30 % of small localized RCC harbor potentially aggressive features and that 40 to 50 % invade into or beyond the pseudocapsule. However, both proponents and detractors agree that a well-designed prospective study of TE versus PN will be required to provide definitive data on this controversial topic.

In our series, positive surgical margins were more often seen in TE specimens than in PN specimens (17 vs. 0 %, $p < 0.001$). This may be attributable to pathologic processing and artifactual positive margins from specimen handling. However, no tumor recurrence was found during post-operative follow-up. When compared with PN, TE maximally preserved renal parenchyma; it also allowed for the performance of "off-clamp" surgery in >50 % of cases. In our experience, for most off-clamp enucleation surgeries, bleeding can be easily controlled by stuffing the tumor cavity with gauze for 10–15 min after tumor removal. This may be due to the small size and parallel distribution of blood vessels in the pseudocapsule [13]. Moreover, vascular compression and prominent subintimal fibrosis contributed to lumen narrowing.

In terms of surgical outcome, TE had a shorter procedure time and hospital stay, fewer post-operative complications and a much lower hospital re-admission rate than PN.

Although the significance of tumor margin positivity is still debated, our results argue that TE may produce oncologic results comparable to those of PN; similar observations have also been published by others [12, 29, 30]. Moreover, in our series, also surgical outcome was favorable for TE as patients who underwent TE had a significantly shorter procedure time, hospital stay, less blood loss, and fewer post-operative complications, compared to patients who underwent PN. Even in the presence of a positive margin in a TE specimen, no tumor recurrence was observed during follow-up. We also argue that a positive surgical margin in a TE specimen does not necessarily indicate that residual tumor was left in the preserved kidney tissue. Moreover, surgical maneuvers, such as vacuum suction during tumor removal, can cause pseudocapsular rupture, leading to a false-positive surgical margin.

The current study has some limitations, including (1) the study design is retrospective; (2) false EPE may exist due to manipulation of the tumor during the surgical procedure (especially enucleation) and specimen grossing; (3) although this study was conducted at a single institution with only minor variations in the experience of pathologists, as compared to a multi-center study, inter-observer variation in grading the completeness of the pseudocapsule is still possible; (4) the relatively small sample size remains a significant limitation; and (5) long-term outcomes are still unknown.

We conclude that in our series, a positive surgical margin is more frequently seen in TE specimens than in PN specimens (17 vs. 0 %), but during post-operative follow-up, no tumor recurrence was found. TE maximally preserves renal parenchyma, allows for performance of "off-clamp" surgery in >50 % of cases and has a shorter procedure time and hospital stay, fewer post-operative complications, and a much lower hospital re-admission rate. TE is therefore a reasonable choice for pT1 renal tumors, especially for those lacking a prominent infiltrative growth pattern. However, a longer period of follow-up and a larger patient cohort are needed to confirm these findings.

Compliance with ethical standards The study was approved by the Institutional Review Board for the Protection of Human Subjects.

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals Not applicable.

Informed consent Not applicable.

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