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Histopathologic Analysis of Peritumoral Pseudocapsule and Surgical Margin Status after Tumor Enucleation for Renal Cell Carcinoma

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Abstract

Background: The oncologic safety of blunt tumor enucleation (TE) of renal cell carcinoma (RCC) depends on the presence of a continuous pseudocapsule (PS) around the tumor and on the possibility of obtaining negative surgical margins (SMs).
Objective: To investigate the PS and SMs after TE to define the real need to take a rim of healthy parenchyma around the tumor to avoid the risk of positive SMs. The risk of PS invasion related to other clinical and pathologic variables was also evaluated.
Design, setting, and participants: Between September 2006 and December 2007, data were gathered prospectively from 187 consecutive patients who had kidney surgery. Overall, 90 consecutive patients who had TE for RCC were eligible for the study. All specimens were evaluated using an image analyzer by a dedicated uropathologist.
Intervention: TE was done by blunt dissection using the natural cleavage plane between the tumor and the normal parenchyma.
Measurements: PS, SM, and routinely available clinical and pathologic variables were recorded.
Results and limitations: In 60 RCC tumors (67%) the PS was intact and free from invasion (PS−) while in 30 (33%) there were signs of penetration within its layers, with or without invasion beyond it. Indeed, 26.6% had PS that had been penetrated on the parenchymal side and 6.6% had penetration on the perirenal fat tissue side. The odds of having PS penetration increased significantly with an increase in clinical tumor size. PS penetration was also significantly associated with pathologic tumor dimensions and grade. In all cases the SMs were negative after TE. The present patients, followed for >2 yr, will enable us to correlate the risk of local recurrence with PS status.

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Conclusions: The risk of PS penetration is associated with clinical and pathologic tumor dimensions and grade. If there is PS invasion into normal parenchyma, the presence of a thin layer of tissue allows for negative SM even if a TE is performed.

1. Introduction

Nephron-sparing surgery (NSS) has been widely accepted since the early 1980s [1–2] as an elective procedure for treating single sporadic renal tumors. Several studies have shown this procedure to offer equally effective local control and a similar disease-specific survival rate compared to radical nephrectomy (RN) for treating renal-cell carcinoma (RCC) tumors of <4 cm in their greatest dimension [1–4]. Moreover, recent reports have shown that NSS achieves local tumor control equivalent to RN also for RCC of 4–7 cm [5,6].

The concern about local recurrence due to inadequate tumor excision and the reported risk of pseudocapsule (PS) invasion on the parenchymal side [7–11] led most surgeons to remove a minimal rim of normal-appearing parenchyma around the tumor, and at present this is considered to be the technique of choice in patients undergoing NSS [1,2]. Nevertheless, in recent years there have been several reports on the reduction of the thickness of the safety margins that should be excised with the tumor to avoid the risk of local recurrence. Others have recently gone further, concluding that, if the tumor is completely excised, the width of the resection margin is irrelevant and not correlated with disease progression, thus providing an intriguing insight into the real need to excise an adequate rim of healthy kidney tissue around the tumor [11–15].

The tumor enucleation (TE) technique, which consists of excising the tumor by blunt dissection without a visible rim of normal parenchyma, has been reported in the treatment of benign-looking tumors such as angiomyolipomas. But only a few studies in the 1980s and early 1990s reported on the use of this technique for treating small RCC tumors, and they showed similar 5-yr survival rates to those of partial nephrectomy [16–19]. Recently, other retrospective analyses confirmed that TE can be safely used for treating pT1a–pT1b RCC tumors, and it is not associated with any greater risk of local recurrence than is partial nephrectomy [20–23]. Therefore, the discrepancy between the optimal oncologic results of in vivo TE reported in several recent retrospective analyses [20–23] and the pathologic concerns of incomplete tumor excision based on data obtained by studies after an ex vivo TE or tumor sections of RN specimens remains an unsolved oncologic issue in conservative kidney surgery [8,9–11].

The objective of this prospective study was to investigate the existence, integrity, possible invasion of peritumoral PS and surgical margin (SM) status after NSS, performed as TE for the treatment of RCC, with the aim of characterizing PS in RCC and defining the real need to take a rim of healthy parenchyma around the tumor to avoid the risk of a positive SM.

2. Methods

Between September 2006 and December 2007, data were gathered prospectively from 187 consecutive patients who had kidney surgery. Overall, 104 (55.6%) had a conservative treatment, TE, while 83 (44.4%) had RN. All but one NSS were successful; in one case with imperative indications for a 4-cm tumor, we decided to convert to RN for the intraoperative detection of intrarenal vein thrombosis after TE. The pathologic evaluation in this case confirmed the presence of renal vein thrombosis (pT3b). No patients had laparoscopic NSS.

The decision to proceed with planned NSS was based on the patients' preoperative imaging evaluation, medical history, comorbidity, and age. None of the patients undergoing NSS had preoperative or intraoperative suspicion of positive nodes. All patients were free from distant metastases before surgery (M0). The preoperative evaluation in all patients included computed tomography (CT) of the abdomen, a chest x-ray, and ultrasonography of the kidney, ureter, and bladder.

2.1. *Surgical technique: tumor enucleation*

In all cases, TE was done according to our previously described standard protocol, by blunt dissection and always using the natural cleavage plane between the tumor and normal parenchyma [20–22]. The kidney was directly approached and completely separated from perirenal fat to exclude subcapsular satellite lesions not detected by imaging. Intraoperative ultrasonography was not used during this period. After kidney capsule skeletonization, it was important to visualize the limit between the healthy renal parenchyma and the tumor, leaving the peritumoral fat in situ. The renal pedicle was carefully isolated and usually controlled with vascular clamps before TE. Renal hypothermia with slush was not used during this period. The kidney capsule was then sharply incised starting 1–2 mm away from the lesion toward the PS, and when the PS was visually reached, the tumor was enucleated by blunt dissection, with no visible rim of normal parenchyma (Fig. 1). Biopsies of the surgical bed were not taken during this period. The visible bleeding vessels and

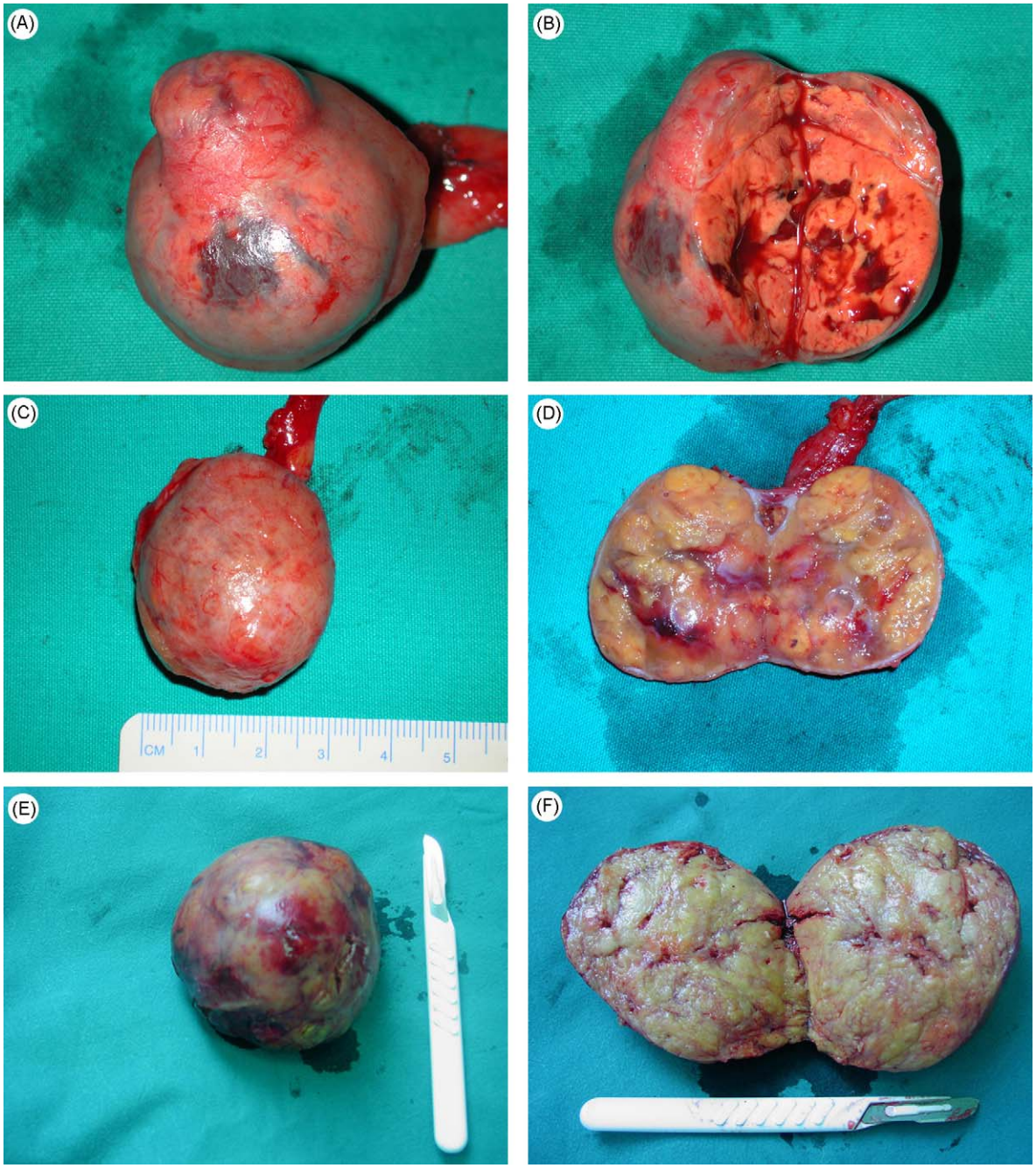

Fig. 1 – Tumor enucleations (TEs).

incidental opening of the calyces were ligated using a running suture with 4-0 monofilament. Diathermy spray or argon-beam coagulation of the surgical bed was not used during this period. The parenchymal defect was closed with horizontal interrupted sutures after sealant (Cyanoacrylate glue, Tachosil, Floseal) and Tabotamp bolster apposition. Most of the procedures were performed by one surgeon (M Carini, 61%).

After TE, the specimens were oriented, positioning a suture at the deepest part of the inner pole of the tumor, and sent for histopathologic examination.

2.2. *Histopathology*

After fixation in a 10% formalin solution, all specimens were step-sectioned at 5-mm intervals, and the entire specimen was analyzed by a dedicated uropathologist (C. di Cristofano). The greatest diameters of the tumors were measured and recorded. All patients were staged according to the 2002 TNM criteria [24], and nuclear grading was assigned according to criteria proposed by Fuhrman et al [25]. The histopathology was reviewed according to the 2004 World Health Organization (WHO) classification [26].

PS status was carefully analyzed. PS thickness was determined as the mean value of the four fields evaluated for each tumor. The existence, integrity, and degree of PS invasion as well as d the thickness of the rim of normal-appearing parenchyma, eventually present in case of tumor beyond PS, were evaluated, capturing the images at ×40 (3.0-megapixel resolution), and analyzed using an image analyzer (Motic Images Plus v.2.0).

Other variables assessed were tumor stage, histologic subtype, Fuhrman grade, histologic necrosis, and sarcomatoid differentiation.

2.3. *Statistical analysis*

The unpaired student *t* test and χ^2 test were used to evaluate the possible statistical correlation between the clinical and pathologic variables and the risk of PS+. The risk of PS invasion related to other clinical and pathologic (continuous and categorical) variables was evaluated using the logistic regression model, and odds ratios and risk ratios were calculated. Significant-difference level was considered to be $p < 0.05$.

3. Results

At diagnosis, 87 of the 104 tumors (84%) were detected incidentally in asymptomatic patients while 17 (16%) were associated with either microscopic or frank hematuria with or without flank pain. Overall, 95 patients were treated with elective TE (91%) while 9 patients received TE for imperative indications (9%).

All patients with histologically confirmed RCC were eligible for the study (90/104, 86.5%), and the 14 who had NSS for histologically confirmed benign tumors were excluded (13.5%). At CT scan before surgery, the mean of the greatest dimensions of the tumors was 3.2 cm (range: 0.8–10 cm; SD: 1.5 cm; median: 3.0 cm; interquartile range [IQR]: 2.0–4.1 cm) and at the pathologic examination the mean was 3.1 cm (range: 0.5–12.5 cm; SD: 1.7 cm; median: 2.9 cm; IQR: 2.1–3.8 cm), respectively.

The pathologic analysis according to the 2002 TNM classification showed that 75.6% of tumors were pT1a, 16.7% of tumors were pT1b, 2.2% of tumors were pT2, 4.4% of tumors were pT3a, and 1.1% of tumors were pT3b. On the basis of Fuhrman nuclear grading, 20% of tumors were G1, 65.6% of tumors were G2, and 14.4% of tumors were G3. The histopathologic evaluation according to the 2004 WHO classification revealed that 75.6% of tumors were clear-cell RCC, 17.8% were papillary; 4.4% of tumors were chromophobe; 1.1% of tumors were mucinous tubular and spindle-cell carcinoma, and 1.1% of tumors were unclassified RCC.

The presence of sarcomatoid differentiation was detected in three cases (mean: 10.5%; range: 1–20%). Histologic tumor necrosis was present in 55.5% of all RCC tumors, and it was often found as microscopic isolated foci. Histologic necrosis was ≤20% in 47 cases (mean: 4.1%; median: 3%; range: 1–20%), while it was >20% in only three RCC tumors.

All 90 RCC tumors were surrounded by a continuous, nonfenestrated, fibrous PS composed of dense connective fibrous tissue. PS thickness presented only mild variations in every single tumor, and in some cases there were signs of neoplastic penetration within its layers, with or without invasion beyond it. The mean (range) thickness of the tumor PS was 0.39 mm (0.048–0.798 mm).

PS status was classified as follows: PS intact and free from invasion (PS−; Fig. 2A); PS with signs of neoplastic infiltration within its layers, with or without invasion beyond it (PS+). PS+ was further divided into four categories:

- PS with signs of neoplastic infiltration on the parenchymal kidney side with no invasion beyond it (PSK+; Fig. 2B)
- PS with signs of neoplastic infiltration and invasion beyond it on the parenchymal kidney side (PSK++; Fig. 2C and 2D)
- PS with signs of neoplastic infiltration on the perirenal adipose tissue side with no invasion beyond it (PSF+; Fig. 2E)
- PS with signs of neoplastic infiltration and invasion of the adipose tissue (pT3a) (PSF++; Fig. 2F).

The PS features are reported in Table 1; in 60 RCC tumors (66.7%) the PS was intact and free from invasion (PS−; Fig. 2A) while in 30 tumors (33.3%) there were signs of infiltration within its layers, with or without invasion beyond it (PS+). Indeed, 26.6% of tumors (24/90) had PS invasion on the parenchymal side; of those, 11 tumors (12.2% overall; 11/24, 45.8% of tumors with PS invasion) had PS penetration (PSK+; Fig. 2B), and 13 tumors (14.4% overall; 13/24, 54.2% of tumors with PS invasion) had PS penetration and invasion beyond it (PSK++; Fig. 2C and 2D). The remaining 6 of 90 patients (6.6%) had PS penetration on the perirenal fat tissue side, and of those 2 patients (2.2%) had PS penetration (PSF+; Fig. 2E) and 4 (4.4%) had penetration and invasion beyond it (PSF++; pT3a; Fig. 2F).

The presence of PS+ by clinical and histologic tumor dimension, tumor stage, nuclear grade, RCC subtype and the presence of histologic necrosis is reported in Table 2. PS+ was significantly associated with clinical and pathologic tumor size, the presence of histologic necrosis and nuclear grade, while there was no statistically significant correlation

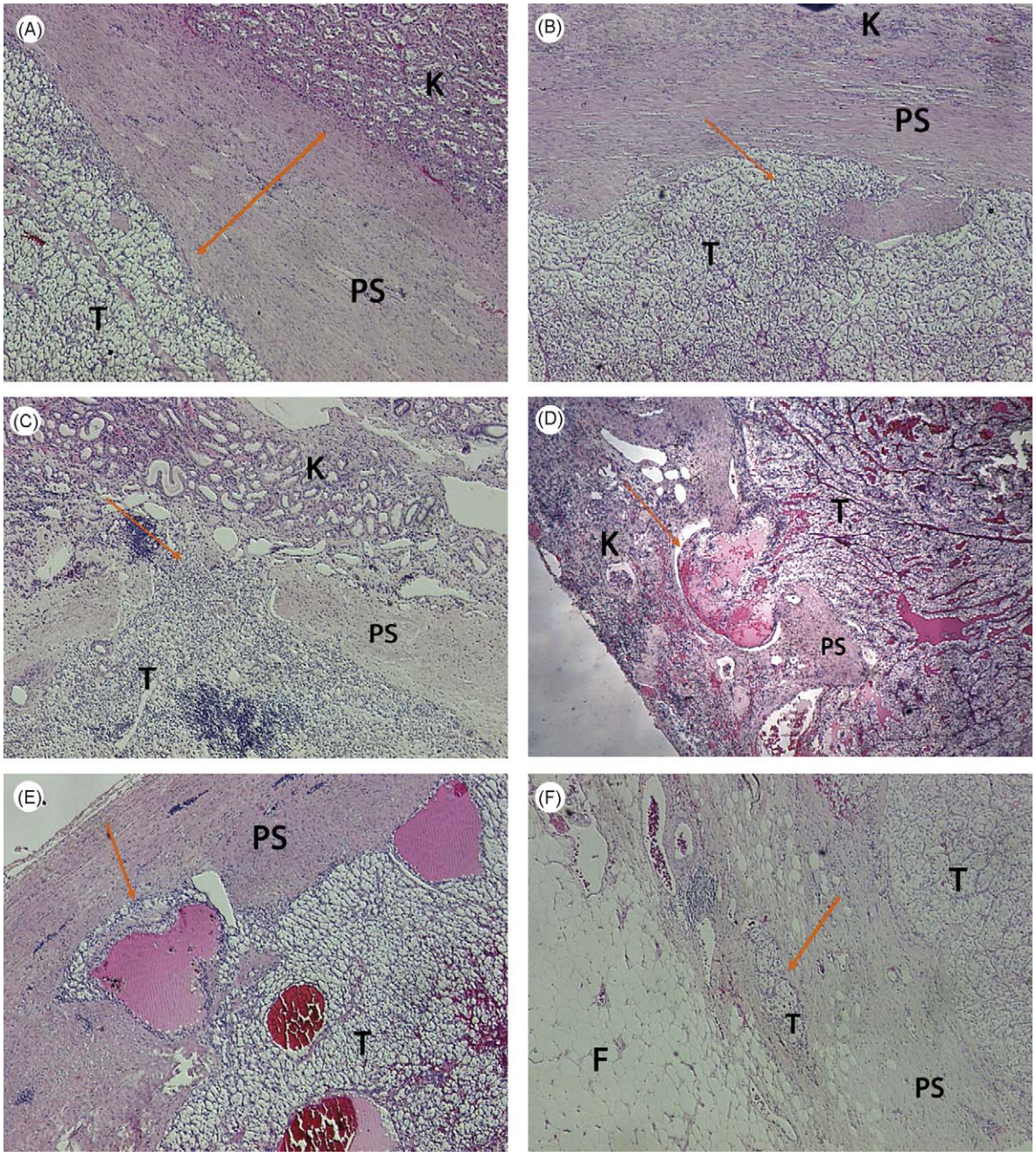

Fig. 2 – (A) Pseudocapsule (PS) intact and free from invasion (PS−); (B) PS with signs of neoplastic infiltration on the parenchymal kidney side with no invasion beyond it (PSK+); (C, D) PS with signs of neoplastic infiltration and invasion beyond it on the parenchymal kidney side (PSK++); (E) PS with signs of neoplastic infiltration on the perirenal adipose tissue side with no invasion beyond it (PSF+); (F) PS with signs of neoplastic infiltration and invasion of the adipose tissue (pT3a) (PSF++). Abbreviations: K, kidney; T, tumor; F, perirenal fat.

between PS+ and both tumor stage (pT1a vs pT1b) and the histologic subtype (clear-cell vs papillary vs chromophobe) (Table 2).

Using logistic regression analysis, the odds of having a PS invasion increased significantly with the increase in clinical tumor size, as measured by CT. The odds ratio for the association of PS invasion with clinical tumor size was 1.412 (95% CI, 1.03–2.018), indicating that each 1-cm increase in clinical tumor size was associated with a 41% increase in the odds of PS invasion.

The presence of PS+ was also significantly associated with pathologic tumor dimensions. The difference between mean (±SD) pathologic tumor size of tumors with (3.8 ± 2.32 cm) and without (2.8 ± 1.27 cm) PS involvement was statistically

Table 1 – Pseudocapsule (PS) features of 90 renal-cell carcinoma (RCC) tumors from patients who had tumor enucleation (TE)

PS status	Number of cases	%
PS−	60	66.7%
PS+	30	33.3%
PSK+	11	12.2% (11/90)
PSK++	13	14.4% (13/90)
PSF+	2	2.2% (2/90)
PSF++	4	4.4% (4/90)
Total	90	100%

PS−, pseudocapsule negative for RCC and free from invasion; PS+, pseudocapsule positive for RCC, with signs of neoplastic infiltration within its layers, with or without invasion beyond it; PSK+, PS with signs of neoplastic infiltration on the parenchymal kidney side with no invasion beyond it; PSK++, PS with signs of neoplastic infiltration and invasion beyond it on the parenchymal kidney side; PSF+, PS with signs of neoplastic infiltration on the perirenal adipose tissue side with no invasion beyond it; PSF++, PS with signs of neoplastic infiltration and invasion of the adipose tissue (pT3a).

Table 2 – Distribution of pseudocapsule-positive (PS+) by clinical and histologic tumor dimension (D), tumor stage by 2002 TNM classification, nuclear grade, renal cell carcinoma (RCC) subtype, and the presence of histologic necrosis

Tumor features	PS status		
	PS−	PS+	*p* value
Clinical (CT) D max (± SD)	3.0 (1.28)	3.7 (1.71)	0.045
Pathological D max (± SD)	2.8 (1.27)	3.8 (2.32)	0.0134
RCC subtype			
Clear-cell	45 (66.2%)	23 (33.8%)	NS (0.77)
Papillary	11 (68.8%)	5 (31.2%)	
Chromofobe	2 (50%)	2 (50%)	
TNM stage			
pT1a	51 (75%)	17 (25%)	NS (0.24)
pT1b	9 (60%)	6 (40%)	
Histologic necrosis			
Absent	31 (77.5%)	9 (22.5%)	0.0512
Present	29 (58%)	21 (42%)	
Nuclear grade			
G1	16 (88.9%)	2 (11.1%)	0.0132
G2	39 (66.1%)	20 (33.9%)	
G3	5 (38.5%)	8 (61.5%)	

PS, pseudocapsule; PS−, pseudocapsule negative for RCC; PS+, pseudocapsule positive for RCC; CT, computed tomography.

significant (*t* value = 2.523; $p = 0.013$) (Table 2). The odds ratio for the association of PS invasion with pathologic tumor size was 1.406 (95% CI, 1.035–1.910), indicating that each 1-cm increase in pathologic tumor size was associated with a 40% increase in the odds of PS invasion.

The risk (R) and risk ratio (RR) of PS+ by clinical and pathologic tumor size for every 1-cm RCC increase is reported in Table 3.

A logistic regression analysis was also performed to predict the independent contribution of the significant pathologic variables (nuclear grade, histologic necrosis, and pathologic tumor dimension) to variations of the dichotomous dependent variable (PS status). The results are shown in Table 4. Pathologic tumor dimension and Fuhrman nuclear grade (G1 vs G3) confirmed their significant predictive value for PS+. In particular, there was an 8.46-fold increase in the risk of having PS+ for G3 RCCs versus G1 RCCs.

In all cases of PS+, the SMs were negative independent of the degree of PS penetration, because even if there was invasion beyond the PS, neoplastic cells were separated from the SM by a thin layer of normal tissue with signs of lymphoplasmocytic inflammation. This happened in all 13 cases with PSK++ (Fig. 2C and 2D). In these cases, the mean thickness of the rim of chronic inflammatory tissue was 1.05 mm (SD: 0.48; median: 1.10; range: 0.38–1.60 mm).

Table 3 – Expected risk (R) and risk ratio (RR, R_i/R_{i-1}) of pseudocapsule-positive (PS+) by clinical and pathological tumor dimension (D) for every centimeter increase (D = *i*)

D (cm)	Clinical (CT) D max		Pathological D max		Pathological D max if grade = 1 and necrosis is absent	
	R (%)	RR	R (%)	RR	R (%)	RR
1	21.1	–	19.0	–	5.3	–
2	27.4	1.3	24.8	1.31	7.1	1.34
3	34.8	1.27	31.6	1.28	9.5	1.33
4	42.9	1.23	39.2	1.24	12.6	1.32
5	51.5	1.2	47.8	1.21	16.5	1.31
6	60.0	1.16	56.3	1.18	21.3	1.29
7	67.9	1.13	64.4	1.14	27.1	1.27

CT, computed tomography.

Table 4 – Logistic regression analysis for different pathological variables

	Odds ratio	*p* value	95% CI	Risk ratio
Pathological D max	1.371	0.0520	0.997–1.885	–
Histologic necrosis	1.09	0.8819	0.362–3.266	1.08
Fuhrman nuclear grade				
G1 vs G2	4.37	0.0863	0.810–23.524	3.86
G1 vs G3	12.14	0.0155	1.607–91.716	8.46

CI, confidence interval; D, tumor dimension.

4. Discussion

To avoid the risk of local recurrence, the excision of a minimal and visible margin of normal-appearing parenchyma around the tumor is considered the standard surgical technique of NSS [2].

Nevertheless, whether or not to excise a rim of healthy parenchyma, theoretically necessary to avoid the risk of a positive SM and local recurrence, is a matter of great controversy, and recent reports concluded that the width of the resection margins does not correlate with disease progression and that if the tumor is completely excised, the margin size is irrelevant, thus providing an intriguing insight into the possibility of bluntly excising the tumor, such as a TE [13,14]. Moreover, from a functional point of view, a narrower excision margin in RCC tumors would lead to additional parenchymal tissue preservation, and a recent report by Huang et al showed that the new onset of GFR of <60 ml/min and of <45 ml/min per 1.73 m^2 in patients with small RCC tumors can occur also after standard partial nephrectomy in 20% and 5% of cases at 3-yr follow-up, respectively [27].

The technical feasibility and oncologic safety of blunt TE of a renal neoplasm depends on the presence of a continuous fibrous PS around the tumor and on the possibility of obtaining negative SMs confirmed at the pathologic examination. The first studies on this topic were reported in the mid-twentieth century. In 1948, Cahill evaluated >30 kidney specimens with clear-cell RCC and concluded that, with rare exceptions, the capsule surrounding the tumor was smooth and had no evidence of rupture [28]. In 1949, Beare and McDonald studied the renal capsule in RCC and found PS invasion in 15% of cases [29]. Then, from the early 1980s, concurrently with the renewed interest in conservative surgery, many reports evaluated PS and SM status either on an RN specimen or on the sole tumor, but after an ex vivo TE, to investigate the real need to remove a rim of healthy tissue around the tumor. These studies noted some degree of PS invasion with RCC, irrespective of tumor size and histologic subtype, with a higher rate in larger and less-differentiated tumors, and thus TE was not recommended because of the significant risk of incomplete excision, although none histologically analyzed the tumor removed during an in vivo TE [8–10]. Indeed, Rocca Rossetti et al noted a continuous PS in 80% of tumors of <7 cm in diameter; in larger tumors this fraction was only 23.5% [8]. Moreover, the degree of tumor differentiation correlated inversely with the risk of PS invasion [8]. In 1984, Rosenthal, in an ex situ TE study on 25 RN specimens, noted some degree of invasion of the PS in all cases, irrespective of tumor size and histologic subtype [8]. Moreover, PS invasion reaching the surface of the enucleated tumor was more frequent in large tumors (>6 cm) and less differentiated tumors [8].

We confirm, in this contemporary consecutive series of patients who were candidates for open NSS, that the PS can be penetrated irrespective of tumor size in those undergoing conservative surgery, with a reported infiltration rate of 26.6% on the parenchymal side and 6.6% on the perinephric adipose tissue side.

Our data confirm those published by Li et al, who recently reported a 27% incidence of PS invasion in 82 kidneys in which RCC tumors of <4 cm were removed by RN [11]. Moreover, our study shows that, as the clinical size of RCC tumors, measured by CT increases, there is a significantly greater probability that the tumor has invaded the PS. Indeed, each 1-cm increase in clinical tumor size was associated with a 41% increase in the odds of PS invasion. The same applied when pathologic tumor size was analyzed; the odds of having a PS invasion increased significantly as pathologic tumor size increased. Moreover we showed that tumor dimension was an independent predictor of PS+ and that the risk ratio of PS+ increased as tumor size increased even in smaller tumors and even in the low-risk group of patients with G1 RCC and no necrosis (Table 3). This is the reason why there was no statistically significant correlation between the risk of PS+ and tumor stage. Indeed the 4-cm cutoff cannot define

two groups of tumors with a statistically significant difference in PS+ rate.

In the present series, the risk of PS invasion was also statistically associated with nuclear grade and histologic necrosis. Nuclear grade appears to be an independent risk factor for PS invasion, with a 3.86-fold increase in the risk of PS invasion for G2 versus G1 RCC, and an 8.46-fold increase in the risk for G3 versus G1, while the presence of necrosis was not significant in the logistic regression analysis.

In this study all patients had an in vivo TE by blunt dissection, thus overcoming the historical bias of series which analyzed this topic using RN specimens or series which correctly evaluated the sole tumor, but after an ex vivo TE. Moreover, this study design provided for the possibility of defining the real risk of positive SM after TE. We observed that if there was PS penetration and invasion beyond it, the presence of a thin layer of parenchymal tissue invariably allowed for negative SM, even if no efforts were made to leave a rim of healthy kidney tissue around the neoplasm. In these cases, the mean thickness of the rim of parenchymal tissue was 1.05 mm (SD: 0.48 mm; median: 1.10 mm; range: 0.38–1.60 mm).

These prospective data explain the excellent results of TE for treating pT1a and pT1b tumors, similar to the results of enucleoresection and RN previously reported in retrospective studies [17–23]. We have routinely performed TE at our institution since the early 1980s, reporting excellent long-term, progression-free, and cancer-specific survival rates with a mean follow-up of the more recent publications ranging between 74 mo and 88 mo [20–22]. This study represents the first pathologic evaluation of the TE technique performed in vivo.

Naturally, the present study can be criticized for the lack of follow-up. The patients in this study, followed for >2 yr, will enable us to further and prospectively confirm that TE is not associated with any greater risk of local recurrence than the standard NSS and to correlate the risk of local recurrence with PS status. Another limitation is that some of the less frequent histologic subtypes and a pT2 stage were present in a very small number of cases and therefore were excluded from the statistical analysis.

5. Conclusions

The PS can be infiltrated with or without invasion beyond it in patients undergoing conservative surgery, and the risk of PS invasion is statistically associated with clinical and pathologic tumor dimensions and nuclear grade. If there is PS penetration and invasion beyond it, the presence of a thin layer of parenchymal tissue allows for negative SM even if no efforts are made to leave a rim of healthy kidney tissue around the neoplasm. Our data clearly represent a rationale for adopting the TE technique as the standard procedure for the excision of pT1a and pT1b RCC tumors.

Author contributions: Andrea Minervini had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Minervini, Carini.
Acquisition of data: Carini, Serni, Lapini, Cristofano, Mancini.
Analysis and interpretation of data: Minervini, Tuccio.
Drafting of the manuscript: Minervini.
Critical revision of the manuscript for important intellectual content: Minervini, Carini, di Cristofano, Serni, Lapini, Bevilacqua, della Rocca.
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