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# Pathological evaluation of peritumoral pseudocapsule status after nephron sparing surgery and its prognostic implication

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**Summary**

*The presence of a capsule/pseudocapsule (PS) with signs of infiltration within its layers or completely penetrated could represent the first pathological evidence of the capacity achieved by tumor cells to infiltrate and invade surrounding tissue and it could eventually have a role as prognostic factor in patients with intracapsular renal cell carcinoma (RCC). Historical reports on the PS surrounding RCC date back to the mid twentieth century with the aim to define the possible role of conservative surgery for small renal tumors. Few authors have recently investigated the morphological appearance of tumor fibrous PS and the prognostic implication of its infiltration after kidney surgery for RCC. The aim of the present review is therefore to report the historical data and the current results of a literature review on the PS status after kidney surgery and to define its prognostic implication.*

KEY WORDS: *Surgical margins; Pseudocapsule; Capsule; Prognostic Factor; Nephron-sparing surgery; Partial nephrectomy; Enucleation; RCC.*

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## INTRODUCTION

Since the mid twentieth century the urological literature have focused the attention on the pathological evaluations of RCC specimen with the aim to define the possible role of conservative surgery and eventually define reliable prognostic factors of local and systemic tumor recurrence (1-3).

The presence of a capsule/pseudocapsule (PS) with signs of infiltration within its layers or completely penetrated could represent the first pathological evidence of the capacity achieved by tumor cells to infiltrate and invade surrounding tissue and it could eventually increase the risk of local recurrence due to positive surgical margins and have a role as prognostic factor in patients with intracapsular RCC.

Few authors have recently investigated the morphological appearance of tumor fibrous PS and the prognostic implication of its infiltration after kidney surgery for RCC (4-9).

The aim of the present review is therefore to report the results of a literature review on the PS status after kidney surgery and to define its prognostic implication.

## RESULTS

*Historical data*

In 1948, Cahill analysed over 30 gross specimens of kidney with clear cell carcinoma and noted that, with rare exception, the PS surrounding the tumor was smooth and there were no evidence of rupture and extension into the perirenal fat (1). In 1949, Beare and McDonald, studied the renal PS in 488 kidney tumors and showed for the first time the presence of tumor cells within the PS in 15% of cases and only in 4 cases (< 1%) there were tumor cells through the fibrous PS to involve the perirenal fat (2). Then in 1950, Vincent Vermooten presented his study on the growth pattern of clear cell carcinoma (3). He reported that clear cell tumors are surrounded by a dense, fibrous PS, with a width that can vary from few collagen fibers to 3 mm or more, which appears to delimit the tumor and that rarely, if ever, except very late, is invaded by tumor cells (3). Notwithstanding the great value of the results reported, no more papers were published due to the technical difficulties of the conservative

approach. Then, from the early 1980s, concurrently with the renewed interest in conservative surgery, many reports evaluated tumor PS and the width of the normal kidney parenchyma around the tumor to be removed to avoid local recurrence (10-13).
Rocca Rossetti and Muto noted a continuous PS in 80% of tumors measuring < 7 cm in diameter. In larger tumors this fraction was only 23.5% (10). Moreover the degree of tumor differentiation correlated inversely with the risk of PS invasion (10). Rosenthal in 1984, in an ex situ tumor enucleation study on 25 radical nephrectomy specimens, noted some degree of invasion of the pseudocapsule in all cases, irrespective of tumor size and histologic subtype (11). Moreover, PS invasion reaching the surface of the enucleate tumor was more frequent in large (> 6 cm) and less differentiated tumors (11).

*Recent data*
Few authors have investigated the morphological appearance of tumor fibrous PS and the prognostic implication of its infiltration after kidney surgery for RCC (4-9). Most of the papers recently published on this topic are retrospective, include patients treated either with RN or with NSS and focus their attention on the prognostic role of renicapsular involvement on the perinephric fat side without examining the PS on the kidney parenchyma side (6-9).

*Morphological appearance of tumor PS*
In daily pathological practice, addressing the PS status is easy and straightforward without the need for special stains or extra slides to be obtained, without additional expense in time and cost. For an optimal evaluation of PS the tumor specimen should be oriented in the operating theatre, positioning a suture at the deepest part of the inner pole of the tumor (4). In our experience, after formalin fixation (10%), all specimens must have inked and step-sectioned a 5-mm intervals and the entire specimen analyzed (4). Moreover, in our patients, we evaluate PS thickness as the mean value of four fields for each tumor at the four cardinal points (4). The existence, integrity and degree of PS invasion, and the thickness of the rim of normal-appearing parenchyma eventually present in case of tumor beyond PS are evaluated, capturing the images at x40 (3.0 mpixel resolution), and analyzed using an image analyzer (Motic images plus vers. 2.0) (4). This procedure allows to completely visualize the PS and to measure the width of PS infiltration.
The largest part of RCCs, especially the papillary cell and the clear cell histotype, are surrounded by a continuous, not fenestrated fibrous pseudocapsule constituted by dense connective fibrous tissue.
PS width can vary between cases. We have recently evaluated PS thickness in a prospective series of patients treated conservatively and showed that in our series the mean (range) thickness of tumor PS was 0.39 (0.048–0.798) mm and PS thickness presented only mild variations in every single tumor (4). In some cases (21%; unpublished data) a pericapsular tumor lymphocytic infiltration can be present around the PS. Moreover PS thickness seems not to correlate to tumor size, TNM stage, histotype, nuclear grade, presence of tumor necrosis or pericapsular tumor lymphocytic infiltration at the univariate analysis (unpublished data). Although a positive trend between pathologic maximum tumor diameter and increased PS thickness can be found (unpublished data).
In most of the cases the fibrous PS is complete, intact and free from invasion, but in same cases it can be penetrated within its layers by neoplastic cells, with or without invasion beyond it. In a series of patients that had NSS, we confirmed that the tumor PS can be penetrated, with an overall PS invasion rate of 33% (4). Most of our tumors with PS invasion had a penetration of PS on the parenchymal side (26.6%) while a minority of them (6.6%) showed PS invasion on the perinephric adipose tissue side (4). Half of the tumors with PS infiltration showed tumor cell invasion beyond it (4). In all cases, the surgical margins were negative, even in the case of tumor invasion beyond the pseudocapsule toward the renal parenchyma (4). Indeed, a thin layer of normal tissue with signs of lymphoplasmocytic inflammation is always present around the tumor (4, 5).
Other studies evaluating large retrospective series,

***Table 1.***

| Authors | N° of Pts | Treatment | TNM 2002 | Mean D max | CI | Clear Cell RCC (%) | Mean Follow up (Range) | 5-yrs DFS with CI | 5-yrs DFS without CI | P value |
|---|---|---|---|---|---|---|---|---|---|---|
| *Cho 2009* (6) | 299 | RN 89.3%<br>NSS 10.7% | pT1 84.3%<br>pT2 15.7% | 4.7 (0.8-20) | 106 (35.5%) | 100% | 60.5 (1-249) | 77.7% | 92.3% | 0.004 |
| *May 2009* (7) | 635 | RN 82.3%<br>NSS 17.7% | pT1a 45.2%<br>pT1b 40.6%<br>pT2 14.2% | 4.8 (0.8-17) | 146 (23%) | 78.1% | 86.1 | 76.9% | 86.3% | <0.01 |
| *Jeong 2006* (8) | 288 | RN 100% | pT1 79.8%<br>pT2 20.2% | 4.4** | 108 (37.5%) | 100% | 61 (20-145) | 73.8% | 90.5% | 0.031* |
| *Klatte 2006* (9) | 519 | RN 58.8%<br>NSS 41.2% | pT1a 52.2%<br>pT1b 28.5%<br>pT2 19.3% | 4.0*** (0.4-18) | 112 (21.6%) | 78.8% | 49***(1-199) | 76.5% | 86.9% | 0.007 |

* P value was significant in the pT2 tumors group, only.
** Range not reported
*** Median value
CI = Capsular Involvement; DFS = Disease free survival.

homogeneous for what concern TNM stage and tumor size, focused on the prognostic role of pericapsular involvement in intracapsular tumors and showed a PS invasion rate that ranged between 21.6% and 37.5% (Table 1) (6-9). One possible explanation to this variability is the different clear cell RCC rate between studies although ourselves and Klatte and coworkers did not find an association between tumor histotype and PS invasion (Table 1) (4, 9). Another possible reason is related to the different magnifying resolution possibly used to define PS invasion between studies but unfortunately these data were not reported in most of the studies on this topic (6-9). Indeed, a standardized method to analyze the PS is necessary in order to exclude this bias from future studies.

*Prognostic implication of tumor PS infiltration*

Tumor PS evaluation as prognostic factor is not new for pathologists. Indeed, in other tumors as in the follicular thyroid neoplasm the invasion of fibrous PS is associated to a malignant phenotype (14). In case of neoplastic invasion beyond PS, is of outmost importance to evaluate the side of invasion. Some recent papers have shown that a PS invasion on the perinephric tissue side without perinephric fat infiltration is associated with a worse prognostic outcome while it is still uncertain if the same unfavourable prognostic outcome applies in case of PS infiltration on the parenchymal side with or without tumor cells beyond the PS with negative SM (4-9). In this pathological setting, the prognostic impact is still to be determined (4).

The presence of a PS with signs of infiltration within its layers or completely penetrated could represent the first pathological evidence of the capacity achieved by tumor cells to infiltrate and invade surrounding tissue.

Very recently, few paper analyzed the correlations of PS invasion without perinephric fat infiltration with other pathological and clinical variables and its prognostic value in patients with localized RCC (6-9). All papers observed a statistically significant association of PS involvement with tumor size (6-9). We have recently confirmed this association (4). Moreover, our study shows that as the clinical size of RCCs, 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 (4). Tumor dimension was an independent predictor of PS invasion and the risk ratio of PS invasion increases as tumor size increased even in smaller tumors and even in the low-risk group of patients with G1 RCC and no necrosis (4).

*Cho H-J et al.* also found a significant correlation of PS invasion with symptoms at presentation, pathologic stage (pT1a, pT1b, pT2), nuclear grade, age, microvascular invasion and collecting system invasion (6). The association between PS invasion, tumor stage and nuclear grade was also confirmed by *Klatte et al.* (9). On the contrary, *Jeong IG et al.* found a significant correlation between tumor stage (pT1 vs pT2) and PS invasion, while failed to find a correlation between Fuhrman nuclear grade and PS invasion (8). The study by Klatte and coworkers addressed also the possible correlation between PS invasion and tumor histotype and showed no significant association between these two parameters (9). We have recently confirmed this lack of association between these two parameters (4) but interestingly the two papers that analyzed a pure population of clear cell RCC have found an higher rate of PS invasion around 35.5%-37.5% that was higher than those reported in papers that included all tumor histotypes (6, 8).

All these papers examined the prognostic relevance of capsular involvement with no invasion of the perinephric fat (6-9). Overall, over 1700 patients with intracapsular RCC were followed up (6-9). The mean follow up ranged between 49 and 86 months (6-9). All papers showed capsular involvement to have a significant impact on disease-free survival (6-9), although Jeong and coworkers, reported a prognostic impact of PS invasion for pT2 tumors, only (8) (Table 1). This result might be attributable to the relatively low number of pT1 tumors with PS involvement investigated in this study. Interestingly, two studies showed that patients with capsular involvement had the same recurrence-free survival as patients diagnosed as having pT3a N0 M0 RCC (7-9). In multivariate analyses, capsular involvement was an independent predictor of recurrence-free survival (6-9).

## Conclusions

In daily pathological practice, addressing the PS status is easy and straightforward without the need for special stains or extra slides to be obtained, without additional expense in time and cost.

The largest part of RCCs, especially the papillary cell and the clear cell histotype, are surrounded by a continuous, not fenestrated fibrous pseudocapsule constituted by dense connective fibrous tissue.

PS width can vary between cases. In most of the cases the fibrous PS is complete, intact and free from invasion, but in same cases it can be penetrated within its layers by neoplastic cells, with or without invasion beyond it with a PS invasion rate that ranged between 21.6% and 37.5% for intracapsular RCC (6-9). In case of neoplastic invasion beyond PS, is of outmost importance to evaluate the side of invasion. Some recent papers have shown that a PS invasion on the perinephric tissue side without perinephric fat infiltration is associated with a worse prognostic outcome while it is still uncertain if the same unfavourable prognostic outcome applies in case of PS infiltration on the parenchymal side with or without tumor cells beyond the PS with negative SM (4-9). In this pathological setting, the prognostic impact is still to be determined. The presence of a PS with signs of infiltration within its layers or completely penetrated could represent the first pathological evidence of the capacity achieved by tumor cells to infiltrate and invade surrounding tissue. All papers showed capsular involvement to have a significant impact on disease-free survival (6-9). Interestingly, two studies showed that patients with capsular involvement had the same recurrence-free survival as patients diagnosed as having pT3a N0 M0 RCC (7-9). In multivariate analyses, capsular involvement was an independent predictor of disease-free survival (4-9).

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