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ORIGINAL ARTICLE

Effect of histopathologic characteristics on pseudocapsular invasion in the case of partial nephrectomy for renal tumours

Burhan Baylan [a,*], Sertac Cimen [a], Can Tuygun [a], Ata Turker Arikok [b], Goksen Inanc Imamoglu [c], Nevzat Can Sener [d], Ufuk Ozturk [a], Muhammed Abdurrahim Imamoglu [a]

[a] *Ministry of Health, Diskapi Yildirim Beyazid Education and Research Hospital, Department of Urology, Ankara, Turkey*
[b] *Ministry of Health, Diskapi Yildirim Beyazid Education and Research Hospital, Department of Pathology, Ankara, Turkey*
[c] *Ministry of Health, Diskapi Yildirim Beyazid Education and Research Hospital, Department of Medical Oncology, Ankara, Turkey*
[d] *Ministry of Health, Adana City Training and Research Hospital, Department of Urology, Adana, Turkey*

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Renal tumour;
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Summary *Objective:* It is aimed to define the existence of pseudocapsular structure on renal tumours, illuminate the relation between pseudocapsular invasion and Fuhrman grade histological type that are among histopathologic prognostic risk factors and determine the relation between surgical margin positivity and existence of pseudocapsular invasion. Sequential partial nephrectomy series and relevant pathological preparations were retrospectively reviewed in order to evaluate these issues.
Methods: The study includes 123 patients diagnosed with T1 renal tumour and treated with partial nephrectomy in between January 2007 and June 2016. Benign angiomyolipoma was excluded due to complete non-existence of pseudocapsule. 99 T1 patients diagnosed with renal cell cancer whose pathological slides can be duly analysed were included in the study. Clinical and pathological details were evaluated for all patients. Existence of pseudocapsule was revealed for all patients. Pseudocapsule invasion was classified by existence of expansive and infiltrative type and non-existence of pseudocapsule invasion. The groups have been assessed by their histopathologic characteristics.
Results: Compared to the group in which pseudocapsular invasion was not detected, clear-cell histological subtype was observed more frequently in a statistically significant way in the group

* Corresponding author.
E-mail address: baylanburhan@gmail.com (B. Baylan).

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with expansive pseudocapsular invasion and infiltrative pseudocapsular invasion respectively ($p = 0.017$ and $p < 0.001$). Pathological tumour sizes were found out to be statistically similar ($p = 0.874$). There was not a statistically significant difference in terms of Fuhrman grade ($p = 0.220$). There was not a statistically significant difference in terms of surgical positive margin ($p = 0.609$).

Conclusion: It was indicated in our study that only the histological subtype affected pseudocapsular invasion in group of patients treated with partial nephrectomy but tumour size, tumour stage, tumour location as well as endophytic and exophytic character did not affect invasion. It has also been revealed that surgical margin positivity is not correlated with pseudocapsular invasion.

1. Introduction

Nephron-sparing surgery is still the gold standard treatment approach for T1 renal cell carcinoma (RCC).[1,2] Compared to radical nephrectomy, long-term survival results of nephron-sparing surgery is inspiring in terms of protection of renal function.[3,4] Tumour-free surgical margin takes an important role regarding prevention of local tumour recurrence. Renal tumours frequently have demarcated boundaries from the normal renal parenchyma and are surrounded with the peritumoural pseudocapsule. This feature provides a natural area of cleavage ensuring blunt dissection between tumour pseudocapsule and normal renal parenchyma in the cases of simple tumour enucleation.[5] Similar oncological results were found out in the studies comparing simple tumour enucleation and partial nephrectomy.[6–9] Tumoural invasion of the pseudocapsule that totally encircles the renal tumours represent the other potential prognostic factor for RCC. Renal capsule and tumour pseudocapsule are entirely different entities. It is quite difficult to distinguish these structures on the perirenal tumour space. It has been known since the last years of 1940's that tumour pseudocapsule is a structure surrounding the renal tumour from both the parenchyma and perirenal space.[10,11] Some researchers assessed the pseudocapsule of the patients who underwent partial nephrectomy and revealed that the tumour pseudocapsule existing in 96—100% of the cases was a tight fibrous layer of connective tissue that was continuously non-fenestrated and totally encircled the tumour.[7,12] It was observed for the first time in the studies conducted by Rosenhal et al and Rokka Rosetti et al in 1980 that pseudocapsular invasion was seen more frequently in poorly differentiated renal tumours. It was suggested that the risk of clinical progression might increase in organ confined renal tumours with pseudocapsular invasion.[13,14]

As of today, there is not a standardized pseudocapsular invasion classification. Existence of the tumour pseudocapsule in all RCC cases was set forth in the study conducted by Volpe et al on pseudocapsular invasion classification. In this study, two main renal tumour pseudocapsular invasion patterns, namely expansive and infiltrative, were defined.[15] It was observed that expansive tumour cells settled into the pseudocapsule by leaning on it regularly and incessantly. Certain cases of thinning and fluctuation might arise on the pseudocapsular structure. On the other hand, tumour cells penetrating into the pseudocapsule down to different depths were observed for the infiltrative type. Irregular fluctuations and erosions also might be seen.

In our study, it was aimed to define the existence of pseudocapsular structure in renal tumours, detect and classify pseudocapsular invasion and illuminate the correlation between pseudocapsular invasion and histological subtype and Fuhrman grade that are among histopathologic prognostic risk factors and determine the correlation between surgical margin positivity and existence of pseudocapsular invasion. Sequential partial nephrectomy series and relevant pathological preparations were retrospectively reviewed in order to evaluate these issues.

2. Materials and methods

2.1. Methods

The study includes 123 patients who underwent partial nephrectomy in our clinic with the diagnosis of organ-confined renal tumour in between January 2007 and June 2016. All these patients underwent 'partial nephrectomy' rather than enucleation and the resection included a thin rim of normal renal parenchyma. The patients diagnosed with multiple tumour, synchronous bilateral tumour, recurring tumour and congenital disease (Von-Hippel-Lindau Disease) were excluded. Benign angiomyolipoma was also excluded due to complete non-existence of pseudocapsule. Clinic and pathologic details were reviewed for all of the patients.

Routine pre-operative assessment including physical examination, routine blood laboratory analyses, pulmonary computerized tomography scan (CT) and abdominal CT scan, was performed for all patients. Oncological follow-up protocol included one abdominal CT and chest radiography scanned on a semi-annual basis for a period of 3 years.

All pathological specimens were examined and reported by a single pathologist. The excised specimens were processed in accordance with the tumour size and standard pathological procedures. Histological subtypes and tumour grading were determined as per WHO 2004[16] and Fuhrman grading.[17,18] All preparations were examined in detail in order to assess peritumoural pseudocapsule and status of tumoural pseudocapsular invasion. Existence of pseudocapsule was revealed in the preparations of the patients

and those not appropriate for examination were assessed by re-sectioning. In pathological examinations, the cases with regular and continuous pseudocapsule of homogenous thickness and without tumoural extension were described as non-existence of pseudocapsular invasion (Fig. 1). For the remaining cases, pseudocapsular tumour invasion was examined by two different patterns, namely expansive and infiltrative (Figs. 2 and 3). RCC cases were divided into two groups of low level (grade 1—2) and high level (grade 3—4) in accordance with Fuhrman grading system in order to analyse the correlation between tumour grade and pseudocapsular invasion rates. Surgical margin status of the patients were re-evaluated and confirmed.

2.2. Statistical analysis

The data were analysed by IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) software. Whether distribution of continuous digital variables was near-normal was checked by Kolmogorov Smirnov test. Defining statistics were indicated by ± standard deviation or median (minimum — maximum) and number of cases and rate (%) for continuous digital variables and categorical variables respectively. Significance of the difference between groups in terms of pathological tumour stage and pathological tumour size was examined by Mann Whitney U test as there were two independent groups and significance of the difference among more than two independent groups was examined by Kruskal Wallis test. When the statistical result of Kruskal Wallis test was found out to be significant, the group(s) leading to the difference was identified by using Conover's test of multiple comparison. Categorical variables were examined by using Pearson's Chi-Square, Fisher's Exact Test of Independence or Likelihood Ratio Rest. The results were accepted to be statistically meaningful for $p < 0.05$.

3. Results

99 patients diagnosed with organ confined renal cell carcinoma for whom pathological slides can be duly analysed were included in the study. The average age of the cases was 56.2 ± 12.9 (25—83) years and 58 (58.6%) and 41% (41.4) of them were men and women respectively. The median pathological tumour size was 3.5 cm and the size of pathological tumours ranged between 1.3 cm and 8 cm. On the other hand, the median radiological tumour size was 3.6 cm and radiological tumour sizes ranged between 1.6 cm and 7.7 cm.

52 (52.5%) of the tumours were localized on the right side. 35 (35.4%), 27 (27.3%) and 37 (37.4%) of the tumours were placed on the top, in the middle and on the bottom respectively. While tumour structure was solid in 77 (77.8%) of the cases, it was cystic in 22 (22.2%) of them.

While pathological tumour stage was 1A in 72 (75.8%) of the cases, it was 1B in 22 (23.2%) of them. On the other hand, the tumour stage was identified to be 3B in 1 (1.0%) of the cases. While Fuhrman grade was 1 in 22 (23.7%) of the cases, it was grade 2 and grade 3 in 56 (60.2%) and 15 (16.1%) of the cases respectively.

Defining statistics regarding demographical and clinical features of the cases have been provided in the Table 1.

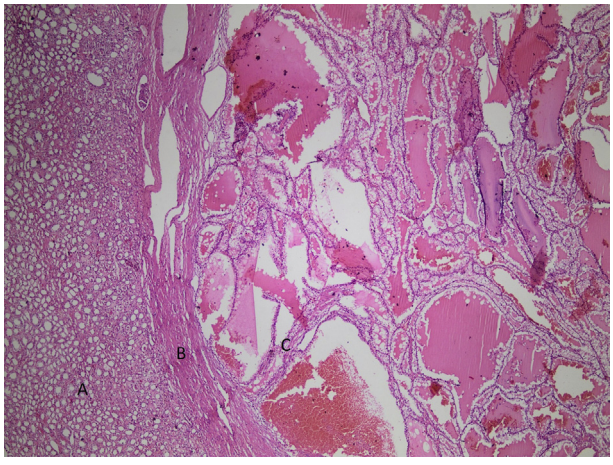

Figure 1 Pseudocapsule in a partial nephrectomy specimen. A: Tumour side, B: Pseudocapsule, C: Normal renal parenchyma (Hematoxylen-Eosin staining 4).

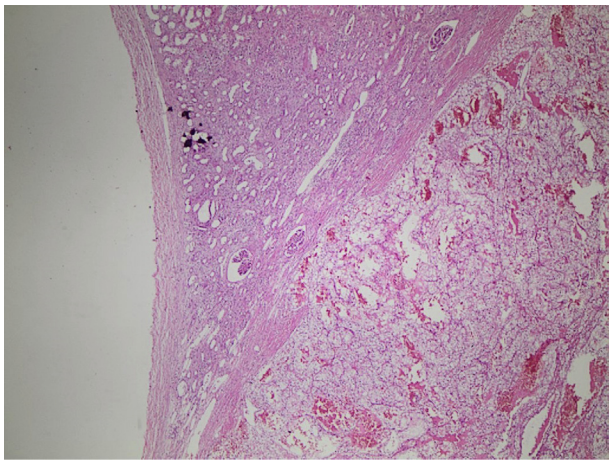

Figure 2 Pseudocapsular invasion, expansive type (Hematoxylen- Eosin staining; x4 magnification).

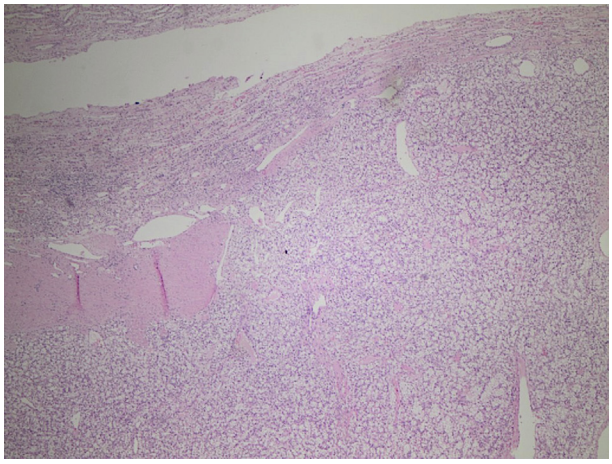

Figure 3 Pseudocapsular invasion, infiltrative type (Hematoxylen-Eosin staining; x4 magnification).

Table 1 Defining statistics regarding demographical and clinical features of the cases.

Variables	n = 99
Age (year)	56.2 ± 12.9
Age range (year)	25–83
Sex	
Male	58 (58.6%)
Female	41 (41.4%)
Pathological tumour size (cm)	3.5 (1.3–8.0)
Radiological tumour size (cm)	3.6 (1.6–7.7)
Tumour side	
Right	52 (52.5%)
Left	47 (47.5%)
Tumour location	
Top	35 (35.4%)
Middle	27 (27.3%)
Bottom	37 (37.4%)
Tumour structure	
Cystic	22 (22.2%)
Solid	77 (77.8%)
Pathological tumour stage	
1A	72 (72.7%)
1B	26 (26.3%)
3A	1 (1.0%)
Fuhrman grade	
1	22 (23.7%)
2	56 (60.2%)
3	15 (16.1%)

While histological variant was clear-cell in 67 (67.7%) of the cases, it was papillary RCC type 1, chromophobe, papillary RCC type 2, unclassified and multilobular in 17 (17.2%), 4 (4.0%), 2 (2.0%), 2 (2.0%) and 1 (1.0) of the cases respectively.

While necrosis was detected in 12 (12.1%) of the cases, sarcomatoid differentiation was detected in 1 (1.0%) of them. Pseudocapsular invasion was observed in 83 (83.8%) of the cases. 38 (45.8%) and 45 (54.2%) of the cases, in which pseudocapsular invasion was diagnosed, were of expansive type and infiltrative type respectively.

77 (77.8%) and 22 (22.2%) of the cases had undergone open surgery and laparoscopic surgery respectively. Respectively 68 and 9 retroperitoneal and transperitoneal interventions were applied for 77 patients who underwent open surgeries. On the other hand, respectively 14 and 8 retroperitoneal and transperitoneal interventions were applied for 22 patients who underwent laparoscopic surgeries. While retroperitoneal intervention was applied for 82 (82.8%) of the cases, transperitoneal intervention was applied for 17 (17.2%) of them. 86 (86.9%) of the patients suffered from ischemia. Median warm ischemia time was 17 min and the warm ischemia times varied between 2 and 40 min. Surgical margins were positive in 10 (10.1%) of the cases. Surgical margin positivity could definitely be revealed in histopathologic terms in 4 of these 10 cases. 6 cases were examined by being re-sectioned as pathologic preparations were deformed. It was observed in this second examination that the nearest tumour cell was as close as less than 0.1 mm to surgical margin. The patients detected to experience this situation were included in the group considered to have positive surgical margin for prevention of bias.

In one patient who had a positive surgical margin as seen in Table 3 the uro-pathologist reported that there was no pseudocapsule formation in 2–3% of the specimen. He suspected that the surgical resection line perforated the pseudocapsule at this site. We considered this case as surgical margin positive despite the fact that pseudocapsule was not invaded by the tumour itself.

Defining statistics regarding other clinical features have been provided in the Table 2.

There was not a statistically meaningful difference between the groups in which pseudocapsular invasion was/was not observed in terms of the distribution of tumour stages ($p = 0.901$).

There was not a statistically meaningful difference between the groups in which pseudocapsular invasion was/was not observed in terms of Fuhrman grade, either.

No statistically meaningful difference was observed between the groups in which pseudocapsular invasion was/was not detected in terms of prevalence of histological variants except for the clear-cell histological subtype ($p > 0.05$). Compared to the group in which pseudocapsular invasion was not detected, clear-cell histological subtype was observed more frequently in a statistically meaningful way in the group in which pseudocapsular invasion was detected ($p < 0.001$) (Fig. 4).

Median pathological tumour sizes were found out to be statistically similar for the groups in which pseudocapsular invasion was/was not observed ($p = 0.717$).

There was not a statistically meaningful difference between the groups in which pseudocapsular invasion was/was not observed in terms of endophytic/exophytic types of

Table 2 Defining statistics regarding other clinical features of the cases.

Variables	n = 99
Histological subtype	
Papillary RCC Type 1	17 (17.2%)
Papillary RCC Type 2	2 (2.0%)
Clear-cell	73 (73.8%)
Chromophobe	4 (4.0%)
Unclassified	2 (2.0%)
Multilobular	1 (1.0%)
Existence of necrosis	12 (12.1%)
Sarcomatoid differentiation	1 (1.0%)
Pseudocapsular invasion	83 (83.8%)
Pseudocapsular invasion type	
Expansive	38 (45.8%)
Infiltrative	45 (54.2%)
Surgery type	
Open	77 (77.8%)
Closed	22 (22.2%)
Surgery method	
Transperitoneal	17 (17.2%)
Retroperitoneal	82 (82.8%)
Ischemia	86 (86.9%)
Warm ischemia time (min.)	17 (2–40)
Surgical margin positivity	10 (10.1%)

Table 3 Clinical findings of the cases by groups in which pseudocapsular invasion (PCI) was/was not detected.

Variables	No PCI (n = 16)	PCI (n = 83)	p-value
Pathological tumour stage			0.901
1A	10 (76.9%)	62 (75.6%)	
1B	3 (23.1%)	19 (23.2%)	
3A	0 (0.0%)	1 (1.2%)	
Fuhrman grade			1.000
Low	9 (81.8%)	69 (%84.1)	
High	2 (%18.2)	13 (%15.9)	
Histological subtype			
Papillary RCC Type 1	3 (18.8%)	14 (16.9%)	1.000
Papillary RCC Type 2	1 (6.3%)	1 (1.2%)	0.298
Clear-cell	4 (25.0%)	63 (75.9%)	<0.001
Chromophobe	2 (12.5%)	2 (2.4%)	0.121
Unclassified	0 (0.0%)	2 (2.4%)	1.000
Multilobular	1 (6.3%)	0 (0.0%)	0.162
Pathological tumour size (cm)	3.5 (2.0–6.5)	3.5 (1.3–8.0)	0.717
Type			0.594
Endophytic	0 (0.0%)	7 (8.4%)	
Exophytic	16 (100.0%)	76 (91.6%)	
Tumour Location			0.261
Top	8 (50.0%)	27 (32.5%)	
Middle	2 (12.5%)	25 (30.1%)	
Bottom	6 (37.5%)	31 (37.3%)	
Surgical margin positivity	1 (6.3%)	9 (10.8%)	1.000
Sarcomatoid differentiation	0 (0.0%)	1 (%1,2)	1.000
Existence of necrosis	1 (6.3%)	11 (13.3%)	0.684

tumours and tumour locations respectively ($p = 0.594$ and $p = 0.261$).

There was not a statistically meaningful difference between the groups in which pseudocapsular invasion was/was not observed in terms of surgical margin positivity, sarcomatoid differentiation and existence of necrosis, either ($p = 1.000$; $p = 1.000$ and $p = 0.684$).

Clinical findings of the cases by groups in which pseudocapsular invasion was/was not observed have been indicated in Table 3.

There was not a statistically meaningful difference among the groups without pseudocapsular invasion and those with expansive pseudocapsular invasion and infiltrative pseudocapsular invasion in terms of distribution of pathological tumour stages ($p = 0.840$).

There was not a statistically meaningful difference among the groups without pseudocapsular invasion and those with expansive pseudocapsular invasion and infiltrative pseudocapsular invasion in terms of Fuhrman grade, either ($p = 0.220$).

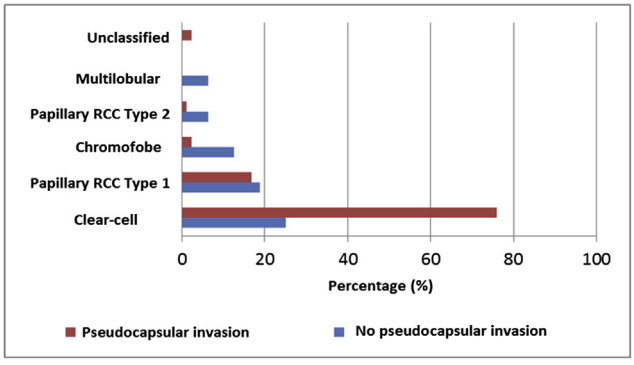

Figure 4 Pseudocapsular invasion rates.

No statistically meaningful difference was observed among the groups without pseudocapsular invasion and those with expansive pseudocapsular invasion and infiltrative pseudocapsular invasion in terms of prevalence of histological variants except for the clear-cell histological subtype ($p > 0.05$). Compared to the group in which pseudocapsular invasion was not detected, clear-cell histological subtype was observed significantly more frequently in the groups with expansive pseudocapsular invasion and infiltrative pseudocapsular invasion respectively ($p = 0.017$ and $p < 0.001$). Moreover, clear cell histological subtype was observed more frequently in a statistically meaningful way in the group with infiltrative pseudocapsular invasion compared to the group with expansive pseudocapsular invasion ($p = 0.003$).

Clinical findings of the cases by groups without pseudocapsular invasion and those with expansive and infiltrative pseudocapsular invasion have been indicated in Table 4.

4. Discussion

Local recurrence risk in simple enucleation cases indicates mixed results in the literature. When some results are compared to partial nephrectomy, excellent progression-free long term cancer specific survival rates were observed for local recurrence risk.[6,19] No increase in metastatic progression and long-term local recurrence risk was found out in terms of positive surgical margin.[20] It was shown that

Table 4 Clinical findings of the cases by groups without pseudocapsular invasion and those with expansive and infiltrative PCI.

Variables	No PCI (n = 16)	Expansive (n = 38)	Infiltrative (n = 45)	p-value
Pathological tumour stage				0.840
1A	10 (76.9%)	29 (78.4%)	33 (73.3%)	
1B	3 (23.1%)	8 (21.6%)	11 (24.4%)	
3A	0 (0.0%)	0 (0.0%)	1 (2.2%)	
Fuhrman grade				0,220
Low	9 (81.8%)	34 (91.9%)	35 (77.8%)	
High	2 (18.2%)	3 (8.1%)	10 (22.2%)	
Histological subtype				
Papillary RCC Type 1	3 (18.8%)	10 (26.3%)	4 (8.9%)	0.109
Papillary RCC Type 2	1 (6.3%)	1 (2.6%)	0 (0.0%)	0.242
Clear-cell	4 (25.0%)	23 (60.5%)	40 (88.9%)	<0.001
Chromophobe	2 (12.5%)	1 (2.6%)	1 (2.2%)	0.271
Unclassified	0 (0.0%)	2 (5.3%)	0 (0.0%)	0.143
Multilobular	1 (6.3%)	0 (0.0%)	0 (0.0%)	0.157
Pathological tumour size(cm)	3.5 (2.0–6.5)	3.5 (1.3–8.0)	3.6 (1.5–7.2)	0.874
Type				0.273
Endophytic	0 (0.0%)	3 (7.9%)	4 (8.9%)	
Exophytic	16 (100.0%)	35 (91.2%)	41 (91.1%)	
Tumour location				0.478
Top	8 (50.0%)	12 (31.6%)	15 (33.3%)	
Middle	2 (12.5%)	10 (26.3%)	15 (33.3%)	
Bottom	6 (37.5%)	16 (42.1%)	15 (33.3%)	
Surgical margin positivity	1 (6.3%)	3 (7.9%)	6 (13.3%)	0.609

the extent of resection margin was not correlated with disease progression in fully excised tumours.[7,21]

Post-operative life expectancy strategies took the tumour stage as the main factor. It was found out that some of pathological characteristics, namely nuclear grade, coagulative necrosis, microvascular and collecting system invasion, had prognostic effects on organ-confined RCC. It was considered in certain retrospective studies that tumour invasion of renal capsule had a prognostic role.

It was observed in 1980 for the first time in the studies by Rosenthal et al[13] and Rokka Rossetti et al[14] that pseudocapsular invasion was seen more frequently in less differentiated renal tumours. They stated that pseudocapsular invasion could be characterized with increasing clinical progression in the cases of organ-confined renal tumours.[14]

It was detected by scanning former studies such as the one performed by Jeong et al with a population of 288 cancer patients that pseudocapsular invasion was correlated with the tumour size and thus the pathological tumour stage but not with the tumour grade.[22] It was found out in the study conducted by Klatte et al with the largest population of 519 cancer patients that pseudocapsular invasion was correlated with the tumour size, stage and grade but not with the histological subtype.[23]

In the study conducted by Volpe et al, tumour pseudocapsule was exposed in all RCC cases. In this study, two different patterns of pseudocapsular invasion, namely expansive and infiltrative, were defined. At the same time, it was accepted that Fuhrman grade and aggressive biology of tumours detected to have infiltrative pseudocapsular invasion were correlated. It was found out that although 74.3% of high grade tumours were characterized with infiltrative pseudocapsular invasion, tumours without pseudocapsular invasion corresponding to 11.8% in total also led to high grade disease. It was also seen that tumour histotype was correlated with pseudocapsular invasion. It was observed that chromophobe tumours appeared with an infiltrative patent less frequently. However, no correlation was detected between pseudocapsular invasion and tumour size and grade.[15]

In our study, no statistically meaningful difference was detected between the groups with and without pseudocapsular invasion in terms of Fuhrman grade in discordance with that study. It was found out that only 22.2% of the high grade tumours had infiltrative pseudocapsular invasion. Similarly, pathological tumour sizes were identified to be statistically similar among the groups without pseudocapsular invasion and those with expansive and infiltrative pseudocapsular invasion. No correlation was detected between pseudocapsular invasion and tumour size. Clear-cell subtype was observed more frequently in the groups with expansive pseudocapsular invasion (60.5%) and infiltrative pseudocapsular invasion (88.9%). Moreover, clear-cell histological subtype was observed more frequently in the group with infiltrative pseudocapsular invasion compared to the groups with expansive type.

Metastatic progression with positive surgical margin and increase in long-term local recurrence risk were not detected in the study that was conducted by Lu wang et al and included patients treated with partial nephrectomy and simple enucleation. Local recurrence was not observed in the average follow-up period of 26 months.[24]

When the patient groups, identified to have pseudocapsular invasion, in our study were examined, a statistically meaningful difference could not be detected for existence of pseudocapsular invasion as well as

pseudocapsular invasion type and surgical margin positivity. It was believed that partial nephrectomy, which was performed for all of the cases included in the study by taking safe surgical margin into consideration, impacted this result. In order to definitely demonstrate this hypothesis, the studies to be performed with larger patient groups are needed. In long term follow-up of the patient groups, local recurrence was detected in only one patient diagnosed with surgical margin positivity. Radical nephrectomy was applied for this patient. Other patients were still under follow-up without recurrence or metastasis. Therefore, there was no difference in terms of cancer-specific survival and overall survival between the groups in which pseudocapsular invasion was/was not detected. There was no association between pseudocapsular invasion and cancer-specific and overall survival.

The limitations of our study can be summarized as following: the study was retrospective, had a small sample size and pretty short follow-up period. At the same time, multivariate analysis could not be performed due to low level of local recurrence in our low stage population.

5. Conclusion

It was found out in our study that only histological subtype affected the pseudocapsular invasion but tumour size, tumour stage, tumour location, endophytic and exophytic character did not affect it in the patient group that underwent partial nephrectomy. It has also been revealed that surgical margin positivity is not correlated with pseudocapsular invasion. There was no association between pseudocapsular invasion and cancer specific and overall survival. However, this study should be supported with larger populations and long-term scientific studies.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2018.12.001.

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