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Original Article

Differences in peritumoral pseudocapsule characteristics according to clinicopathological factors in clinical T1a renal tumors

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Abstract: Objectives: To evaluate the status of peritumoral pseudocapsules in renal tumors and the effects of clinicopathological factors on their formation. Methods: From January 2011 to December 2012, 258 patients with solitary clinical stage T1a renal tumors who underwent partial nephrectomy were analyzed. Status of pseudocapsule was re-evaluated by a pathologist. Results: The mean long diameter (± SD) of the tumor and the width of the safety margin were 2.17 (± 0.94) cm and 3.2 (± 2.4) mm, respectively. A complete pseudocapsule was identified in 152 (58.9%) tumors, an incomplete pseudocapsule was identified in 69 (26.7%) tumors, and no pseudocapsule was identified in 37 (14.3%) tumors. Out of 152 tumors with complete pseudocapsules, 45 (29.6%) were confirmed to directly invade the renal parenchyma. In a multivariable analysis, age (odds ratio [OR], 1.045; 95% confidence interval [CI], 1.021-1.070, P < 0.001) and histologic subtype (chromophobe type: OR, 19.455; 95% CI, 4.233-89.471, P < 0.001; oncocytoma: OR, 11.307; 95% CI, 1.357-94.198, P = 0.025) were significant factors for an incomplete or absent pseudocapsule. Conclusions: Peritumoral pseudocapsules are absent or incomplete in a significant portion of renal tumors. Old age as well as chromophobe and oncocytoma histologic subtypes were significant risk factors for an incomplete or absent peritumoral pseudocapsule.

Keywords: Renal tumor, partial nephrectomy, peritumoral pseudocapsule, surgical margin, pathologic finding

Introduction

Nephron sparing surgery (NSS) has been established as a gold standard for the treatment of clinical T1 renal cell carcinoma (RCC) [1, 2]. NSS has demonstrated favorable long-term survival results compared to radical nephrectomy with the advantage of preserving renal function [3-6]. A tumor-free surgical margin following NSS is generally recommended to avoid local tumor recurrence [1]. However, there has been no consensus on the preferable range of a safety surgical margin in NSS.

Some groups recommended excising an additional 0.5-2 cm of tissue to ensure a true negative margin [7, 8]. However, other groups reported that a tumor-free margin of resection, irrespective of the width of the margin, is sufficient to achieve local control of RCC [9, 10]. Furthermore, certain surgical groups reported comparable long-term oncologic outcomes with tumor enucleation (TE), which enables tumor excision by blunt dissection using the natural plane between the tumor and the normal parenchyma [11, 12].

A peritumoral pseudocapsule composed of fibrous tissue and compressed renal parenchyma is a pathological feature known to be frequent in RCC [13]. The maturation of the pseudocapsule establishes the natural cleavage plane for TE and tumor-free status of the enucleated surface. Recently, Minervini et al. reported that a pseudocapsule was present in nearly all TE cases and that all were tumor-negative at the surgical margins [14]. The authors concluded that because of this, patients can remain recurrence-free for over 24 months

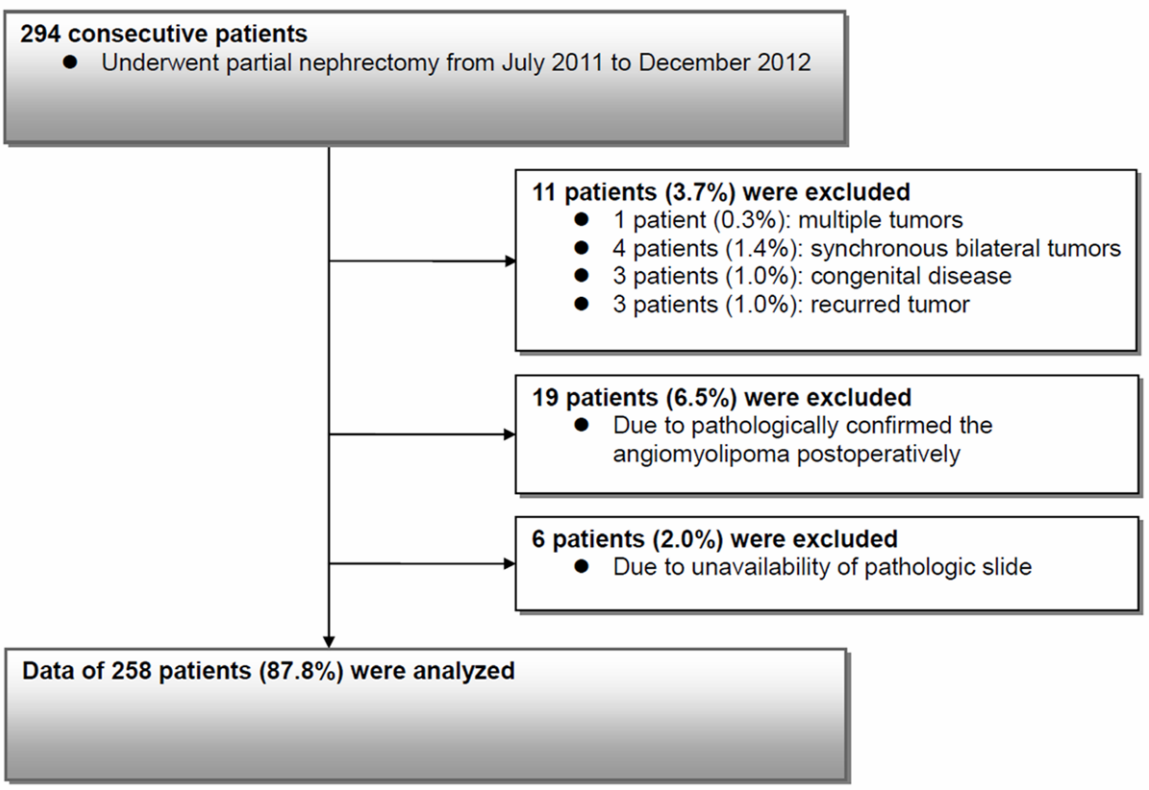

Figure 1. Inclusion and exclusion criteria used in the current study.

after TE. However, others insisted that the tumor may invade the kidney parenchyma beyond the pseudocapsule [8, 15, 16].

The purpose of the current study was to confirm the status of peritumoral pseudocapsules of renal tumors and to identify clinicopathological risk factors for absent or incomplete pseudocapsules. To examine these issues, a consecutive partial nephrectomy series and the associated pathology slides were reviewed retrospectively.

Materials and methods

Patient selection

This study protocol was approved by the institutional review board of Seoul National University Hospital, Seoul, Republic of Korea. The study population comprised 294 consecutive patients who received partial nephrectomy due to T1a renal tumors between January 2011 and December 2012 at our institution. Patients with multiple tumors (N = 1, 0.3%), synchronous bilateral tumors (N = 4, 1.4%), congenital diseases such as von Hippel-Lindau disease (N = 3, 1.0%), recurred tumor (N = 3, 1.0%), pathologically confirmed angiomyolipoma (N = 19, 6.5%), and unavailability of pathological specimen (N = 6, 2.0%) were excluded (**Figure 1**). Ultimately, 258 patients with solitary stage T1a renal tumors and available pathology slides were analyzed.

Preoperative evaluation and treatments

Preoperative evaluation was performed routinely and included the following: physical examination, routine blood laboratory tests, chest radiography, and an abdominal computerized tomography scan. Intraoperative frozen section margin evaluation was performed routinely except in cases of laparoscopic partial nephrectomy (LPN) or robot-assisted partial nephrectomy (RAPN). Lymph node dissection was not performed if there was no visible node on preoperative evaluations.

Pathological evaluation and review of the peritumoral pseudocapsule

All the specimens were evaluated and reviewed by a single dedicated uropathologist (KCM).

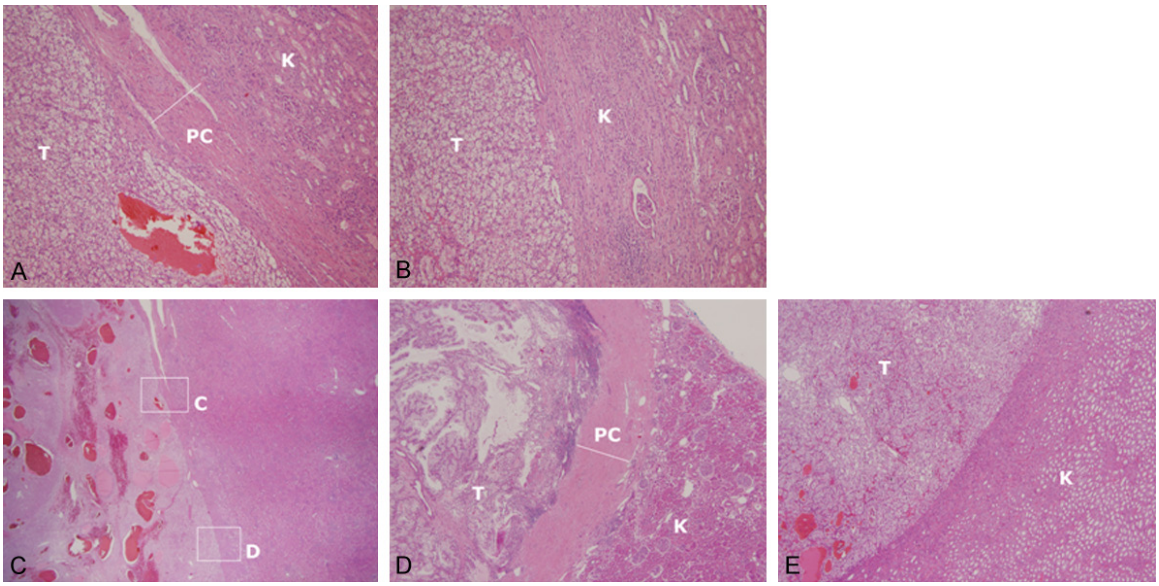

Figure 2. Histologic analysis of peritumoral pseudocapsules in partial nephrectomy specimens. A. Presence of pseudocapsule with complete continuity: The tumor is completely encapsulated by pseudocapsule (hematoxylin and eosin [H&E] stain, × 40). B-D. Partial pseudocapsule formation: Pseudocapsule formation between the tumor and renal parenchyma in the upper portion, but not in the lower portion (B; H&E stain, × 10). At higher magnification of the upper portion in the same case, pseudocapsule is present between the tumor and renal parenchyma (C; H&E stain, × 100); however, in the lower portion, pseudocapsule is absent (D; H&E stain, × 100). E. Absence of pseudocapsule: No PC formation (H&E stain, × 40); T, tumor; K, kidney parenchyma; PC, pseudocapsule.

Excised specimens were examined for tumor size and processed according to standard pathological procedures. Pathological staging of the tumor was based on the 7th revised recommendation of the American Joint Cancer Committee 2010 [17]. Histologic subtypes and tumor grades were assessed according to the 2004 World Health Organization classification and the recommendations of Fuhrman et al. [18, 19]. To identify the status of the peritumoral pseudocapsule including its existence, completeness, and tumor invasion, all previously processed slides of all specimens were reviewed. The status of the pseudocapsule was classified as follows: 1 present with complete continuity (**Figure 2A**), present but with incomplete continuity (**Figure 2B-D**), and 3 absent (**Figure 2E**).

Statistical analyses

The rates of pseudocapsule presence or absence were analyzed. Clinicopathological characteristics including sex, age, body mass index (BMI), tumor size, histologic tumor subtype, and Fuhrman nuclear grade were compared between patients with a complete pseudocapsule, incomplete pseudocapsule, and no pseudocapsule. Parameters were compared using the one-way ANOVA test (mean values), Kruskal-Wallis test (median values), and Chi-square test (categorical values) with a post-hoc analysis. To identify positive factors associated with the presence of a complete pseudocapsule, univariate and multivariate analyses were performed using binary logistic regression. The predictive factors assessed were age, sex, BMI, laterality, tumor size, histologic subtype, and Fuhrman nuclear grade. All variables significant in the univariate analysis were included in a multivariate logistic regression model. All tests were two-sided with a significance level of 0.05. The statistical analysis was performed using commercially available software (SPSS version 21.0, Chicago, IL, USA).

Results

Baseline characteristics

The descriptive characteristics of all 258 patients are shown in **Table 1**. The mean subject age (± SD) at operation was 54.3 (± 12.9) years. The mean tumor diameter was 2.17 (± 0.94) cm. The median R.E.N.A.L nephrometry score [20] was 7.0 (range: 4 to 10). Of the 258

Table 1. Clinicopathological characteristics of the study population

	Mean (± SD), Median (range), or Number (%)
Number of patients	258
Patient characteristics	
Male	177 (68.6%)
Age at operation (years)	54.3 (± 12.9)
Body mass index (Kg/m^2)	24.6 (± 3.1)
Hypertension	91 (35.3%)
Diabetes mellitus	32 (12.4%)
Tumor characteristics	
Right	143 (55.4%)
Long diameter of tumor (cm)	2.17 (± 0.94)
R.E.N.A.L score	7.0 (4.0 to 10.0)
Clinical N1 stage	1 (0.4%)
Clinical M1 stage	0 (0.0%)
Perioperative parameters	
Operation type	
Open partial nephrectomy	169 (65.5%)
Laparoscopic partial nephrectomy	17 (6.6%)
Robot-assisted partial nephrectomy	72 (27.9%)
Type of hilar control	
Warm ischemia	228 (88.4%)
Cold ischemia	22 (8.5%)
Not done	8 (3.1%)
Ischemic time (min)	26.6 (± 11.9)
Pathological characteristics	
Tumor involvement on resection margin	1 (0.4%)
Length of resection margin from tumor (mm)	3.16 (± 2.39)
Histologic subtype	
Clear cell type	214 (82.9%)
Papillary type	12 (4.7%)
Chromophobe type	22 (8.5%)
Oncocytoma	10 (3.9%)
Other non-conventional types	0 (0.0%)
Fuhrman nuclear grade	
G1	32 (12.4%)
G2	150 (58.1%)
G3	61 (23.6%)
G4	3 (1.2%)
GX (unclassified)	12 (4.7%)
Sarcomatoid differentiation	0 (0.0%)
Lymphovascular invasion	0 (0.0%)

patients, 169 (65.5%) underwent open partial nephrectomy, 17 (6.6%) underwent LPN, and 72 (27.9%) underwent RAPN. The mean ischemic time was 26.6 (± 11.9) minutes. The confirmed histologic subtype was clear cell type in 214 (82.9%) tumors, papillary type in 12 (4.7%) tumors, chromophobe type in 22 (8.5%) tumors, and oncocytoma in 10 (3.9%) tumors. Other non-conventional RCC types were not detected in this series.

The status of peritumoral pseudocapsule

Table 2 shows the status of peritumoral pseudocapsule. Of all 258 renal tumors, 152 (58.9%) had a pseudocapsule with complete continuity. However, in 49 (30.8%) of these 159 cases with a complete pseudocapsule, the tumor invaded beyond the pseudocapsule. Peritumoral pseudocapsules with incomplete continuity were present in 69 (26.7%) tumors, while 37 (14.3%) of the total 258 tumors had no peritumoral pseudocapsule.

Comparison of clinicopathological features according to peritumoral pseudocapsule status

Clinicopathological features were compared according to peritumoral pseudocapsule status (**Table 3**). All subjects were divided into three groups according to their peritumoral pseudocapsule status as follows: complete pseudocapsule (N = 152), incomplete pseudocapsule (N = 69), and no pseudocapsule (N = 37). There were fewer male patients in the no pseudocapsule group than in the other two groups ($P < 0.001$). The mean age of the complete pseudocapsule group was lower than that of the other two groups ($P < 0.001$). The distribution of histologic subtypes was statistically different among all 3 groups ($P < 0.001$). The chromophobe and oncocytoma subtypes occurred more frequently in the incomplete and no pseudocapsule groups. However, other parameters including BMI, past medical history, laterality, long diameter of the tumor, R.E.N.A.L nephrometric score, and Fuhrman nuclear grade did not differ significantly among the groups (**Table 3**).

Table 2. Peritumoral pseudocapsule status in 258 consecutive renal tumors

	Number (%)
Number of patients	258
Complete pseudocapsule	
Without tumor invasion	107 (41.5%)
With tumor invasion into renal parenchyma	45 (17.4%)
Incomplete pseudocapsule	69 (26.7%)
No pseudocapsule	37 (14.3%)

The risk factors for incomplete peritumoral pseudocapsule

Table 4 shows the univariate and multivariate models for predicting absent or incomplete peritumoral pseudocapsule in all patients after partial nephrectomy. In the univariate analysis, sex, age, and chromophobe or oncocytoma histologic subtype represented highly significant predictors of an incomplete peritumoral pseudocapsule. In a multivariate analysis that included these parameters, age (odds ratio [OR], 1.045; 95% confidence interval [CI], 1.021-1.070, P < 0.001) and histologic subtype (chromophobe type: OR, 19.455; 95% CI, 4.233-89.471, P < 0.001; oncocytoma: OR, 11.307; 95% CI, 1.357-94.198, P = 0.025) remained independent predictors of an incomplete peritumoral pseudocapsule. However, age did not influence the risk of an absent or incomplete pseudocapsule.

Discussion

Comparison with previous studies

Our current study found 58.9% of patients had a complete pseudocapsule and 14.3% had no pseudocapsule (**Table 2**). Our results are different from those of Minervini et al., who studied 90 RCC tumors treated by TE [14]. They reported that all tumors were surrounded by a continuous, non-fenestrated, fibrous pseudocapsule [14]. However, only 90 RCC cases out of the 187 patient consecutive NSS series in whom TE was possible were investigated. There was no mention of definite selection criteria for patients who received TE [14]. This implies that patients who had a definite pseudocapsule on preoperative evaluation, and therefore were favorable candidates for TE, may have been selected from the consecutive NSS series. Hence, there may have been a selection bias regarding pseudocapsule status. However, in the current study, to rule out the possibility of such a bias, consecutive partial nephrectomy cases were reviewed. Other researchers reported that tumor invasion into the renal parenchyma beyond the pseudocapsule is frequent in ex vivo TE of partial nephrectomy specimens or in vivo TE specimens [8, 15, 16]. They all recommended excising an additional sufficient tissue range from the tumor to ensure a negative margin.

Moreover, there were signs of tumor penetration beyond the pseudocapsule in some cases. However, this was considered a negative surgical margin regardless of the degree of pseudocapsule penetration because the tumor cells were separated from the renal parenchyma by a thin layer of inflammatory cells [14]. Nevertheless, these standards of determining negative surgical margins are controversial. In our series, the absence of an inflammatory cell layer was frequent in the incomplete pseudocapsule group (**Figure 2B**) and the no pseudocapsule group (**Figure 2C**). In these cases, tumor cells are not separated from the normal renal parenchyma. On these grounds, the high peritumoral pseudocapsule rate reported by Minervini et al. is thought to be exaggerated. Because the present study population comprised consecutive cases without selection, the result regarding the status of peritumoral pseudocapsule is deduced to be more reliable.

Risk factors for incomplete pseudocapsule

This current study demonstrated that age (OR, 1.045; 95% CI, 1.021-1.070, P < 0.001) and chromophobe (OR, 19.455; 95% CI, 4.233-89.471, P < 0.001) or oncocytoma (OR, 11.307; 95% CI, 1.357-94.198, P = 0.025) histologic subtypes were independent risk factors for an absent or incomplete pseudocapsule in the multivariate analysis (**Table 4**). Of the 22 chromophobe subtype tumors in our series, 9 (40.9%) and 11 tumors (50.0%) had incomplete and absent pseudocapsules, respectively. Moreover, 9 (90.0%) of the 10 oncocytomas were absent a pseudocapsule. The rates of incomplete or absent pseudocapsules among those with the chromophobe (90.9%) and oncocytoma (90.0%) subtypes were higher than the rates among those with clear cell (73 of 214, 34.1%) and papillary (4 of 12, 33.3%) subtypes.

Table 3. Comparison of clinicopathological features according to peritumoral pseudocapsule status

	Complete pseudocapsule	Incomplete pseudocapsule	No pseudocapsule	*p*-value
Number of patients	152 (58.9%)	69 (26.7%)	37 (14.3%)	-
Patient characteristics				
Male	117 (77.0%)	48 (69.6%)	12 (32.4%)†	< 0.001
Age	51.8 (± 13.6)†	56.9 (± 11.6)	59.8 (± 9.5)	< 0.001
Body mass index (Kg/m^2)	24.6 (± 2.8)	25.0 (± 3.5)	24.3 (± 3.3)	0.543
Hypertension	49 (32.2%)	26 (37.7%)	16 (43.2%)	0.403
Diabetes mellitus	17 (11.2%)	11 (15.9%)	4 (10.8%)	0.580
Tumor characteristics				
Right	82 (53.9%)	41 (59.4%)	20 (54.1%)	0.738
Long diameter (cm)	2.12 (± 0.96)	2.31 (± 0.87)	2.04 (± 0.94)	0.273
R.E.N.A.L nephrometry score	7.0 (4 to 10)	7.0 (4 to 10)	7.5 (4 to 10)	0.848
Pathological characteristics				
Histologic subtype				
Clear cell type	141 (92.8%)†	57 (82.6%)†	16 (43.2%)†	< 0.001
Papillary type	8 (5.3%)†	3 (4.3%)†	1 (2.7%)†	
Chromophobe type	2 (1.3%)†	9 (13.0%)†	11 (29.7%)†	
Oncocytoma	1 (0.7%)†	0 (0.0%)†	9 (24.3%)†	
Fuhrman grade				
G1	18 (11.8%)	10 (14.5%)	4 (10.8%)	0.541
G2	96 (63.2%)	36 (52.2%)	18 (48.6%)	
G3	34 (22.4%)	21 (30.4%)	6 (16.2%)	
G4	1 (0.7%)	2 (2.9%)	0 (0.0%)	
GX (Unclassified)	3 (2.0%)	0 (0.0%)	9 (24.3%)	-

Mean values, compared by one-way ANOVA test; Median values, compared by Kruskal-Wallis test; Categorical values, compared by Chi-square test; †Significantly different from the other two groups according to the post-hoc analysis.

Our results are different from those of Minervini et al., who reported that the distributions of histologic subtypes were not statistically different between those with or without tumor involvement on pseudocapsule [14]. The reason for these differences is postulated to be the number of chromophobe subtypes (4 of 90 tumors, 4.4%) in that study, which was too small to obtain statistical power. However, our results are consistent with those of Leese et al., suggesting that absent or incomplete pseudocapsules are more frequent in chromophobe and oncocytoma subtypes than in other subtypes [21].

In this study, there were fewer male patients in the absent pseudocapsule group (32.4%) than in the complete and incomplete pseudocapsule groups (77.0% and 69.6%, P < 0.001). However, sex was not an independent risk factor for an incomplete or absent pseudocapsule in the multivariate analysis (P < 0.094, **Table 4**). The female dominance among chromophobe subtype and oncocytoma (23 of 32 tumors, 71.9%) cases in our series is postulated as the cause of the non-independence of sex as a risk factor.

Patient age at operation time was also identified as an independent risk factor in this study. Age was not considered a risk factor for incomplete pseudocapsule in previous studies [14, 21]. There were no statistical differences among histologic subtypes according to age (P = 0.457 by one-way ANOVA test). To the best of our knowledge, there have been no reports regarding the correlation of age and pseudocapsule formation. Dehner et al. reported that 73% of RCCs in children (mean age = 9 years) had peritumoral pseudocapsules, but the rate was not compared to other age groups [22]. Old age has been proposed as an independent risk factor for poor prognosis in RCC by some researchers [23-25]. The correlation between

Table 4. Univariate and multivariate binary logistic regression analyses of risk for an absent or incomplete pseudocapsule

	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex				
Male	Reference		Reference	
Female	2.563 (1.496-4.392)	0.001	1.703 (0.913-3.174)	0.094
Age, years	1.041 (1.019-1.063)	< 0.001	1.045 (1.021-1.070)	< 0.001
Body mass index, kg/m^2	1.014 (0.935-1.100)	0.732		
Hypertension				
Absent	Reference			
Present	1.379 (0.823-2.313)	0.223		
Diabetes mellitus				
Absent	Reference			
Present	1.309 (0.622-2.753)	0.478		
Laterality				
Right	Reference			
Left	0.864 (0.524-1.425)	0.567		
Diameter, cm	1.119 (0.856-1.462)	0.411		
R.E.N.A.L score	1.040 (0.892-1.212)	0.617		
Histologic subtype				
Clear cell type	Reference		Reference	
Papillary type	0.966 (0.281-3.314)	0.956	1.053 (0.284-3.903)	0.939
Chromophobe type	19.315 (4.393-84.915)	< 0.001	19.455 (4.233-89.471)	< 0.001
Oncocytoma	17.384 (2.160-139.875)	0.007	11.307 (1.357-94.198)	0.025
Fuhrman nuclear grade				
G1, G2	Reference			
G3, G4	1.389 (0.780-2.472)	0.264		

OR, odds ratio; CI, confidence interval.

age and pseudocapsule formation in our current study can serve as a possible reason for those results.

Tumor size and Fuhrman nuclear grade were proposed as risk factors for an incomplete pseudocapsule in a previous study by Minervini et al. [14]. However, tumor size (P = 0.411) and Fuhrman nuclear grade (P = 0.264) were not found to be significant in a univariate analysis of our data (**Table 4**). The reason for this difference is postulated to be our inclusion of clinical stage T1a cases only, as opposed to the previous study that included patients up to clinical stage T3a [14]. Some results of other studies imply that tumor size or Fuhrman nuclear grade may affect peritumoral pseudocapsule status and the permeability of TE [26, 27]. To draw a more definitive conclusion regarding these issues, more well-designed studies are needed.

Clinical implications of the current study

Unlike previous reports, a substantial portion (41.0%) of renal tumors in our series demonstrated an incomplete or absent peritumoral pseudocapsule. In the current study, chromophobe and oncocytoma histologic subtypes were identified as independent risk factors. These two subtypes of renal tumor comprised 12.4% (32 of 258 tumors) of our consecutive series. However, these two types of tumors are known to be difficult to distinguish form other subtypes of renal tumors by preoperative imaging studies [28, 29]. Moreover, old age was also a risk factor for incomplete pseudocapsule. The cut-off age of 47.5 years demonstrated the highest accuracy at a level of 89.6% sensitivity and 35.5% specificity in a receiver operating curve analysis of our subjects (figures are not presented). On these grounds, the application

of TE as a treatment modality for renal tumors should be considered with caution.

Limitations of this study

Our study was limited by the retrospective nature of the analysis and the relatively small number of patients. In addition, because we performed reviews of pathology slides, only representative sections could be reviewed. So, the completeness of tumor sampling might not be archieved. However, with only these representative sections, substantial portions of incomplete pseudocapsule continuity, tumor involvement into the renal parenchyma, or pseudocapsule absence can be identified. Our pathologic slide re-evaluations were performed by an experienced urologic pathologist (KCM) rather than relying on reports from potentially multiple sources. Moreover, only clinical T1a renal tumors were included in this study. The low stage of renal tumor in patients with partial nephrectomy might lead to an undefined bias regarding pathological outcomes. Lastly, oncologic outcome could not be analyzed due to the relatively short period of follow up. To draw a clearer conclusion regarding pseudocapsules in patients with RCC, more well-designed prospective studies that ensure an in-depth review of whole tumor sections are needed.

Conclusions

Significant portions of renal tumors were identified as having absent or incomplete peritumoral pseudocapsules. Moreover, tumor invasion into the renal parenchyma was confirmed in a substantial portion of complete pseudocapsules. Old age and chromophobe and oncocytoma histologic subtypes were significant factors for incomplete or absent peritumoral pseudocapsule.

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Disclosure of conflict of interest

None.

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References

[1] Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, Mulders P, Powles T, Staehler M, Volpe A, Bex A. EAU guidelines on renal cell carcinoma. Eur Urol 2015; 67: 913-24.

[2] Motzer RJ, Jonasch E, Agarwal N, et al. NCCN Clinical practice guidelines in Oncology, Kidney Cancer Version 1. 2015. available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.

[3] Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, Colombel M, Klotz L, Skinner E, Keane T, Marreaud S, Collette S, Sylvester R. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2011; 59: 543-52.

[4] Becker F, Siemer S, Humke U, Hack M, Ziegler M, Stöckle M. Elective nephron sparing surgery should become standard treatment for small unilateral renal cell carcinoma: long-term survival data of 216 patients. Eur Urol 2006; 49: 308-13.

[5] Antonelli A, Cozzoli A, Nicolai M, Zani D, Zanotelli T, Perucchini L, Cunico SC, Simeone C. Nephron-sparing surgery versus radical nephrectomy in the treatment of intracapsular renal cell carcinoma up to 7 cm. Eur Urol 2008; 53: 803-9.

[6] Leibovich BC, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. J Urol 2004; 171: 1066-70.

[7] Polascik TJ, Pound CR, Meng MV, Partin AW, Marshall FF. Partial Nephrectomy: technique complications and pathological findings. J Urol 1995; 154: 1312-8.

[8] Blackley SK, Ladaga L, Woolfitt RA, Schellhammer PF. Ex-situ study of the effectiveness of enucleation in patients with renal cell carcinoma. J Urol 1988; 140: 6-10.

[9] Sutherland SE, Resnick MI, Maclennan GT, Goldman HB. Does the size of the surgical margin in partial nephrectomy for renal cell cancer really matter? J Urol 2002; 167: 61-4.

[10] Van Poppel H, Joniau S. How important are surgical margins in nephron-sparing surgery? Eur Urol Supple 2007; 6: 533-9.

[11] Carini M, Minervini A, Masieri L, Lapini A, Serni S. Simple enucleation for the treatment of

pT1a renal cell carcinoma: our 20-year experience. Eur Urol 2006; 50: 1263-8.
[12] Pertia A, Managadze L. Long-term results of simple enucleation for the treatment of small renal cell carcinoma. Int Braz J Urol 2006; 32: 640-5.
[13] Yamashita Y, Takahashi M, Watanabe O, Yoshimatsu S, Ueno S, Ishimaru S, Kan M, Takano S, Ninomiya N. Small renal cell carcinoma: pathologic and radiologic correlation. Radiology 1992; 184: 493-8.
[14] Minervini A, di Cristofano C, Lapini A, Marchi M, Lanzi F, Giubilei G, Tosi N, Tuccio A, Mancini M, della Rocca C, Serni S, Bevilacqua G, Carini M. Histopathologic analysis of peritumoral pseudocapsule and surgical margin status after tumor enucleation for renal cell carcinoma. Eur Urol 2009; 55: 1410-8.
[15] Marshall FF, Taxy JB, Fishman EK, Chang R. The feasibility of surgical enucleation for renal cell carcinoma. J Urol 1986; 135: 231-4.
[16] Rosenthal CL, Kraft R, Zingg EJ. Organ-preserving surgery in renal cell carcinoma: tumor enucleation versus partial kidney resection. Eur Urol 1984; 10: 222-8.
[17] Edge SB, Byrd DR, Compton CC, et al. In: Edge SB, Byrd DR, Compton CC, et al. editors. AJCC cancer staging manual. 7th Edition. New York: Springer; 2010. pp. 479-90.
[18] Lopez-Beltran A, Scarpelli M, Montironi R, Kirkali Z. 2004 WHO Classification of the renal tumors of the adults. Eur Urol 2006; 49: 798-805.
[19] Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982; 6: 655-63.
[20] Schmit GD, Thompson RH, Kurup AN, Weisbrod AJ, Boorjian SA, Carter RE, Geske JR, Callstrom MR, Atwell TD. Usefulness of R.E.N.A.L. Nephrometry scoring system for predicting outcomes and complications of percutaneous ablation of 751 renal tumors. J Urol 2013; 189: 30-5.
[21] Leese JA, Williamson SR, Grignon DJ, et al. Variance and characteristics of peritumoral pseudocapsule of renal cell carcinoma based on histologic tumor subtype. J Urol 2013; 189 Supple 4: e535-6.
[22] Dehner LP, Leestma JE, Price EB Jr. Renal cell carcinoma in children: a clinicopathologic study of 15 cases and review of the literature. J Pediatr 1970; 76: 358-68.
[23] SÁNchez-Ortiz RF, Rosser CJ, Madsen LT, Swanson DA, Wood CG. Young age is an independent prognostic factor for survival of sporadic renal cell carcinoma. J Urol 2004; 171: 2160-5.
[24] Griffiths D, Verghese A, Golash A, Kynaston HG, Matthews PN, Hart AJ, Court JB. Contribution of grade, vascular invasion and age to outcome in clinically localized renal cell carcinoma. BJU int 2002; 90: 26-31.
[25] Chang JS, Park YH, Ku JH, Kwak C, Kim HH. Predicting factors for death from other causes in patients with localized renal cell carcinoma. Korean J Urol 2012; 53: 18-22.
[26] Roy C Sr, El Ghali S, Buy X, , Lindner V, Lang H, Saussine C, Jacqmin D. Significance of the pseudocapsule on MRI of renal neoplasms and its potential application for local staging: a retrospective study. AJR Am J Roentgenol 2005; 184: 113-20.
[27] Tochimoto M, Matsumoto T. Histological evaluation of enucleation for renal cell carcinoma using radical nephrectomy specimens. Nihon Hinyokika Gakkai zasshi 1994; 85: 1097-105.
[28] Rosenkrantz AB, Hindman N, Fitzgerald EF, Niver BE, Melamed J, Babb JS. MRI features of renal oncocytoma and chromophobe renal cell carcinoma. AJR Am J Roentgenol 2010; 195: 421-7.
[29] Wang XK, Wang HY, Wang J, Wang YW, Wang Y, Tang YH, Ye HY. Magnetic resonance imaging findings of chromophobe renal cell carcinoma. Zhonghua Yi Xue Za Zhi 2013; 93: 1016-9.