

Is Preoperative Magnetic Resonance Imaging in a Daily Clinical Setting Useful to Evaluate Tumor Invasion Beyond the Pseudocapsule in Renal Cell Carcinoma?

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ABSTRACT

Background We wanted to clarify whether preoperative magnetic resonance imaging (MRI) in the clinical setting can evaluate the pathologic pseudocapsule (PC) morphology with high accuracy in renal cell carcinoma (RCC).

Methods We retrospectively analyzed 34 consecutive patients who underwent MRI (1.5 or 3.0T, 5 mm slices) prior to partial nephrectomy (PN) for RCC at our institution between January 2010 and December 2019. First, the correlation between PC morphology (complete or incomplete) and tumor infiltration to the renal parenchyma was examined as pathologic validation. Second, the concordance rate of PC morphology between pathologic tissue and preoperative MRI was evaluated as radiologic validation. Third, risk factor for renal parenchymal invasion in RCC was analyzed.

Results In the pathologic validation, parenchymal invasion rates were 11% and 28% in the “complete PC” and “incomplete PC” groups, respectively. In the radiologic validation, pathological PC morphology could be diagnosed on preoperative MRI in 17 patients (50.0%). “None PC” on MRI had the lowest positive predictive value (PPV) (0%), “partial PC” on MRI had a good PPV (76.5%), “complete PC” on MRI had a relatively low PPV (33.3%). Unfortunately, these data were insufficient for diagnostic accuracy. As risk factor for renal parenchymal invasion in RCC, only pathologic subtype (non-clear cell) was found to have significant differences in the multivariate analysis.

Conclusion The results of this study suggest that renal tumors with pathologically incomplete PC have a high possibility of renal parenchymal invasion. However, it is currently difficult to accurately evaluate pathologic PC morphology by preoperative MRI in the clinical setting.

Key words renal cell carcinoma; pseudocapsule; renal parenchymal invasion; preoperative magnetic resonance imaging; partial nephrectomy

Pseudocapsule (PC) is an interstitial fibrous capsule that forms around renal cell carcinoma (RCC) and is considered to occur secondarily following inflammatory reaction due to displacement of healthy renal parenchyma by tumor. The PC is usually ≤ 2.5 mm thick, and in the case of incomplete loculation, tumor invasion can be observed into the interstitium of the capsule and into renal parenchyma beyond the capsule.^{1–3}

Partial nephrectomy (PN) for small RCC is as effective as radical nephrectomy (RN) in controlling cancer and reduces the likelihood of cardiovascular events.^{4–7} Therefore, PN has become the gold standard procedure specifically for treating T1a RCC having a tumor diameter of ≤ 4 cm.⁸ In recent years, good treatment outcomes have been reported sporadically in T1b RCC, mainly at high-volume centers, leading to a trend of expanding indications for PN.^{9–11}

However, positive surgical margin (PSM) in PN have been reported to occur at a rate of 4.9%–8.1% in laparoscopic PN and 0%–8.7% in robotic-assisted PN.¹² In addition, multiple recent studies have reported that tumor enucleation (TE) is as effective as standard PN in controlling cancer and preserving renal function.^{13–15} Given that the TE technique involves the incision of PC that has formed around the renal tumor along the renal parenchyma, this procedure is advantageous in terms of decreasing hemorrhage volume. However, it must be taken into account that there is some probability of PSM. Wang et al. compared 59 patients who underwent TE with 58 patients who underwent PN, and reported that the TE patients had less hemorrhage volume and fewer postoperative complications than those in the PN patients; however, PSM was significantly more frequent

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Abbreviations: MRI, magnetic resonance imaging; NPV, negative predictive value; OS, overall survival; PC, pseudocapsule; PN, partial nephrectomy; PPV, positive predictive value; PSM, positive surgical margin; RCC, renal cell carcinoma; RN, radical nephrectomy; TE, tumor enucleation

in the TE patients than in the PN patients (17.2% vs 0%).¹⁶ Numerous studies of the influence of PSM on prognosis have reported that PSM did not affect cancer-specific survival or overall survival (OS),^{17, 18} but several studies have reported PSM as a poor prognostic factor for OS. Shum et al. analyzed 20,762 patients who underwent PN for T1/T2N0M0 RCC using propensity score matching, and reported that PSM, old age, high Charlson Comorbidity Index, and large tumor size were poor prognostic factors for OS.¹⁹ In this regard, these findings remain controversial, and PSM should be avoided as much as possible in any case.

In the actual PN procedure, PC is excised with some normal renal parenchyma outside the PC, aiming to secure a safety margin. However, it is currently impossible to rule out tumor invasion beyond the PC either by preoperative imaging or based on the intraoperative findings, which contributes to the occurrence of PSM. If tumor invasion beyond the PC could be evaluated accurately on preoperative imaging, it may become possible to effectively avoid PSM by setting a thick safety margin at the invasion site.

Papalia et al. investigated tumor invasion into the PC in pathological tissues (i-Cap score) and in preoperative MRI images (MRI-Cap score) in 58 patients who underwent PN and examined the degree of concordance between them. Overall, concordance was observed in 50/58 patients (86%). Regarding the concordance by score, AUC was 0.86–0.96, which indicates highly accurate diagnostic performance.²⁰ However, the MRI parameters (3.0T, 2–3 mm slices) used in their study were different from those in daily clinical use. Meanwhile, Cho et al. examined the correlation between tumor invasion into the PC and the pathological morphology of PC in 161 patients who underwent PN or RN. Their results showed that 94 patients (58.4%) had complete capsule, 62 patients (38.5%) had incomplete capsule, and 5 patients (3.1%) had no capsule. In addition, PC invasion and renal parenchymal invasion were observed in 58 (36.0%) and 47 (29.2%) patients, respectively. They reported the following as significant risk factors for renal parenchymal invasion: histologic diameter greater than ≥ 4 cm, non-clear cell histology, and incomplete PC. They concluded that “surgeons must prepare for the possibility of a positive surgical margin if a tumor has at least one of these risk factors”.²¹ However, “incomplete PC” in their study was diagnosed pathologically; hence, preoperative determination was impossible.

Accordingly, we hypothesized that even though preoperative MRI in the clinical setting cannot be evaluated for minimal tumor invasion into the renal parenchyma, if a combination of the methods of Papalia

et al. and Cho et al. could be used to evaluate whether the PC morphology is “complete” or “incomplete” with high accuracy, could be applied to PN procedure.

MATERIALS AND METHODS

Study population

This study was approved by the Ethics Committee of Tottori University, Japan (approval number 20A019). We retrospectively analyzed 34 consecutive patients who underwent MRI prior to PN for RCC at our institution with negative surgical margin between January 2010 and December 2019. First, the correlation between PC morphology and tumor infiltration to the renal parenchyma was examined as pathologic validation, according to methods of Cho et al. Second, the rate of concordance of PC morphology between pathological tissue and preoperative MRI was evaluated as radiologic validation. Third, the risk factors for renal parenchymal invasion were analyzed.

Pathologic assessment

Pathologic assessment was performed by two uropathologists. If their evaluations of a single sample differed, they consulted to decide on a single answer. All pathological tissues were step-sectioned at 5 mm intervals centering on the maximum split surface of the tumor, entirely embedded in paraffin blocks, and stained with hematoxylin and eosin for microscopic examination. Moreover, in areas in which renal parenchymal invasion was suspected macroscopically, sections were created in that area and evaluated.

Radiologic assessment

Image assessment was carried out by two radiologists with more than 10 years of experience. If their evaluations of a single sample differed, they consulted to decide on a single answer. MRI was performed using a 1.5T MR systems (Achieva; Philips Medical Systems, Best, Netherlands) or 3.0T MR system (Skyra; Siemens Health Care, Erlangen, Germany). T2-weighted images (TR, 600 ms; TE, 82 ms; section thickness, 5 mm; intersection gap, 1.0 mm; acquisition time, 17–20 sec) were obtained in the axial, coronal, and sagittal planes. T1-weighted images (TR, 140 ms; TE, 2.5 ms; section thickness, 5 mm; intersection gap, 1.0 mm; acquisition time, 15 sec) were obtained in the axial and coronal planes. Diffusion-weighted images were obtained in the axial plane during free breathing. Imaging parameters for DW imaging were as follows: TR, 1800 ms; TE, 65 ms; inversion time, 200 ms; b factors, 0–50–800 s/mm²; 160 × 62 matrix; field of view, 380 mm; section thickness, 5 mm; intersection gap, 1.0 mm; acquisition time,

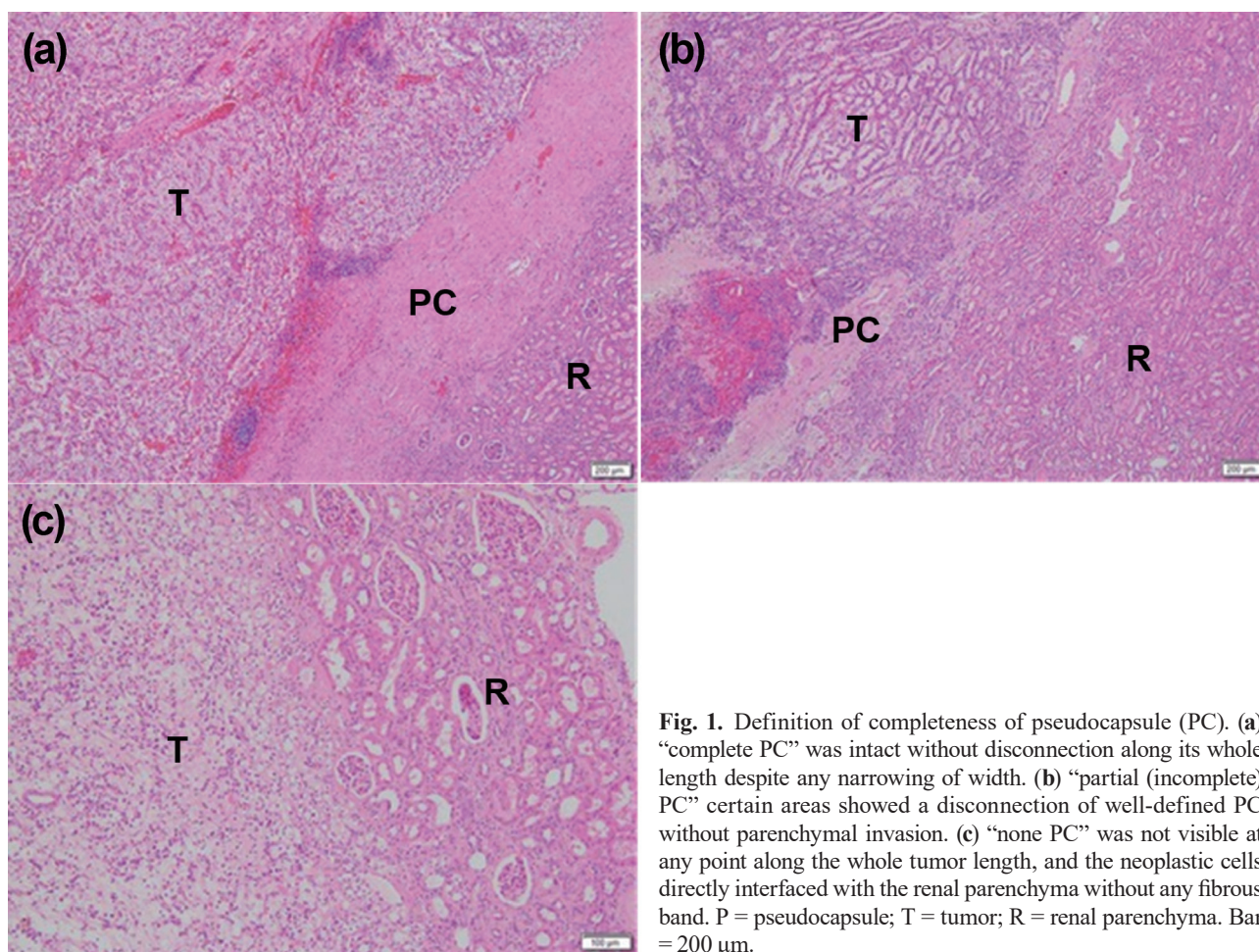


Fig. 1. Definition of completeness of pseudocapsule (PC). (a) “complete PC” was intact without disconnection along its whole length despite any narrowing of width. (b) “partial (incomplete) PC” certain areas showed a disconnection of well-defined PC without parenchymal invasion. (c) “none PC” was not visible at any point along the whole tumor length, and the neoplastic cells directly interfaced with the renal parenchyma without any fibrous band. P = pseudocapsule; T = tumor; R = renal parenchyma. Bar = 200 μ m.

2–3.5 min. The choice of MRI device was made based on scanner availability rather than by any set criteria.

Definition of PC

Regarding pathological definition of PC, the definitions used in the study of Cho et al. were adopted in the present study. A peritumoral PC was defined as a parallel band of fibrocollagenous connective tissue located at the interface of the tumor and adjacent normal renal parenchyma that could be verified on Masson’s trichrome staining; and further subdivided as “intrarenal” or “extrarenal”. We focused on “intrarenal PCs”, as defined by Azhar et al., and “PCs on the parenchymal kidney side” as defined by Minervini et al., and excluded “extrarenal PCs” and “PCs on the perirenal adipose tissue side” from our analysis.^{1, 2, 21} Cho et al. recommend Masson’s trichrome staining for visualization of PC, but in this study, we did not add Masson’s trichrome staining because hematoxylin and eosin staining alone was sufficient to evaluate PC.

In addition, regarding radiological definition of PC, PC was defined as a thin linear regular hypointense

band surrounding the tumor on T2- and T1-weighted images, as with the study of Papalia et al.²⁰

Definition of PC morphology (completeness of PC)

The definitions used in the study of Cho et al. were adopted in the present study. A PC was regarded as “complete” if it was intact without disconnection along its whole length despite any narrowing of width. A PC was regarded as “partial (incomplete)” if any areas showed a disconnection from well-defined PC without parenchymal invasion. A completeness of PC classification of “none” was defined as a PC that was not visible at any point along the whole tumor length, such that the neoplastic cells directly interfaced with the renal parenchyma without any fibrous band (Fig. 1).²¹

Definition of parenchymal invasion of PC

The definitions used in the study of Cho et al. were adopted in the present study. A classification of “free from invasion” was defined as a state in which the PC was intact and had no signs of infiltration of neoplasm along the entire PC length regardless of the completeness of

PC. “Partial invasion” was defined as entrapment or sequestration of tumor cells in the PC, without invasion beyond the PC. “Parenchymal invasion” was defined as neoplastic invasion into the renal parenchyma beyond the PC.²¹

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 25 (IBM, Armonk, NY). Kappa coefficient was used to test concordance between pathologic assessment and radiologic assessment. Fisher’s exact test was used to compare categorical variables, Mann–Whitney *U* test was used for non-parametric comparisons of continuous variables, and multivariate Cox regression analysis was used to evaluate the impact of each variable on renal parenchymal invasion. *P*-values of < 0.05 were considered significant.

RESULTS

Patient demographics

Table 1 shows the demographics of the 34 patients. The median age was 71 years old. Of the 34 patients, 24 (70.6%) were men. The median tumor diameter was 22.5 mm. Most of tumors were classified as T1a (94.1). Regarding pathologic subtypes, clear-cell carcinoma was observed in 26 patients (76.4%), papillary carcinoma in 2 patients (5.9%), and chromophobe carcinoma in 2 cases (5.9%). The median RENAL nephrometry score was 7. Regarding pathological completeness of PC, “Complete” was observed in 9 patients (26.4%), “Partial” in 23 patients (67.7), “None” in 2 patients (5.9%). There were 11 patients had free from invasion (32.4%), 15 had partial invasion (44.1%), and 8 had parenchymal invasion (23.5%).

Pathologic validation

Table 2 shows the ratio of pseudocapsular invasion in each PC morphology, of 9 “complete” group, 33% had free from invasion, 56% had partial invasion and 11% had parenchymal invasion. Of 23 “partial” group, 30% had free from invasion, 44% had partial invasion and 26% had parenchymal invasion. Of the 2 “none” group, 50% were had free from invasion group and 50% had parenchymal invasion. The parenchymal invasion rates were 11% and 28% in “complete” and “partial + none” group, respectively, showing no statistically significant differences between them (*P* = 0.40).

Radiologic validation

Tables 3 and 4 show the degree of concordance between pathologic assessment and radiologic assessment. Of 34 patients, 17 (50%) were able to diagnose pathological

Table 1. Patient demographics

<i>n</i> = 34	
Median age, years (IQR)	71 (48–90)
Male / Female (%)	24 / 10 (70.6 / 29.4)
Median tumor diameter, cm (IQR)	22.5 (11–65)
Pathologic stage	
pT1a (%)	32 (94.1)
pT1b (%)	2 (5.9)
Pathologic subtypes	
Clear cell (%)	26 (76.4)
Papillary (%)	2 (5.9)
Chromophobe (%)	2 (5.9)
Other (%)	4 (11.8)
Fuhrman grade	
Grade 1 (%)	5 (14.7)
Grade 2 (%)	23 (67.7)
Grade 3 (%)	6 (17.6)
Grade 4 (%)	0 (0)
Median R.E.N.A.L score (IQR)	7 (4–10)
(R)adius	
≤ 4 cm	32 (94.1)
4 < and ≤ 7 cm	2 (5.9)
7cm ≤	0 (0)
(E)xophytic properties	
Exophytic ≥ 50%	10 (29.4)
Exophytic < 50%	20 (58.8)
Entirely endophytic	4 (11.8)
(N)earness to the sinus	
7mm <	14 (41.2)
4 < and ≤ 7 mm	7 (20.6)
≤ 4mm	13 (38.2)
(A)nterior or posterior	
Anterior	10 (29.4)
Posterior	17 (50.0)
Axial	7 (20.6)
(L)ocation	
Above	17 (50.0)
Cross	10 (29.4)
Axial midline	7 (20.6)
Pathological PC morphology (completeness of PC)	
Complete	9 (26.4)
Partial	23 (67.7)
None	2 (5.9)
Pseudocapsular invasion	
Free from invasion	11 (32.4)
Partial invasion	15 (44.1)
Parenchymal invasion	8 (23.5)

IQR, interquartile range.

Table 2. The ratio of pseudocapsular invasion in each PC morphology in the pathologic validation

	Pathologic PC morphology		
	Complete (n = 9)	Partial (n = 23)	None (n = 2)
Pseudocapsular invasion			
Free from invasion (%)	3 (33)	7 (30)	1 (50)
Partial invasion (%)	5 (56)	10 (44)	0 (0)
Parenchymal invasion (%)	1 (11)	6 (26)	1 (50)

PC, pseudocapsule.

Table 3. Concordance between pathologic assessment and radiologic assessment of PC morphology

PC morphology		Radiologic (MRI) assessment			
		None	Partial	Complete	Total
Pathologic assessment	None	0	1	1	2
	Partial	3	13	7	23
	Complete	2	3	4	9
	Total	5	17	12	34

MRI, magnetic resonance imaging; PC, pseudocapsule.

Table 4. Sensitivity, specificity, PPV, NPV of radiologic (MRI) assessment compared to pathologic assessment

	MRI / Pathologic None PC	MRI / Pathologic Partial PC	MRI / Pathologic Complete PC
Sensitivity	0 (0/2)	56.5 (13/23)	44.4 (4/9)
Specificity	84.4 (27/32)	63.6 (7/11)	68.0 (17/25)
PPV	0 (0/5)	76.5 (13/17)	33.3 (4/12)
NPV	93.1 (27/29)	41.2 (7/17)	77.3 (17/22)

MRI, magnetic resonance imaging; NPV, negative predictive value; PC, pseudocapsule; PPV, positive predictive value.

PC morphology by MRI (Table 3). Of the 5 cases determined to have “none PC” by MRI, three were pathologically “partial PC” and two were “complete PC”. On the other hand, Of the 12 cases determined to have “complete PC” by MRI, Seven were pathologically “partial PC” and one was, surprisingly, “none PC”. Sensitivity, specificity, positive predictive value (PPV), and positive predictive value (NPV) of whether preoperative MRI could be used to assess pathological PC morphology are shown in Table 4. As for sensitivity, the accuracy for “none PC” was the lowest at 0% and “partial PC” was the highest at 56.5%. As for specificity, the accuracy for “partial PC” was the lowest at 63.6% and “none PC” was the highest at 84.4%. None PC on MRI had the lowest PPV (0%), but the highest NPV (93.1). Partial PC on MRI had a good PPV (76.5%), but a relatively low NPV (41.2%). Complete PC on MRI had a relatively low PPV (33.3%), but a good NPV (77.3%).

Risk factor for parenchymal invasion

In the univariate analysis, significant differences were observed in pathologic subtype (non-clear cell), total RENAL score (7 points or more), location (cross) and Fuhrman grade (G3 or higher). However, only pathologic subtype (non-clear cell) was found to have significant differences in the multivariate analysis (Table 5).

DISCUSSION

The purpose of this study was to investigate whether preoperative MRI in the clinical setting can evaluate the PC morphology (complete or incomplete) with high accuracy and to prove that our hypothesis was correct. In Western countries, MRI is not commonly performed as a preoperative examination for PN because of its expensiveness. However, if our hypothesis proves to be correct, it may be possible to reduce PSM by adjusting the surgical margin during PN, thus increasing the

Table 5. Risk factor for parenchymal invasion

Factors	Univariate	Multivariate	
	<i>P</i> value	OR (95% CI)	<i>P</i> value
Age	0.221	–	–
Karnofsky performance status	0.323	–	–
Tumor diameter	0.343	–	–
Preoperative hemoglobin	0.475	–	–
Preoperative neutrophil cell	0.985	–	–
R.E.N.A.L score (7 ≤ vs 7)	0.047	2.50 (0.08–79.6)	0.604
(R)adius (4 cm < vs ≤ 4 cm)	1.000	–	–
(E)xophytic properties (50% ≤ vs < 50%)	0.390	–	–
(N)earness to the sinus (≤ 7 mm vs > 7 mm)	0.101	–	–
(A)nterior or posterior (AP vs X)	1.000	–	–
(L)ocation (cross vs above)	0.018	7.64 (0.39–150.0)	0.389
Pathologic subtypes (non-clear vs clear)	< 0.001	22.54 (1.23–413.6)	0.036
Fuhrman grade (G3 vs G1-2)	0.016	2.01 (0.11–38.6)	0.642
PC morphology (partial+none vs complete)	0.402	–	–

CI, confidence interval; OR, odds ratio; PC, pseudocapsule.

usefulness of MRI as a preoperative examination. To confirm these, we conducted a step-by-step investigation of pathologic validation, radiological validation and risk factor for parenchymal invasion.

First, as pathologic validation, we investigated the relationship between PC morphology and renal parenchymal invasion in accordance with the report of Cho et al.²¹ Although we found no significant differences, the proportion of renal parenchymal invasion was higher in patients with either “partial PC” or “none PC” than in patients with “complete PC”. The reason why there were no significant differences may be the small number of patients. When we consider that PC is formed by inflammation as a protective reaction by healthy renal parenchyma against tumor, the finding of the higher proportion of renal parenchymal invasion in patients with incomplete PC is not theoretically contradictory. Therefore, we proceeded to radiological validation.

Second, as radiological validation, we classified the morphology of PC based on preoperative MRI, as re-evaluated by two radiologists, and evaluated the diagnostic accuracy for pathologic PC morphology. Overall, we were able to diagnose pathologic PC morphology with a probability of 50% using preoperative MRI, however it was insufficient for diagnostic accuracy. Moreover, the sensitivity and PPV for “none PC” by MRI were both 0%, which means that it was very difficult to prove the absence of PC (Fig. 2a). Similarly, the sensitivity and PPV for “complete PC” by MRI were

both less than 50%, which means that it was very difficult to prove that the thickness of PC was completely uniform. On the other hand, the sensitivity and PPV for “partial PC” by MRI were relatively good, suggesting that the presence of PC of non-constant thickness was easy to read. However, no certain standard was obtained as to what thickness could identify the presence of PC on MRI. In fact, pathological “none PC” was included in the cases that were judged as “partial PC” or “complete PC” on MRI, suggesting that there are other causes for reading as PC other than the actual presence of PC (Fig. 2b). One of the reasons for the lack of sufficient diagnostic accuracy in the present study was assumed to be the small number of cases that were taken by 3.0T MRI. In fact, only five patients underwent MRI at 3.0T and 19 patients (approximately 85%) underwent MRI at 1.5T due to the limited number of 3.0T MRI systems in our institution. If all patients had been scanned at 3.0T with 5 mm slice thickness, the diagnostic accuracy could have been much improved. However, we would like to emphasize that the present study aimed to clarify the diagnostic accuracy of MRI technique as used in daily clinical setting. In other words, at present, it is somewhat difficult to discriminate pathological PC morphology with preoperative MRI technique in daily clinical setting.

Third, Minervini et al. retrospectively analyzed 90 patients who underwent TE in a study of risk factors for renal parenchymal invasion, and observed tumor

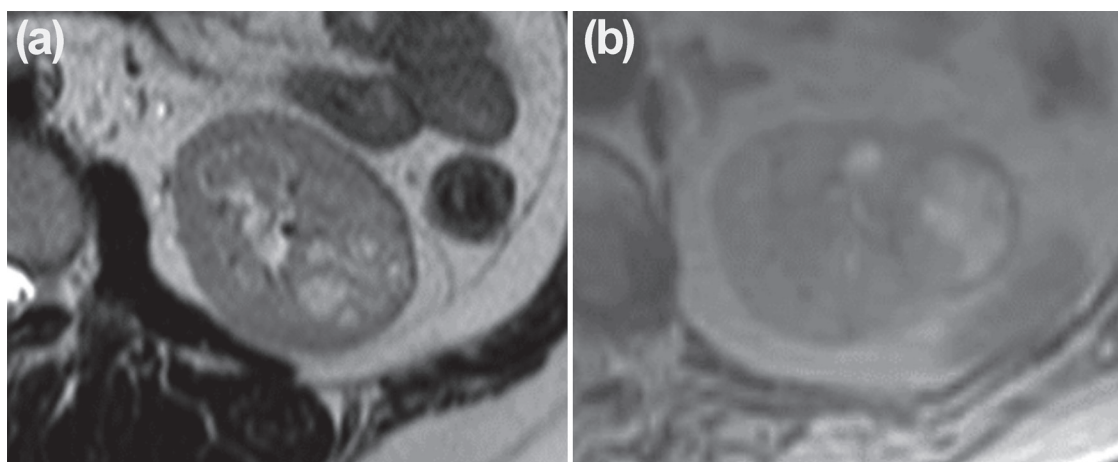


Fig. 2. PC morphology that was difficult to diagnose by preoperative MRI. (a) “none PC” by MRI, “complete PC” by pathology. (b) “complete PC” by MRI, “none PC” by pathology.

invasion of PC in 30 patients (33.3%), of whom 11 (12.2%) had tumor invasion within the PC alone, 13 (14.4%) had renal parenchymal invasion beyond the PC and 6 (6.6%) had PC penetration on the perirenal fat tissue. In addition, they reported tumor diameter and Fuhrman grade 3 as risk factors for invasion of PC.² As mentioned above, Cho et al. reported histologic diameter ≥ 4 cm, non-clear cell histology, and incomplete PC as the risk factors for renal parenchymal invasion.²¹ In our evaluation, a multivariate analysis revealed only RCC subtype (non-clear cell) as a risk factor. The absence of significant difference for tumor diameter may be due to the small number of patients with T1b (two patients). Comprehensive interpretation of these findings indicated that risk could be determined preoperatively in patients with tumor diameter ≥ 4 cm or suspected non-clear cell on preoperative imaging.

In the present study, our hypothesis was rejected. However, if these results were to be applied to PN procedure, they could be summarized as follows. Since there is a high possibility that there is a small amount of PC even in areas that appear to have no PC on MRI images, there is no need to leave an extreme amount of safety margin. However, there is always a risk of PSM in TE technique because there is a slight possibility that there is no PC even in areas that appear to have PC on MRI images. In practice, in terms of avoiding PSM, it seems reasonable to always leave a few millimeters of safety margin, regardless of the PC morphology. In addition, in patients with tumor diameter ≥ 4 cm or suspected non-clear cell on preoperative imaging, more adequate safety margin should be left.

This study has some limitations. First, it was a small-scale retrospective study. Second, we did not

consider the characteristics of large-diameter tumors, for the reason that this study was restricted to patients who underwent partial nephrectomy and thus included only a few patients with tumor size > 4 cm. Third, for the reason mentioned above, the number of patients scanned with 3.0T MRI was small. Considering these limitations, it is necessary to conduct further studies with large numbers of patients.

In conclusion, the findings of the present study suggest that renal tumors with pathologically incomplete PCs have a high possibility of renal parenchymal invasion. However, it is currently difficult to accurately evaluate PC morphology by preoperative MRI in the clinical setting. Therefore, it is not practical to adjust the thickness of the safety margin during PN procedure based on the PC morphology by preoperative MRI to avoid PSM.

The authors declare no conflict of interest.

REFERENCE

- 1 Azhar RA, de Castro Abreu AL, Broxham E, Sherrod A, Ma Y, Cai J, et al. Histological analysis of the kidney tumor-parenchyma interface. *J Urol.* 2015;193:415-22. DOI: [10.1016/j.juro.2014.08.010](https://doi.org/10.1016/j.juro.2014.08.010), PMID: [25111913](https://pubmed.ncbi.nlm.nih.gov/25111913/)
- 2 Minervini A, di Cristofano C, Lapini A, Marchi M, Lanzi F, Giubilei G, et al. Histopathologic analysis of peritumoral pseudocapsule and surgical margin status after tumor enucleation for renal cell carcinoma. *Eur Urol.* 2009;55:1410-8. DOI: [10.1016/j.eururo.2008.07.038](https://doi.org/10.1016/j.eururo.2008.07.038), PMID: [18692300](https://pubmed.ncbi.nlm.nih.gov/18692300/)
- 3 Laganosky DD, Filson CP, Master VA. Surgical Margins in Nephron-Sparing Surgery for Renal Cell Carcinoma. *Curr Urol Rep.* 2017;18:8. DOI: [10.1007/s11934-017-0651-5](https://doi.org/10.1007/s11934-017-0651-5), PMID: [28211006](https://pubmed.ncbi.nlm.nih.gov/28211006/)

- 4 Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Chevillet JC, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol*. 2008;179:468-73. DOI: 10.1016/j.juro.2007.09.077, PMID: 18076931
- 5 Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? *J Urol*. 2009;181:55-62. DOI: 10.1016/j.juro.2008.09.017, PMID: 19012918
- 6 Miller DC, Schonlau M, Litwin MS, Lai J, Saigal CS; Urologic Diseases in America Project. Renal and cardiovascular morbidity after partial or radical nephrectomy. *Cancer*. 2008;112:511-20. DOI: 10.1002/cncr.23218, PMID: 18072263
- 7 Capitanio U, Terrone C, Antonelli A, Minervini A, Volpe A, Furlan M, et al. Nephron-sparing techniques independently decrease the risk of cardiovascular events relative to radical nephrectomy in patients with a T1a-T1b renal mass and normal preoperative renal function. *Eur Urol*. 2015;67:683-9. DOI: 10.1016/j.eururo.2014.09.027, PMID: 25282367
- 8 Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. *Eur Urol*. 2019;75:799-810. DOI: 10.1016/j.eururo.2019.02.011, PMID: 30803729
- 9 Mir MC, Derweesh I, Porpiglia F, Zargar H, Mottrie A, Autorino R. Partial Nephrectomy Versus Radical Nephrectomy for Clinical T1b and T2 Renal Tumors: A Systematic Review and Meta-analysis of Comparative Studies. *Eur Urol*. 2017;71:606-17. DOI: 10.1016/j.eururo.2016.08.060, PMID: 27614693
- 10 Venkatramani V, Koru-Sengul T, Miao F, Nahar B, Prakash NS, Swain S, et al. A comparison of overall survival and perioperative outcomes between partial and radical nephrectomy for cT1b and cT2 renal cell carcinoma—analysis of a national cancer registry. *Urologic Oncology: Seminars and Original Investigations*. 2018;36:90.e9-14. DOI: 10.1016/j.urolonc.2017.11.008, PMID: 29254672
- 11 Tufek I, Mourmouris P, Doganca T, Obek C, Argun OB, Tuna MB, et al. Robot-Assisted Partial Nephrectomy for T1b Tumors: Strict Trifecta Outcomes. *JSLs*. 2017;21:e2016.00113. PMID: 28352149
- 12 Tabayoyong W, Abouassaly R, Kiechle JE, Cherullo EE, Meropol NJ, Shah ND, et al. Variation in surgical margin status by surgical approach among patients undergoing partial nephrectomy for small renal masses. *J Urol*. 2015;194:1548-53. DOI: 10.1016/j.juro.2015.06.076, PMID: 26094808
- 13 Cao DH, Liu LR, Fang Y, Tang P, Li T, Bai Y, et al. Simple tumor enucleation may not decrease oncologic outcomes for T1 renal cell carcinoma: A systematic review and meta-analysis. *Urol Oncol*. 2017;35:661.e15-661.e21. PMID: 28826700. Dong W, Gupta GN, Blackwell RH, Wu J, Suk-Ouichai C, Shah A, et al. Functional Comparison of Renal Tumor Enucleation Versus Standard Partial Nephrectomy. *Eur Urol*. 2017;Focus 34:437-43. PMID: 28753814
- 14 Minervini A, Campi R, Di Maida F, Mari A, Montagnani I, Tellini R, et al. Tumor–parenchyma interface and long-term oncologic outcomes after robotic tumor enucleation for sporadic renal cell carcinoma. *Urologic Oncology: Seminars and Original Investigations*. 2018;36:527.e1-11. DOI: 10.1016/j.urolonc.2018.08.014, PMID: 30268711
- 15 Wang L, Hughes I, Snarskis C, Alvarez H, Feng J, Gupta GN, et al. Tumor enucleation specimens of small renal tumors more frequently have a positive surgical margin than partial nephrectomy specimens, but this is not associated with local tumor recurrence. *Virchows Arch*. 2017;470:55-61. DOI: 10.1007/s00428-016-2031-9, PMID: 27778094
- 16 Bensalah K, Pantuck AJ, Rioux-Leclercq N, Thuret R, Montorsi F, Karakiewicz PI, et al. Positive surgical margin appears to have negligible impact on survival of renal cell carcinomas treated by nephron-sparing surgery. *Eur Urol*. 2010;57:466-73. DOI: 10.1016/j.eururo.2009.03.048, PMID: 19359089
- 17 Kang HW, Lee SK, Kim WT, Yun SJ, Lee SC, Kim WJ, et al.; KORCC (Korean Renal Cell Carcinoma) Group. Surgical margin does not influence recurrence rate in pT1 clear cell renal cell carcinoma after partial nephrectomy: A multicenter study. *J Surg Oncol*. 2016;114:70-4. DOI: 10.1002/jso.24259, PMID: 27074886
- 18 Shum CF, Bahler CD, Sundaram CP. Impact of positive surgical margins on overall survival after partial nephrectomy—A matched comparison based on the National Cancer Database. *Urologic Oncology: Seminars and Original Investigations*. 2018;36:90.e15-21. DOI: 10.1016/j.urolonc.2017.11.009, PMID: 29223360
- 19 Papalia R, Panebianco V, Mastroianni R, Del Monte M, Altobelli E, Faiella E, et al. Accuracy of magnetic resonance imaging to identify pseudocapsule invasion in renal tumors. *World J Urol*. 2020;38:407-15. DOI: 10.1007/s00345-019-02755-1, PMID: 31025082
- 20 Cho S, Lee JH, Jeon SH, Park J, Lee SH, Kim CH, et al. A prospective, multicenter analysis of pseudocapsule characteristics: do all stages of renal cell carcinoma have complete pseudocapsules? *Urologic Oncology: Seminars and Original Investigations*. 2017;35:370-8. DOI: 10.1016/j.urolonc.2017.01.003, PMID: 28188091
- 21 Cho S, Lee JH, Jeon SH, Park J, Lee SH, Kim CH, et al. A prospective, multicenter analysis of pseudocapsule characteristics: do all stages of renal cell carcinoma have complete pseudocapsules? *Urologic Oncology: Seminars and Original Investigations*. 2017;35:370-8. DOI: 10.1016/j.urolonc.2017.01.003, PMID: 28188091