

Multislice spiral computed tomography signs of invasion of the renal capsule by renal cell carcinoma

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Abstract

Capsular invasion is frequently detected in localized renal cell carcinoma (RCC) specimens and is associated with a poor prognosis, but the pretreatment imaging features are poorly known. This study aimed to explore the positions and margin types of RCC and various computed tomography (CT) signs, as well as the correlations with the presence/absence of RCC invasion of the renal capsule.

This was a retrospective study of 158 consecutive patients treated for pathologically confirmed RCC between January 2013 and December 2016 at the Nantong University Affiliated Hospital. The patients were divided into the capsule invasion and noninvasion groups. The CT signs were analyzed (position type, margin type, and CT findings in the perirenal fat).

There were 92 (58.2%) men and 66 (41.8%) women; mean age was 59.1 ± 12.8 . Renal capsule invasion was confirmed in 45 cases. There was no difference in the position types between the 2 groups (all P > .05). The smooth margin was more common in the noninvasion group (53.1% vs 15.6%, P < .01). The deep lobulated type and the saw tooth sign were more common in the invasion group (57.8% vs 7.1%; and 40.0% vs 6.2%; both P < .01). The deep lobulated (OR = 2.03, 95%CI: 1.21–3.39, P = .007) and saw tooth (OR = 1.036, 95%CI: 1.008–1.065, P = .011) signs were independently associated with renal capsule invasion.

Smooth tumor margin suggests the absence of renal capsule invasion, while the deep lobulated and the saw tooth signs strongly suggest the presence of renal capsule invasion in patients with RCC.

Abbreviations: CCRCC = clear cell RCC, CT = computed tomography, MRI = magnetic resonance imaging, RCC = renal cell carcinoma, ROI = regions of interest.

Keywords: kidney, renal capsule, renal cell carcinoma, tomography, x-ray computed

1. Introduction

Renal cell carcinoma (RCC) is a collection of related renal malignancies derived from various parts of the nephron.^[1] RCCs represent 2% to 3% of all cancers in adults and account for 209,000 new cancers each year and 102,000 deaths world-wide.^[1] It was historically known as the "internist's tumor" due to the wide range of manifestations and complications such as paraneoplastic syndromes, but it is now often found incidentally during imaging.^[1] RCC mainly include clear cell RCC (CCRCC) (85%–90% of RCCs), papillary RCC, and chromophobe RCC, as well as rarer types such as collecting duct carcinoma, Bellini ductal carcinoma, and some unclassified renal tumors.^[1,2]

Received: 25 July 2018 / Accepted: 10 October 2018 http://dx.doi.org/10.1097/MD.000000000013075 About 20% to 30% of RCCs invade the renal capsule, but do not invade the perirenal fat space.^[3,4] Recent studies underlined the clinical and prognostic significance of the presence/absence of RCC invasion of the renal capsule.^[5–9] In those large studies, the prognosis of patients with RCC and renal capsule invasion was poorer than that of patients without invasion.^[5–9] A recent study showed that renal capsule invasion was independently associated with prognosis, while lymphovascular invasion was not.^[10] Snarskis et al^[11] proposed a system for scoring renal capsule invasion on surgical specimens, but no system exists for imaging, which would be more valuable because this information could be used when planning the treatments.

Currently, the commonly used classification methods of RCC are the American Joint Committee on Cancer TNM^[12] and Robson staging,^[13] but none of them include the renal capsule invasion of RCC. Therefore, considering that 30% of the patients have capsule invasion but without invasion of the renal perirenal fat space,^[3,4] many patients are not well classified. Considering the different survival in patients with versus without capsule invasion, it is necessary to include this feature in the staging standard. Nevertheless, additional data are still required to determine the exact prognostic value of renal capsule invasion by CCRCC.

Therefore, this preliminary study aimed to explore the positions and margin types of RCC and various computed tomography (CT) signs, as well as the correlations with the presence/absence of RCC invasion of the renal capsule. With the development of minimally invasive treatments of renal tumors (such as partial nephrectomy and percutaneous ablations techniques) knowledge about capsular invasion may be valuable preoperative information for patient selection. In addition,

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prognosis in patients with capsular invasion may be less favorable than in those without, and those patients could require a closer follow-up or more aggressive treatment.

2. Materials and methods

2.1. Study design and patients

This was a retrospective study of 158 consecutive patients treated for RCC between January 2013 and December 2016 at the Department of Medical Imaging of Nantong University Affiliated Hospital. This study was approved by the ethics committee of the Nantong University Affiliated Hospital. The need for individual consent was waived by the committee because of the retrospective nature of the study.

The inclusion criteria were: available clinical, imaging, and pathological data; symptoms of back pain, hematuria, and abdominal mass; and first visit to the Nantong University Affiliated Hospital. The exclusion criteria were: did not receive surgery in our hospital or without pathological information; diagnosis of metastasis before surgery could be done; postoperative pathological results of benign tumors (such as oxyphilic adenoma); allergic to iodinated contrast agent; or renal dysfunction.

Based on the surgical pathological results, the 158 patients were divided into the renal capsule invasion group and the renal capsule noninvasion group.

2.2. CT scanning method

During the study period, all CT scans were performed using either a Brilliance 64-slice spiral CT or a Brilliance 256-ICT (Philips, Best, The Netherlands). The scanning parameters were: tube voltage of 120 kV, tube current of 250 to 300 mA, thread pitch of 1.0, thickness of scanning layer of 5 mm, and thickness of reconstruction layer of 1 mm. The scanning range was from the upper margin of the liver to the bilateral anterior superior iliac spine, totally covering the kidneys. Enhanced scan was performed using an antecubital venous injection of Iobitridol (350 mgI/mL; a nonionic contrast agent; Guerbet, Roissy-Charles-de-Gaulle, France) with a total dose of 80 to 100 mL and injection rate of 3.5 ml/s. After injection of the contrast agent, the cortico-medullary phase scan was carried out at 30 to 40 ms, the parenchymal phase at 60 to 70 ms, and the excretory phase at 120 to 180 ms. The original data were uploaded to the postprocessing workstation (IntelliSpace Portal, Philips, Best, The Netherlands) for image analysis. The radiologists were blind to the clinical pathological data when reviewing the images.

2.3. Image analysis

Two associate chief radiologists read the images and analyzed various CT signs. They were blinded to the clinical and pathological results before reading. They discussed the results and reached an agreement if they had different opinions. According to Hedgire et al,^[14] the position of the lesions was described as central, central-exophytic, exophytic, and restricted (Fig. 1). The central type refers to RCC growing to the center of the kidney and oppressing the renal pelvis. The exophytic type refers to RCC growing to the center and the kidney border. The restricted type refers to RCC that is restricted within the renal parenchyma.

2.3.1. Margin type. The margin type refers to the margin of the RCC convex area beyond the kidney contour. According to Lin



Figure 1. Position of renal cell carcinoma lesions on computed tomography. (A) Central type. (B) Central-exophytic type. (C) Exophytic type. (D) Restricted type.



Figure 2. (A) Chord distance; (B) chord length. (A/B) \leq 0.2 indicates shallow lobulated lobe. (A/B) \geq 0.4 indicates deep lobulated lobe.

et al,^[15] "smooth," "shallow lobulated," "deep lobulated," and "saw tooth sign" were used to describe the RCC margin. The lobulated sign was classified as shallow when the ratio of the arcchord distance to the chord length in a single lobe was ≤ 0.2 , while deep lobulation was defined as a ratio ≥ 0.4 .^[15] The measurement was repeated 3 times, with the average value taken as the final result (Fig. 2). The saw tooth sign was defined as spinous or small triangular protrusions of the RCC at the outer margin of the kidney. One individual patient could display more than one margin type.

2.3.2. *Perirenal fat space.* The presence or absence of soft tissue density grid shadow and enhanced nodules in the perirenal fat space was observed. In the coronal images, 3 regions of interest (ROI) of the same size (artificial delineation) were drawn in the perirenal fat space on the diseased side to measure the perirenal fat density. The average CT value of 3 ROIs was used for analysis.

2.4. Statistical analysis

SPSS 21.0 (IBM, Armonk, NY) was used for statistical analysis. Continuous data were tested using the Kolmogorov–Smirnov test. Normally distributed continuous data were expressed as means \pm standard deviation and analyzed using the Student *t* test. Non-normally distributed continuous variables were expressed as median (interquartile range) and analyzed using the Wilcoxon test. Categorical data were expressed as proportions and analyzed using the Fisher exact test. A binary logistic regression analysis (backward) was performed to analyze the correlation of the margin type and various signs in perirenal fat with the invasion of RCC in the renal capsule. Two-sided *P*-values <.05 were considered statistically significant.

3. Results

3.1. Characteristics of the patients

Table 1 presents the characteristics of the patients. The average time from multi-slice spiral CT (MSCT) to surgery was 2 weeks. Among the 158 patients, there were 147 patients with clear cell RCC (42 with renal capsule invasion), 3 patients with chromophobe cell tumor (no renal capsule invasion), 3 with papillary carcinoma (one with renal capsule invasion), one with clear cell carcinoma associated with sarcomatous change

Table 1

Characteristics of the patients.

Characteristics	Values
Sex, n (%)	
Male	92 (58.2)
Female	66 (41.8)
Age, years	59.1 ± 12.8
Side, n (%)	
Left	80 (50.6)
Right	78 (49.4)
Tumor size, cm	
Mean	5.7 <u>±</u> 2.9
Range	1.6–15
cSurgery, n (%)	
Radical surgery	96 (60.8)
Partial nephrectomy	12 (7.6)
Laparoscopic radical surgery	37 (23.4)
Laparoscopic partial nephrectomy	12 (7.6)
Tumor enucleation	1 (0.6)
Renal capsule invasion, n (%)	45 (28.5)
Pathological types, n (%)	
Clear cell RCC	147 (93.0)
Chromophobe RCC	3 (1.9)
Papillary carcinoma	3 (1.9)
RCC with sarcomatous changes	1 (0.6)
Mucoid tubule and spindle cell carcinoma	1 (0.6)
Multilocular cystic RCC	2 (1.3)
Anaplastic carcinoma	1 (0.6)
Furman grade, n (%)	
	102 (64.6)
III—IV	33 (20.9)

RCC=renal cell carcinoma.

(invasion of the renal capsule, no invasion of the perirenal fat space), one with mucoid tubule and spindle cell carcinoma (no invasion of the renal capsule), 2 with multilocular cystic RCC (no invasion of the renal capsule), and one with anaplastic carcinoma (invasion of the renal capsule and perirenal fat). There were 56 patients with high-grade tumor (Furman III–IV) (33 with invasion of the renal capsule, 58.9%), and 102 with low-grade tumor (Furman I–II) (12 with invasion of the renal capsule, 11.8%).

3.2. Position types of RCC

There was no significant difference between the 2 groups regarding the position types of RCC (Table 2).

3.3. Margin type

The smooth margin was more common in the noninvasion group (P < .01). The deep lobulated type (Fig. 3) and the saw tooth sign were more often seen in the invasion group (Fig. 4) (P < .01).

Table 2

Position types of RCC according to invasion of the renal capsule.

	Invasion	Noninvasion	
	group (n=45)	group (n=113)	Р
Central type	6 (13.3)	11 (9.7)	.075
Central-exophytic type	17 (37.8)	28 (24.8)	.055
Exophytic type	16 (35.6)	46 (40.7)	.081
Restricted type	6 (13.3)	28 (24.8)	.062

Results are shown as n (%).

RCC=renal cell carcinoma.



Figure 3. A 46-year-old man with right renal clear cell carcinoma with sarcomatoid change. The lesion margin was of the deep lobulated type. A nodule shadow was seen above the lesion. Pathology showed clear cytoplasm of tumor cells, with large heteromorphic nucleus, and obvious mitosis. The cancer invaded the renal capsule (HE, ×200).



Figure 4. A 71-year-old man with right renal clear cell carcinoma of grade III. The lesion margin showed the saw tooth type. Pathology showed clear cytoplasm, with small heteromorphic nucleus, and no nucleus. The cancer invaded the renal capsule and perirenal fat (HE, ×200).

Table 3

Margin types of RCC.

	Smooth margin	Deep lobulated	Shallow lobulated	Saw tooth sign
Invasion group $(n = 45)$ Noninvasion group $(n = 113)$	7 (15.6) 60 (53.1)	26 (57.8) 8 (7.1)	12 (26.7) 29 (25.7)	18 (40.0) 7 (6.2)
P	<.01	<.01	>.05	<.01

One individual patient could display more than one margin type. Results are shown as n (%). RCC=renal cell carcinoma.

Table 4

CT findings in the perirenal fat space according to renal capsule invasion.

	Enhanced nodule	Grid shadow
Invasion group (n = 45)	9 (20.0)	26 (57.8)
Noninvasion group $(n = 113)$	0	66 (58.4)
Р	<.01	.705

Results are shown as n (%).

There was no significant difference between the 2 groups regarding the shallow lobulated type (P > .05) (Table 3).

3.4. Perirenal fat

Enhanced nodules in the perirenal fat space (Fig. 3) were more often seen in the invasion group (P < .01) (Table 4). Mean perirenal fat density was -91.12 ± 14.41 HU in the invasion group, while -96.43 ± 8.38 HU in the noninvasion group (P > .05) (Table 5).

3.5. Logistic regression analysis on various CT signs in the peripheral fat and margin types of tumor

The binary logistic regression analysis showed that among the margin types of RCC and various CT signs in the peripheral fat space, only the deep lobulated type and the saw tooth sign were significantly associated with renal capsule invasion (Table 6).

4. Discussion

Capsular invasion is frequently detected in localized RCC specimens and is associated with a poor prognosis,^[5–9] but the pretreatment imaging features are poorly known. Therefore, this study aimed to explore the positions and margin types of RCC and various CT signs, as well as the correlations with the presence/absence of RCC invasion of the renal capsule. The results strongly suggest that smooth tumor margin is associated with the absence of renal capsule invasion, while the deep lobulated and the saw tooth signs are independently associated with the presence of renal capsule invasion in patients with RCC. Even though the study was preliminary, Figure 5 presents a summary of those findings.

Table 6

Binary logistic regression analysis of factors associated with rena	al
capsule invasion.	

Variables	Р	OR (95% confidence interval)
Smooth	.484	0.374 (0.02-5.88)
Deep lobulated	.007	2.028 (1.21-3.39)
Shallow lobulated	.493	0.409 (0.03-5.27)
Saw tooth sign	.011	1.036 (1.008-1.065)
Grid shadow	.733	1.216 (0.40–3.74)

During histopathological examination, renal capsule invasion of RCC refers to the tumor invading the renal capsule but not into perirenal tissues.^[5] Among restricted RCC, about 30% of the cases invade the renal capsule.^[8] Multiple studies have reported that the prognosis of RCC is worse in patients with renal capsule invasion than in those without renal capsule invasion.^[3,5,9] Currently, the TNM staging^[12] and Robson staging^[13] are widely applied for RCC staging, and the Robson staging system is widely used in China.^[16] Tumor size, perirenal fat invasion, and renal vein invasion are well-known prognostic factors of RCC.^[1] According to the latest version of the TNM staging, restricted RCC refers to RCC that is restricted to the renal parenchyma and does not invade the perirenal tissues and vessels;^[12] recurrence or distant metastasis may occur in about 30% of patients with restricted RCC.^[6] Therefore, it is clear that those staging systems are incomplete since cancers with supposedly good prognosis show high rates of recurrence and progression. If renal capsule invasion of RCC were to be included as a prognostic factor in staging systems, those systems could probably be improved.

Hedgire et al^[14] divided RCC into 3 types (central type, central-exophytic type, and exophytic type) and they consider that the position type is not related to whether RCC invades the renal perirenal fat or not. Since RCC invading the perirenal fat must first have invaded the renal capsule, the present study divided RCC into the central type, central-exophytic type, exophytic type, and restricted type.

Lin et al^[15] reported that smooth RCC margin was an important indicator that RCC did not invade the capsule, while the deep lobulated and saw tooth signs were indicators of renal capsule invasion of RCC. The present study used the same margin types of RCC (deep lobulated, shallow lobulated, smooth and saw tooth sign) for analysis, and the results are consistent with the Lin et al.^[15] Furthermore, according to the binary logistic regression analysis, the deep lobulated and saw tooth signs were independently associated with renal capsule invasion. In lung cancer, the lobulated sign is due to the uneven growth speed of the tumor toward different directions or growth limitation by stronger anatomical tissues. The spinous protuberance is the pathological infiltration of the tumor cells, or more specifically a part of the tumor where cells have a lower differentiation degree and faster growth.^[17] On this basis, it can be hypothesized that the lobulated and saw tooth signs represent more aggressive tumors.

10.0			0	5	
	<u> </u>	2.1	-	<u> </u>	

Mean perirenal fat density according to renal capsule invasion.					
	Affected side	Unaffected side	Renal capsule invasion	Renal capsule noninvasion	
Density of the perirenal fat, HU	-96.01 ± 5.09	-105.05 ± 0.90	-91.12 ± 14.41	-96.43 ± 8.38	
Р	<.05		>.05		



Tsili et al^[18] reported that perirenal fat density was obviously higher when RCC invaded the perirenal fat compared with perirenal fat without invasion. On the other hand, the present study did not make this observation. Li et al^[17] reported that enhanced nodules and grid shadow in the perirenal fat were considered important signs for renal capsule invasion of RCC. Because RCCs that invade the perirenal fat space must first have invaded the renal capsule, the present study suggested that enhanced nodules can be considered as signs of RCC invading the renal capsule, while the grid shadow sign had no association with renal capsule invasion. The grid shadow sign is due to uneven thickened of the bridging septa in the perirenal fat space related to edema, vascular engorgement, chronic inflammation, perirenal hematoma, fat necrosis,^[18] and perirenal collateral veins.^[19] According to the literature,^[18–20] more than half of the restricted RCC cases show grid shadow in the perirenal fat space. Nevertheless, in the present study, the CT signs in the perirenal fat were not independently associated with renal capsule invasion.

The present study could not analyze survival and recurrence because of too short follow-up and missing data, but a number of studies suggest that renal capsule invasion is associated with poor prognosis of RCC,^[5–10] but this is controversial.^[21] Renal capsule invasion is usually observed in the surgical specimen, after treatments. A recent magnetic resonance imaging (MRI) study showed that arterial spin labeling can be used to predict renal capsule invasion.^[22] Other studies showed that the characterization of the renal capsule using MRI could reach 95% accuracy.^[23-25] The present study suggests signs that could predict renal capsule invasion prior to initiating any treatment. Therefore, the treatments could be tailored accordingly and a more aggressive approach could be taken in the presence of signs highly suggestive of renal capsule invasion. Nevertheless, additional studies are necessary to determine the best imaging modality or whether a combination of imaging modalities could even be better. Indeed, Zokalj et al^[26] showed that CT had 92% sensitivity and 51% specificity for renal capsule invasion.

The present study is not without limitations. This study is a retrospective study and is limited to the routine CT scan parameters. According to the epidemiology of RCC, most cases were clear cell RCC and the results may not apply to rarer types of RCC since the natural history is different among the subtypes of RCC.^[27] In addition, the follow-up was too short to perform Kaplan–Meier analyses, hence the preliminary nature of the present study. Additional studies are necessary to examine the prognostic impact of renal capsule invasion.

In conclusion, the results strongly suggest that smooth tumor margin is associated with the absence of renal capsule invasion, while the deep lobulated and the saw tooth signs are independently associated with the presence of renal capsule invasion in patients with RCC.

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