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ORIGINAL PAPER

Predictive features of pre-operative computed tomography and magnetic resonance imaging for advanced disease in renal cell carcinoma

Musab Ali Kutluhan [1], Selman Unal [1], Serhan Eren [2], Asim Ozayar [1], Emrah Okulu [1], Hüseyin Cetin [3], Onder Kayigil [1]

[1] Department of Urology, Yildirim Beyazit University, School of Medicine, Ankara, Turkey;
[2] Department of Radiology, University of Health Sciences, Etlik Zubeyde Hanım Research and Training Hospital, Ankara, Turkey;
[3] Department of Radiology, Yildirim Beyazit University, School of Medicine, Ankara, Turkey.

Summary ***Objective: We evaluated predictive features of pre-operative computed tomography and magnetic resonance imaging for advanced disease in renal cell carcinoma.***

Materials and methods: 92 patients with pathologically confirmed diagnosis of renal cell carcinoma were included in our study. Patients were divided into two groups according to pre-operative imaging as computed tomography (CT) (55 patients) and magnetic resonance imaging (MRI) (37 patients). Within the imaging groups, the patients were divided into two groups according to pathological tumor stage: 1-2 (pT1-2) versus ≥ pT3a. It was evaluated whether there was a difference between the two groups in terms of the presence of pre-operative imaging (CT and MRI) features. Predictive value of these features for ≥ pT3a disease was evaluated both for CT and MRI.

Results: The cut-off value for the Gerota's fascia thickness in predicting ≥ pT3a disease was calculated as 0.205 cm. Positive predictive value (PPV) for Gerota's fascia thickness was 52.4% (31.0-73.7) and 66.7% (40.0-93.3) for CT and MRI respectively. The PPV value for renal capsule invasion was 75.0% (53.8-96.2) and 90.0% (71.4-108.6) for CT and MRI respectively. PPV of perirenal fat invasion for CT and MRI was 69.2% (44.1-94.3) and 81.8% (59.0-104.6) respectively.

Conclusion: Renal capsular invasion and perirenal fat invasion are reliable signs for locally advanced (≥ pT3a) renal cell carcinoma both in CT and MRI. Gerota's fascia thickness has relatively low PPV value for prediction of locally advanced disease. Presence of enlarged collateral vessels, tumor necrosis, perinephric stranding are not reliable signs. For all predictors MRI seems more reliable than CT.

KEY WORDS: Renal cell carcinoma; Computed tomography; Magnetic resonance imaging; Predictive features.

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INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common urinary system cancers and accounts for 3% of all cancers (1). With the frequent use of imaging methods most renal masses are detected when localized (2). The standard treatment option in localized RCC is *radical nephrectomy* (RN) or *nephron-sparing surgery* (NSS). NSS is preferred in patients with *tumor stage 1* (T1) and has been shown to be comparable to RN in terms of oncologic outcomes (3). Although there is no prospective randomized study comparing NSS with RN in terms of oncological and renal functions in T2 patients, there are retrospective studies conducted to date (4). According to the current European Urology Association guideline, the standard approach in patients with ≥ T2 is RN (5). Pre-operative clinical staging is performed with *computed tomography* (CT) or *magnetic resonance imaging* (MRI), and patients may develop local recurrence despite surgical procedures based on clinical stage (6). In clinical practice, pre-operative CT and MRI provide information about tumor size, tumor localization, presence of tumor invasion into vascular structures and adjacent organs (7). However, apart from these frequently reported findings, there are CT and MRI findings that can be used to predict advanced disease. According to 2017 *Tumor, Node, and Metastasis* (TNM) classification, invasion of the pelvicalyceal system, perirenal or renal sinus fat invasion has been included in the T3a category (8). There are studies evaluating predictive value of CT to indicate renal sinus fat or perirenal fat invasion (9). Although not included in the standard TNM classification, it has been shown that renal capsule invasion is an independent prognostic variable for advanced disease and can be detected on CT (10, 11). On the other hand, it has been indicated that thickening of the Gerota's fascia, the presence of enlarged collateral vessels, and the presence of intra-tumoral necrosis may be imaging findings that can be used to predict advanced disease (12). We also think that these markers can be used in prediction of advanced disease in RCC. Although renal capsule invasion and perirenal fat invasion has been considered reliable markers in advanced disease, additional markers can make imaging more reliable. Consequently, in our study we decided to investigate these markers that could be used for prediction of ≥ pT3a disease. We also think that the predictive value of MRI may be higher than CT. Therefore, in this study we evaluated the role of some features (renal capsule invasion, perirenal fat invasion, thickening of the Gerota's fascia, presence of enlarged collateral vessels, tumor necrosis, perinephric stranding) of pre-operative computed tomography and magnetic

No conflict of interest declared.

resonance imaging for predicting advanced disease in renal cell carcinoma.

Materials and methods

Study design and patient selection

After local ethics committee approval (26379996/58), patients who had RN or NSS operation due to renal mass in our clinic were retrospectively screened. In total, 92 patients with pathologically confirmed diagnosis of RCC and pre-operative CT or MRI images were included in our study. Patients who had metastatic RCC, who had unclear CT or MRI images, who had undergone surgery on the same side before the onset of kidney mass due to other urological pathologies, and who had pathology results other than RCC (oncocytoma, etc.) were excluded from the study. Patients were divided into two groups according to pre-operative imaging as CT (55 patients) and MRI (37 patients). Pre-operative CT and MRI images were evaluated by a dedicated blinded radiologist.

Postoperative pathology results of the patients were screened. Within the imaging groups, the patients were divided into two groups according to pathological tumor stage as 1-2 (pT1-2) (Group 1) and ≥ pT3a (Group 2).

It was evaluated whether there was a difference between the two groups in terms of the presence of pre-operative imaging (CT and MRI) features (renal capsule invasion, perirenal fat tissue invasion, thickening of the Gerota's fascia, presence of enlarged collateral vessels, intra-tumoral necrosis, perinephric stranding). Predictive value of these features for ≥ pT3a disease was evaluated both for CT and MRI.

Radiological evaluation

CT acquisition

CT examination was performed using a 128-slice multidetector CT scanner (*GE, Revolution EVO, USA*). The CT parameters and scanning sequence were as follows: 1:1 pitch, 200-250 mAs, 120 kVp, and 0.5-0.625 isotropic spatial resolution, window width 250~450 HU, and window level 30-50 HU; for cortical phase, medullary phase, and excretion phase, the duration of scanning was 30-35, 50-60, and 180 s after the injection of contrast agent, respectively. 100 mL of non-ionic intravenous contrast agent was administered through antecubital veins with an automated injector at 3mL/sec (*Ulrich Medizin version, 2004, Germany*). All patients were examined in a supine position with 6-8 hours fasting.

MRI acquisition

MRI examinations were performed with 1.5-Tesla MRI (*Signa, GE Medical Systems*) with 5 mm slice thickness and 2.0 mm gap spacing by using surface phased array coil. MRI sequence parameters were coronal T2-weighted half-Fourier single-shot fast spin-echo (TR/TE msec 800-1100/60; slice thickness 4 mm; gap 1 mm; matrix size 192 × 256; flip angle 130°-155°), axial T1-weighted in-phase and opposed-phase gradient-echo (180-205/2.2-2.7, 4.5-5.2; flip angle, 80°; slice thickness, 6-8 mm; gap, 1 mm; matrix, 160 × 256), and 3D T1-weighted *liver imaging with volume acceleration* (LAVA) with fat suppression (TR/TE msec 1.4/4.3; slice thickness 2.5 mm; matrix size 132x320; flip angle, 10-12°; FOV 25x35 cm).

In dynamic imaging, the delay time was 20 seconds for corticomedullary phase, 60 seconds for nephrographic phase, and 120 seconds for the coronal delayed phase after the intravenous injection of 15 ml of Magnevist (*0.1 mmol/kg; Bayer Schering, Pharma AG, Berlin, Germany*) at a rate of 2 ml/s. *Diffusion weighted imaging* (DWI) was performed with two b values (0 and 600 mm^2/s).

Image analysis

One dedicated radiologist for abdominal radiology reviewed all images in archiving system blinded to histopathologic information. Imaging features of perinephric fat tissue, perinephric stranding, perinephric vascularity, and irregular contours was evaluated both in CT (Figure 1) and MRI. Tumor margins were identified as smooth or lobulated for evaluation of capsule invasions (Figure 2). In quantitative measurements, Gerota's fascia thickness was measured in magnified images of CT and MRI (Figure 3). Presence of tumor necrosis and collateral vessels were also evaluated both in MRI and CT.

Statistical analyzes

Statistical analyses of the study were performed using SPSS 23.0 program (*SPSS, Version 23.0; IBM Corp, Armonk, NY*). Number, percentage, mean and standard deviation were used for descriptive statistics. Analyses of differences between groups were performed with t-test and chi-square test in independent groups as significance tests. Crosstabs were used for sensitivity, specificity, and predictive value calculations. The diagnostic value of Gerota's fascia thickness in predicting cancer stage was analyzed by ROC curve by considering 0.05 as the significance threshold for p-value.

Figure 1.
A 50-year-old woman with high-grade clear cell RCC (Fuhrman grade IV) in left kidney. Axial contrast-enhanced computed tomography image shows a 15-cm hyper vascular centrally necrotic renal mass. Gerota.s fascia (anterior perirenal fascia) thickness was 0.41 cm.

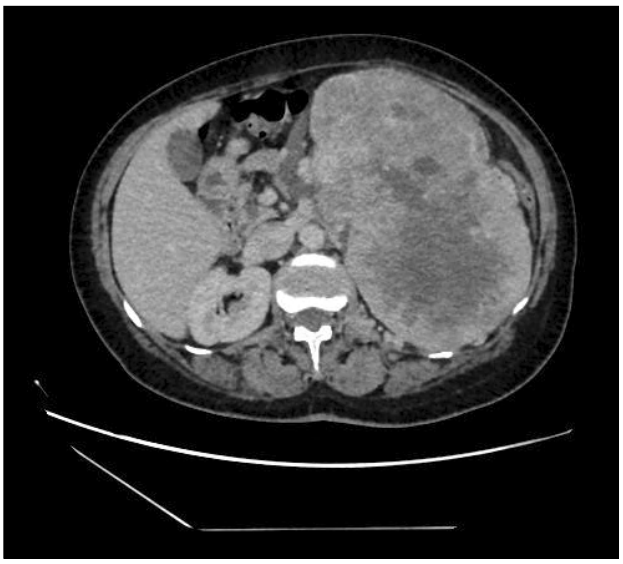


Figure 2.
A 62-year-old man with high-grade clear cell RCC (Fuhrman grade IV) in left kidney. Axial computed tomography image shows lesion margin was ill-defined and lobulated. The tumor showed invasion of the renal capsule and perirenal fat. Perirenal fat stranding was prominent.

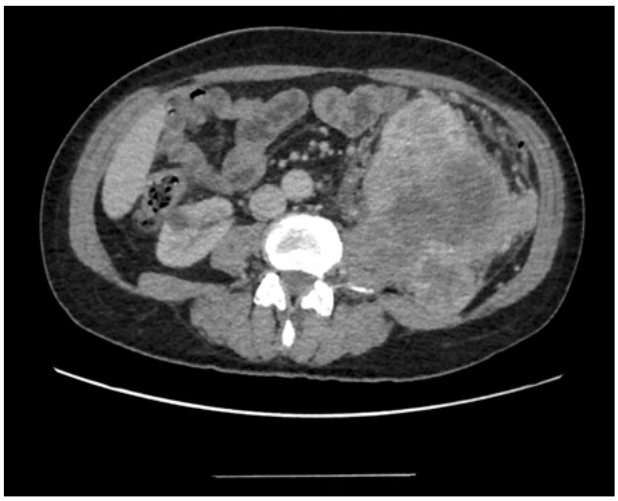
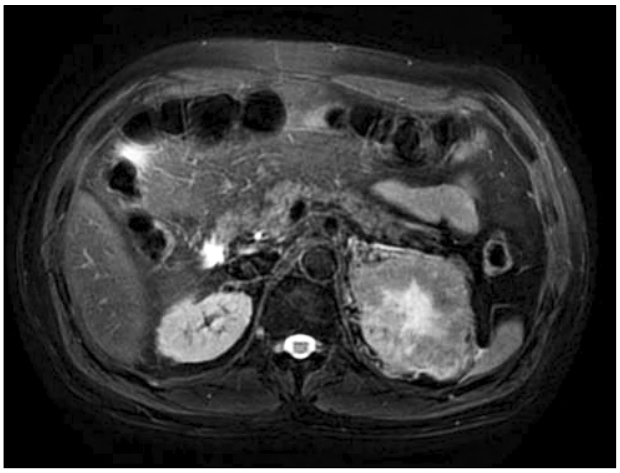


Figure 3.
A 58-year-old man with 8 cm high-grade clear cell RCC (Fuhrman grade III) in left kidney. Axial T2 weighted fat saturated images show heterogenous ill-defined tumor in left kidney. Gerota fascia was thickened and measured 0.3 cm.



Results

The mean age of the patients included in the study was 58.08 ± 11.58. 59.8% of patients had CT as pre-operative imaging, while 40.2% had MRI. The clinical features of the patients are summarized in Table 1.

When the groups were compared in terms of pre-operative CT features, the mean Gerota's fascia thickness of group 2 was statistically significantly thicker than group 1 (0.15 ± 0.01 *vs* 0.30 ± 0.12 cm $p < 0.001$). There was a statistically significant difference between the groups in terms of the presence of collateral vessels ($p = 0.008$). There was a statistically significant difference between the groups in terms of renal capsule invasion ($p < 0.001$). In addition, there was a statistically significant difference between the groups in terms of perinephric stranding and perirenal fat invasion ($p = 0.04$, $p < 0.001$). Comparison of CT predictors according to groups was summarized in Table 2.

When the groups were compared in terms of pre-operative MRI features, the mean Gerota's fascia thickness of group 2 was statistically significantly thicker than group 1 (0.38 ± 0.24 *vs* 0.13 ± 0.06 cm, $p < 0.001$). There was a statistically significant difference between the groups in terms of the presence of collateral vessels and intratumoral necrosis ($p = 0.015$, $p = 0.015$). There was a statistically significant difference between the groups in terms of renal capsule invasion ($p < 0.001$). In addition, there was a statistically significant difference between the groups in terms of perinephric stranding and perirenal fat

Table 1.
Characteristics of the patients.

Number of patients		92
Mean age (years)		58.08 ± 11.58
		n (%)
Pre-operative imaging	CT	55 (59.8)
	MRI	37 (40.2)
Tumor side	Right	50 (54.3)
	Left	42 (45.7)
Operation	Radical nephrectomy	42 (45.7)
	Partial nephrectomy	50 (54.3)
Pathological T stage	T1a	37 (40.2)
	T1b	17 (18.5)
	T2a	7 (7.6)
	T2b	6 (6.5)
	T3a	16 (17.4)
	T3b	6 (6.5)
	T4	3 (3.3)
Pathological type	Clear cell RCC	71 (77.2)
	Papillary RCC	12 (13.0)
	Chromophobe RCC	9 (9.8)

CT: Computed tomography; MRI: Magnetic resonance imaging; T: Tumor; RCC: Renal cell carcinoma.

Table 2.
Comparison of CT predictors according to pT stage.

Pre-operative CT predictors	**pT stage**		**p-value**
	Group 1 = < T3a (n = 40)	**Group 2 = ≥ T3a (n = 15)**	
Gerota's fascia thickness mean sd (cm)	0.15 ± 0.01	0.30 ± 0.12	< 0.001
Presence of enlarged collateral vessels			0.008
Positive	19 (47.5%)	13 (86.7%)	
Negative	21 (52.5%)	2 (13.3%)	
Tumor necrosis			0.078
Positive	19 (47.5%)	11 (73.3%)	
Negative	21 (52.5%)	4 (26.7%)	
Renal capsule invasion			< 0.001
Positive	5 (10.3%)	12 (80.0%)	
Negative	35 (89.7)	3 (20.0%)	
Perirenal fat invasion			< 0.001
Positive	4 (10.0%)	9 (60.0%)	
Negative	36 (90.0%)	6 (40.0%)	
Perinephric stranding			0.040
Positive	17 (42.5%)	11 (73.3%)	
Negative	23 (57.5%)	4 (26.7%)	

CT: Computed tomography; pT: Pathological tumor.

Table 3.
Comparison of MRI predictors according to pT stage.

Pre-operative MRI predictors	pT stage		p-value
	Group 1 = < T3a (n = 27)	Group 2 = ≥ T3a (n = 10)	
Gerota's fascia thickness mean sd (cm)	0.13 ± 0.06	0.38 ± 0.24	< 0.001
Presence of enlarged collateral vessels			0.015
Positive	9 (33.3%)	8 (80.0%)	
Negative	18 (66.6%)	2 (20.0%)	
Tumor necrosis			0.015
Positive	9 (33.3%)	8 (80.0%)	
Negative	18 (66.6%)	2 (20.0%)	
Renal capsule invasion			< 0.001
Positive	1 (3.7%)	9 (90.0%)	
Negative	26 (96.3%)	1 (10.0%)	
Perirenal fat invasion			< 0.001
Positive	2 (7.4%)	9 (90.0%)	
Negative	25 (92.6%)	1 (10.0%)	
Perinephric stranding			< 0.001
Positive	7 (25.9%)	10 (10.0%)	
Negative	20 (74.1%)	0 (0.0%)	

MRI: Magnetic resonance imaging; pT: Pathological tumor.

invasion ($p < 0.001$, $p < 0.001$). Comparison of MRI predictors according to groups was summarized in Table 3.
The diagnostic value of Gerota's fascia thickness in estimating pathological stage was evaluated with the ROC curve.
According to this evaluation, the cut-off value for the Gerota's fascia thickness in predicting ≥ pT3a disease was calculated as 0.205 cm.
Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CT and MRI predictors was summarized in Table 4.
Accordingly, the PPV value for Gerota's fascia thickness was 52.4% (31.0-73.7) and 66.7% (40.0-93.3) for CT and MRI respectively.
The PPV value for renal capsule invasion was 75.0% (53.8-96.2) and 90.0% (71.4-108.6) for CT and MRI respectively. PPV of perirenal fat invasion for CT and MRI was 69.2% (44.1-94.3) and 81.8% (59.0-104.6) respectively.

Discussion

In patients with renal mass, tumor stage is important for the prognosis of the disease. Perirenal fat invasion, renal sinus fat invasion, renal capsule invasion and renal vein invasion are important factors that may affect the prognosis. In a study conducted on 563 patients with pT3a tumor and *negative node* (N0), *Shah et al.* demonstrated that although there was no difference between perirenal fat invasion, renal sinus fat invasion and renal vein invasion in terms of the prognosis of the disease, the combination of these factors could negatively affect the prognosis of the disease (13). In another multicentric study by *Brookman-May et al.*, it was shown that perirenal fat invasion may be an independent prognostic factor for cancer specific survival (14). It has also been shown that renal capsule invasion may be an independent prognostic factor for RCC (10). Pre-operative detection of prognostic factors has recently become more important for the management of the disease, with the increase in neo-adjuvant and adjuvant treatment modalities. In a study conducted by Renard et al., the predictive value of CT for pT3a disease was evaluated and the PPV values of perirenal fat invasion, renal sinus fat invasion and venous invasion were detected to be 49%, 68% and 90%, respectively (15).
In another study by *EL-Hefnawy et al.* including 693 patients, the PPV value of CT in predicting pT3a disease was reported as 43.7% (16). In our study, PPV of perirenal fat invasion in predicting ≥ pT3a was 69.2% and 81.8% in CT and MRI respectively. When compared to literature (15, 16), PPV of perirenal fat invasion seems to be higher according to CT. In addition, MRI seems to be more reliable for detecting perirenal fat invasion. Although it is thought that it is difficult to detect renal capsule invasion in pre-operative imaging, it has been reported in studies that some CT findings may indicate renal capsule invasion (11). In addition, in a study conducted by Nazım et al. PPV of renal capsule invasion in CT was 75.3% in predicting local advanced RCC (17).
In our study PPV of renal capsule invasion was 75.0% (53.8-96.2) and 90.0 (71.4-108.6) for CT and MRI respectively. Our results demonstrated that PPV value of renal capsule invasion on CT in predicting T3a and above

Table 4.
CT and MRI predictions for pT Stage > pT3a.

Predictors	Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
	BT (CI)	MR (CI)	BT (CI)	MR (CI)	BT (CI)	MR (CI)	BT (CI)	MR (CI)
Gerota's fascia thickness 0.205 cm <	73.3 (51.0-95.7)	80.0 (55.2-104.8)	75.0 (61.6-88.4)	85.2 (71.8-98.6)	52.4 (31.0-73.7)	66.7 (40.0-93.3)	88.2 (77.4-99.1)	92.0 (81.4-102.6)
Presence of enlarged collateral vessels Positive	86.7 (69.5-103.8)	80.0 (55.2-104.8)	52.5 (37.0-67.8)	66.7 (48.9-84.4)	40.6 (23.6-57.6)	47.1 (23.3-70.8)	91.3 (79.8-102.8)	90.0 (76.9-103.1)
Tumor necrosis Positive	73.3 (51.0-95.7)	80.0 (55.2-104.8)	52.5 (37.0-68.0)	66.7 (48.9-84.4)	36.7 (19.4-53.9)	47.1 (23.3-70.8)	84.0 (69.6-98.4)	90.0 (76.9-103.1)
Renal capsule invasion Positive	80.0 (59.8-100.2)	90.0 (71.4-108.6)	89.7 (80.2-99.3)	96.3 (89.2-103.4)	75.0 (53.8-96.2)	90.0 (71.4-108.6)	92.1 (83.5-100.6)	96.3 (89.2-103.4)
Perinephric stranding Positive	73.3 (50.1-95.7)	100.0	57.5 (42.2-72.8)	74.1 (57.5-90.6)	39.3 (21.2-57.4)	58.8 (35.4-82.2)	85.2 (71.8-98.6)	100.0
Perirenal fat invasion Positive	60.0 (35.2-84.8)	90.0 (71.4-108.6)	90.0 (80.7-99.3)	92.6 (82.7-102.5)	69.2 (44.1-94.3)	81.8 (59.0-104.6)	85.7 (75.1-96.3)	96.2 (88.8-103.5)

CT: Computed tomography, MRI: Magnetic resonance imaging, pT: Pathological Tumor, PPV: Positive predictive value, NPV: Negative predictive value.

disease is similar to the literature. In addition, MRI seems to be more reliable for detecting renal capsule invasion.
In locally advanced RCC, thickening of the Gerota's fascia adjacent to the tumor may be expected due to the spread of the tumor. However, increase in the thickness of Gerota's fascia may also develop due to other reasons such as infectious pathologies. In a study by *Bradley et al.*, it was stated that the Gerota's fascia thickness on CT has 90% specificity and 81% PPV for T3a and above disease, and it has been shown that Gerota's fascia thickness is a reliable predictor of locally advanced disease (12). In our study, we measured the thickness of the Gerota's fascia adjacent to the tumor for the first time in the literature, and in our ROC analysis, we determined that the cut-off value for the Gerota's fascia thickness in predicting advanced disease was 0.205 cm. According to this cut-off value, the specificity of the Gerota's fascia thickness in predicting a stage > T3a is 75% and 85% for CT and MRI respectively. We also determined that the PPV value was 52% and 66% for CT and MRI respectively. According to our results, we think that the Gerota's fascia thickness has less predictive value for locally advanced disease in contrast to literature and that MRI is more reliable than CT.
Presence of enlarged collateral vessels and tumor necrosis are thought to be predictive markers for advanced RCC. In meta-analyses, indication of tumor necrosis as a factor that adversely affects prognosis in RCC makes the predictive value of the presence of necrosis in advanced stage disease more important in pre-operative imaging (18). There are studies indicating that tumor necrosis on CT has high specificity and PPV in predicting T3a disease (12).
In our study, even though there was a significant difference between the groups in terms of the presence of necrosis, we found that the presence of necrosis had a low predictive value for advanced disease in both CT and MRI (PPV= 37% and 47% respectively). However, the absence of tumor necrosis indicates that pathological stage could be < T3a (NPV= 84% and 90% for CT and MRI). On the other hand, in a study conducted by Suo et al., it was shown that patients with collateral vessel diameter > 0.2 cm had a higher pT stage than patients with < 0.2 cm. They also showed that the presence of a collateral vessel is an independent prognostic factor for overall survival in RCC (19). In another study, the presence of enlarged collateral vessels was shown to have an 88% PPV value in predicting > pT3a disease (12).
In our study, there was a significant difference between the groups in terms of the presence of enlarged collateral vessels on CT and MRI (p = 0.008 and p = 0.015 respectively). However, although the NPV value of the presence of enlarged collateral vessels in both CT and MRI was high in predicting > pT3a disease (91% and 90% respectively), the PPV value was low (41% and 47% respectively). In contrast to literature, we don't think that presence of enlarged collateral vessels can predict locally advanced disease in RCC.
Perinephric fat stranding develops mostly due to pyelovenous or pyelolymphatic backflow due to acute ureteral obstruction (20). Studies have shown that perinephric fat stranding has a low predictive value for locally advanced disease in RCC (10, 14). In our study, we found that the power of perinephric fat standing to predict local advanced disease was low in both CT and MRI (PPV = 39% and 58% respectively). On the other hand, MRI seems more reliable than CT. Nevertheless, our study has some limitations. Firstly, our study is retrospective and the number of patients in the groups is limited. Secondly, the patients in the MRI and CT groups were different, and not every patient had both CT and MRI as imaging so CT and MRI were not statistically compared for predictive values of preoperative imaging markers. However, it can be said that MRI may be more reliable because it has higher PPV values than CT for all predictors. Thirdly, we did not measure the diameter of the collateral vessels. We considered patients with significant enlarged collateral vessels to be positive.

Conclusions

In conclusion, renal capsular invasion, perirenal fat invasion are reliable signs for locally advanced (> pT3a) renal cell carcinoma both in CT and MRI. Gerota's fascia thickness has relatively low PPV value for prediction of locally advanced disease. Presence of enlarged collateral vessels, tumor necrosis, perinephric stranding are not reliable signs. On the other hand, for all predictors MRI seems more reliable than CT. Prospective large cohort studies are needed for more defined conclusions.

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Correspondence

Musab Ali Kutluhan, MD
dr.musab151@gmail.com

Selman Unal, MD (Corresponding Author)
drselmanunal@gmail.com
Universiteler District Bilkent Avenue No: 1 Ankara, 06800 (Turkey)

Serhan Eren, MD
serhanerenhu@gmail.com
Etlik Avenue No: 55 Kecioren/Ankara, 06010 (Turkey)

Asim Ozayar, MD
aozayar@gmail.com

Emrah Okulu, MD
eokulu@yahoo.com

Huseyin Cetin, MD
hcetinrad@gmail.com

Onder Kayigil, MD
kayigilo@yahoo.com.tr
Universiteler District Bilkent Avenue No: 1 Ankara, 06800 (Turkey)