

## Original Article

# Perirenal fat associated with high-grade renal cell carcinoma in chinese patients

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**Abstract:** Purpose: To evaluate the relationship between obesity and renal cell carcinoma, we examined the association between obesity, adipose tissue distribution and Fuhrman grade in patients with renal cell carcinoma. Methods: The medical records of 342 consecutive patients who underwent nephrectomy at Peking University People's Hospital from September 2009 to January 2015 were retrospectively reviewed. Different fat measurements were taken on pre-operative computed tomography scans. Fuhrman grade was assessed by two experienced pathologists who were blinded to the fat measurement information. Logistic regression analysis was used to determine features associated with high-grade disease (Fuhrman grade III or IV). Results: Thirty-five (10.23%) of the tumors were classified as high-grade disease. Patients in the high-grade group had a higher percentage of perirenal adipose tissue (P = 0.019) and larger average tumor size (P = 0.012) than those in the low-grade disease group. However, body mass index, total adipose tissue, visceral adipose tissue and subcutaneous adipose tissue were comparable between the low-grade and high-grade groups. The results of logistic regression analysis showed that percentage of perirenal adipose tissue was associated with tumor grade (OR 2.684, 95% CI 1.107-6.507, P = 0.029). Conclusions: Higher percentage of perirenal adipose tissue was associated with higher Fuhrman disease grade in patients with renal cell carcinoma.

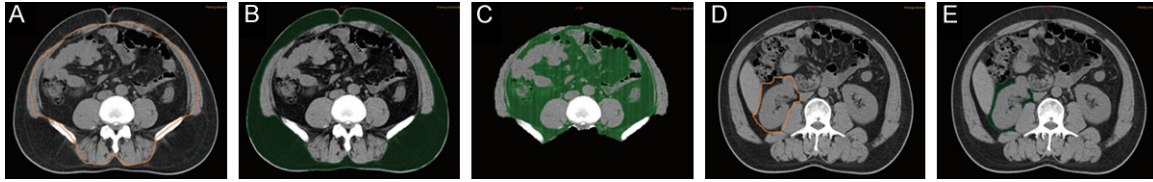
**Keywords:** Renal cell carcinoma, perirenal fat, obesity, visceral fat, computed tomography

## Introduction

Renal cell carcinoma (RCC) is the most common renal malignant disease and accounts for 2% to 3% of all malignancies, with 338,000 new cases reported worldwide in 2012 [1]. The incidence of RCC is increasing globally, with an annual increase of approximately 2% over the last two decades [2]. In China, the incidence of RCC was 3.96 per 100,000 in 2005; in 2012, this incidence increased to 9.47 per 100,000 [3]. Over half of patients with RCC remain asymptomatic until the late stages of the disease. Approximately 30% of patients with RCC present with metastatic disease at diagnosis, and 30% to 50% of patients with initially localized disease relapse distantly after nephrectomy [4]. The overall five-year survival rate is only 50% to 60%.

Despite the high prevalence and mortality of RCC, the etiology of the disease is not well elu-

cidated. Apart from genetic variations, lifestyle variables also play an important role in the development and progression of RCC [2]. Recently, increasing evidence has suggested that obesity is associated with the development and prognosis of RCC [5]. Wang and Xu summarized 21 cohort studies evaluating the relationship between body mass index (BMI) and RCC risk and found that increased BMI is associated with increased risk of RCC [6]. Interestingly, another meta-analysis conducted by Choi et al. showed that preoperative BMI is significantly correlated with survival among patients with RCC. High BMI significantly improved overall survival (hazard ratio [HR] 0.57, 95% CI 0.43-0.76), cancer-specific survival (HR 0.59, 95% CI 0.48-0.74) and recurrence-free survival (HR 0.49, 95% CI 0.30-0.81) [7]. Faced with these paradoxical findings, it is necessary to further investigate the association between obesity and RCC.



**Figure 1.** Representative examples of visceral adipose tissue, subcutaneous adipose tissue and perirenal fat measurements on a CT scan. After outlines were placed around abdominal skeletal muscle (A), SAT (B) and VAT (C) were calculated. The perirenal fat was traced (D), and the perirenal fat area was automatically calculated (E).

BMI has been widely used as a measure of obesity. Although BMI can represent the condition of a patient, it fails to represent abnormalities in body mass distribution. Growing evidence suggests that adipocytes from different anatomical locations have distinct phenotypes and functions [8]. Therefore, we conducted the present study to investigate whether body fat distribution is associated with Fuhrman grade in RCC.

## Methods

### Patients

After institutional review board approval, the medical records of 407 consecutive patients who underwent radical or partial nephrectomy at Peking University People's Hospital from September 2009 to January 2015 were retrospectively reviewed. The inclusion criteria were 1) histologically proven RCC, 2) older than 40 years, 3) pre-operative abdominal cross-sectional CT available (within 2 weeks before surgery), 4) no significant weight loss prior to surgery and 5) no previous renal surgery, ablative therapies, targeted therapy or immunotherapy for RCC. After applying these criteria, 342 patients were enrolled in the study.

### Data collection

Baseline demographic and clinical characteristics, including age, gender, smoking status, height, weight, BMI (calculated by dividing body weight by the square of height), waist circumference and tumor size, were collected from medical records. Measurements of the surface areas of perirenal, visceral and subcutaneous fat were conducted in a standardized manner on preoperative axial CT scans using AW Volume Share 5 software [9], which is a stand-alone image analysis and image processing software suite dedicated to DICOM images. The

quantities of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and total adipose tissue (TAT) were measured on pre-operative CT scans at the level of the umbilicus with patients in the supine position as previously described [10]. Briefly, the abdominal muscular wall was manually traced to separate the visceral from the subcutaneous compartment, and then the cross-sectional areas of different compartments could be calculated by AW Volume Share 5 software on the basis of pre-defined Hounsfield unit thresholds (-190 to -30) (**Figure 1**). The degree of visceral obesity was defined by the percentage of VAT, as  $VAT\% = [VAT/(VAT+SAT)] \times 100\%$ . Measurement of perirenal fat (PF) area was performed using an axial CT slice at the level of the renal hilum following the anterior renal fascia to the lateroconal ligament and encompassing the posterior perirenal fat [9] (**Figure 1**). The degree of PF accumulation was defined by the percentage of PF,  $PF\% = [PF/(VAT+SAT)] \times 100\%$ . These measurements were performed by the same radiologist, who was unaware of the clinicopathological outcomes.

Fuhrman grade was assessed by two experienced pathologists who were blinded to the fat measurement information. Due to the low probability (2.0%) of Fuhrman grade IV disease, the 4-tier grading system was simplified into a 2-tier classification. Low-grade disease was defined as Fuhrman grades I and II, and high-grade disease included Fuhrman grades III and IV.

### Statistical analysis

Continuous variables were presented using the mean and standard deviation. Given that no clearly defined categories exist for VAT% or PF%, these measures of obesity were divided into dichotomous variables with cutoffs at the median based on the entire cohort. The chi-

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**Table 1.** Demographic parameters, adiposity measurements and clinicopathological characteristics according to tumor grade

Variable	Low grade (N = 307)	High grade (N = 35)	P value
Age			0.916
<60 yr	152 (49.5%)	17 (48.6%)	
≥60 yr	155 (50.5%)	18 (51.4%)	
Gender			0.188
Male	203 (66.1%)	27 (77.1%)	
Female	104 (33.9%)	8 (22.9%)	
Smoking			0.495
No	202 (65.8%)	21 (60.0%)	
Yes	105 (34.2%)	14 (40.0%)	
BMI			0.277
<23 kg/m <sup>2</sup>	74 (25.7%)	11 (36.7%)	
23-24.9 kg/m <sup>2</sup>	66 (22.9%)	8 (26.6%)	
≥25 kg/m <sup>2</sup>	148 (51.4%)	11 (36.7%)	
TAT			0.362
<160 cm <sup>2</sup>	148 (49.0%)	15 (42.9%)	
≥160 cm <sup>2</sup>	154 (51.0%)	20 (57.1%)	
VAT%			0.362
<43.7%	154 (51.0%)	15 (42.9%)	
≥43.7%	148 (49.0%)	20 (57.1%)	
PF%			0.019
<6.53%	158 (52.3%)	11 (31.4%)	
≥6.53%	144 (47.7%)	24 (68.6%)	
Tumor size			0.012
≤4 cm	190 (61.9%)	14 (40.0%)	
>4 cm	117 (38.1%)	21 (60.0%)	
Histology subtype			0.241
ccRCC	288 (93.81%)	31 (88.57%)	
Other	19 (6.19%)	4 (11.43%)	

square test was used to compare demographic and clinical variables between the different groups. The associations between different co-variables and high-grade disease were analyzed by univariate and multivariate logistic regression analyses. All statistical analyses were performed using SPSS software, version 15.0 (SPSS Inc, Chicago, IL, USA). All *P* values were 2-tailed, and values of *P*<0.05 were considered statistically significant.

### Results

#### Patient characteristics

In total, 342 patients' medical records were retrospectively reviewed and analyzed. The mean

age of the patients was 60.28±10.67 years, 67.25% of the subjects were male, and 34.80% of the subjects were smokers. Using current Asia-Pacific criteria for obesity, 85 (26.73%) of the subjects were underweight or normal weight (less than 23 kg/m<sup>2</sup>), 74 (23.27%) of the subjects were overweight (23 to 24.9 kg/m<sup>2</sup>), and 159 (50.00%) of the subjects were obese (more than 25 kg/m<sup>2</sup>). The mean BMI, TAT, VAT% and PF% were 25.11±3.49 kg/m<sup>2</sup>, 15,920.95±6995.62 mm<sup>2</sup>, 43.47±10.66% and 7.18±3.57%, respectively. The mean tumor size was 4.23±2.40 cm. A total of 319 (93.27%) patients had clear cell RCC, and 51 (14.91%) patients had advanced RCC (AJCC stage III or IV). Thirty-five (10.23%) of the tumors were classified as high-grade disease.

#### Associations between tumor grade and different measures of obesity

We divided the patients into two groups according to Fuhrman grade and then compared variables between them. The patients in the high-grade group had higher PF% (*P* = 0.019) and a larger average tumor size (*P* = 0.012). However, BMI, TAT and VAT% values were comparable between the low-grade and high-grade groups (**Table 1**).

Univariate logistic analysis showed that PF% was significantly associated with RCC grade, with an OR of 2.394 (95% CI 1.132-5.060, *P* = 0.019). Moreover, larger tumor size also had an effect on tumor grade.

Using multivariate analysis, after adjustment for age, gender, smoking status, histology subtype and tumor size, PF% was still associated with adverse outcome (OR 2.684, 95% CI 1.107-6.507, *P* = 0.029). This result also confirmed that tumor size, a well-known prognostic factor, was strongly correlated with Fuhrman grade (OR 2.671, 95% CI 1.280-5.574, *P* = 0.009) (**Table 2**).

### Discussion

Obesity is increasing in prevalence worldwide and has become a major social and health issue. Obese people are predisposed to develop various diseases, including hypertension, coronary heart disease, diabetes mellitus and

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**Table 2.** Predictors of high-grade RCC

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
<b>Age</b>						
<60 yr	1			1		
≥60 yr	1.038	[0.516-2.090]	0.916	0.992	[0.958-1.028]	0.673
<b>Gender</b>						
Female	1			1		
Male	1.729	[0.759-3.940]	0.188	1.018	[0.369-2.810]	0.973
<b>Smoking</b>						
No	1			1		
Yes	1.283	[0.627-2.625]	0.495	1.070	[0.480-2.382]	0.869
<b>PF%</b>						
<6.53%	1			1		
≥6.53%	2.394	[1.132-5.060]	0.019	2.684	[1.107-6.507]	0.029
<b>Tumor size</b>						
≤4 cm	1			1		
>4 cm	2.436	[1.192-4.976]	0.012	2.671	[1.280-5.574]	0.009
<b>Histology subtype</b>						
ccRCC	1			1		
Other	1.956	[0.625-6.116]	0.249	2.245	[0.685-7.362]	0.182

several types of malignant tumors, such as RCC [11]. Epidemiological studies have consistently shown an increased relative risk of RCC with increased BMI [12]. In a prospective study of over 900,000 adults in the USA, obesity was shown to increase the risk of RCC [13]. A strong association between obesity and RCC was also confirmed by Renehan et al. [5] with a meta-analysis that included 17 datasets. Interestingly, although high BMI predisposes individuals to RCC, patients with an increased BMI were more likely to present with a less aggressive form of RCC [14]. These inconsistencies suggest that there may be complex metabolic mechanisms between obesity and RCC that warrant further investigation.

Obesity is the result of excess fat accumulation. Recently, researchers have recognized that adipose tissue is distributed throughout two main compartments within the body, namely, the visceral and subcutaneous regions. Beyond energy storage, VAT and SAT share little similarity in function [15]. Indeed, they differ in type of adipocytes involved, lipolytic activity, endocrine function and responses to insulin and other hormones. In addition, both ectopic fat and fat accumulation in specific compartments of the body have been found to detri-

mentally contribute to various health conditions [16]. Therefore, to investigate the effect of obesity in the development and progression of RCC, body fat distribution and different fat compartments must be considered.

In several studies, VAT, SAT and VAT% have been shown to be better markers of health issues than BMI itself. Wang et al. investigated 487 patients with localized RCC and found that increased VAT was associated with clear cell RCC subtype and that the significance of VAT outweighed the effects of BMI for the prediction of RCC pathology subtypes [3]. Kaneko et al. reported that high VAT is a positive predictive biomarker for better recurrence-free survival after curative surgeries for localized RCC [17]; however, BMI was not a predictor, in line with another study reported by Naya et al. [18]. In another study involving 706 patients with localized RCC, researchers observed a U-shaped association between VAT% and risk of RCC recurrence [19]. In a study of 186 patients with surgically treated T1a RCC, Zhu et al. found that VAT% is an independent predictor of high-grade RCC [20]. In contrast, in our current study, we did not observe a significant association between VAT% and tumor grade. This disparity might be attributable to differences in the study

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populations, as our results were based on older patients (older than 40 years). Therefore, these results need to be refined and further investigated in a larger set of patients. However, we did find that high PF% is associated with high-grade disease.

As a component of abdominal visceral fat, PF may have a closer relationship to kidney disease than other visceral fat deposits. First, it surrounds the kidney directly, seeping into the renal sinus, compressing the renal parenchyma and renal vessels, and leading to increased renal interstitial hydrostatic pressure and reduced renal blood flow that ultimately may result in renal cell hypoxia and malignant transformation [21]. Second, perirenal fat may exert its effects through its direct lipotoxicity, as excessive release of free fatty acids (FFAs) from perirenal fat increases renal FFA intake and leads to renal lipotoxicity by both endocrine and paracrine pathways [22]. Third, as a component in visceral fat, perirenal fat could release numerous molecules into the bloodstream, such as interleukin 6, vascular endothelial growth factor, TNF- $\alpha$ , plasminogen activator inhibitor 1 and adiponectin, which may promote cancer growth and angiogenesis [23-25].

To the best of our knowledge, our current study is the first to investigate the association between increased perirenal fat and elevated risk of aggressive RCC and to suggest that CT-based assessment of perirenal fat surface area is superior to both BMI and VAT% in predicting higher grade disease. However, there are several limitations in the present study. First, the study population was relatively small and limited to patients at a single hospital. Thus, a larger confirmatory study is needed. Second, 24 patients were excluded because no images were available for analysis, which could have introduced potential bias. Third, the retrospective design of the present study only allowed us to examine the temporal coexistence of perirenal fat and RCC grade, but not causal inferences. Finally, all the participants were Chinese. Different from Western populations, Asian populations tend to have lower BMIs but a higher probability of visceral obesity [26]. Therefore, further study is required to validate the current results in other ethnic groups.

In conclusion, the current study showed that higher percentage of perirenal adipose tissue

is associated with higher Fuhrman disease grade in patients with RCC. Further studies are needed to confirm these findings and to investigate the underlying pathophysiology and molecular mechanisms by which fat could be involved in tumorigenesis.

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### Disclosure of conflict of interest

None.

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