

Comparison of perinephric fat measurements between malignant and benign renal tumours

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Abstract

Objective: To investigate different parameters derived from the quantity and quality of perinephric fat, and to compare their effectiveness in predicting the malignant pathology of renal tumours.

Methods: Data from patients diagnosed with renal tumour between April 2014 and December 2020 were retrospectively reviewed, and patients were categorized into malignant or benign tumour groups. Fat parameters, including perinephric fat volume (PFV), perinephric fat area (PFA), perinephric fat thickness (PFT), and Mayo adhesive probability (MAP) score were measured using abdominal computed tomography scans. Between-group differences were assessed by analysis of variance and χ^2 -test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the performance of perinephric fat parameters in diagnosing malignancy.

Results: A total of 109 patients were included. MAP score, PFV, PFA, and PFT were significantly increased in the malignant versus benign tumour group, and after correction for body mass index (BMI), the indexed PFV/BMI, PFA/BMI, and PFT/BMI values remained significantly higher in the

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malignant tumour group. All parameters showed fair predictivity of malignancy, with comparable area under the curve values in the ROC curve.

Conclusion: An increased amount of perinephric fat is predictive of malignant pathology for renal tumours. The predictive accuracy for each perinephric fat parameter remained fair after correcting for BMI.

Keywords

Renal tumour, perinephric fat, prediction of malignancy, Mayo adhesive probability, body mass index, computed tomography

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Introduction

The incidental discovery of renal masses has risen due to the increasing accessibility and popularity of abdominal image modalities, with a reported 13–27% of abdominal examinations revealing renal masses.¹ Although most are clinically insignificant, small, simple cysts, and about 15% of surgically resected suspicious malignant lesions are proven to be benign,² there remains increased concern regarding asymptomatic malignant tumours in clinical practice. In fact, the incidence of renal cell carcinoma (RCC) has been on an upward trend worldwide, in parallel with the increasing use of axial imaging.³

A renal tumour biopsy is sometimes performed for definite histology when the malignant potential of a tumour remains uncertain in imaging studies. Due to the invasive nature of this procedure, there may be inevitable associated complications, and it yields a maximum 22.6% non-diagnostic rate.⁴ As such, the use of advanced imaging techniques has been investigated for the noninvasive characterization of renal tumours.³

Obesity has been linked to the incidence of multiple malignant conditions, with a higher body mass index (BMI) found to be associated with the incidence of RCC.^{5,6}

Additional parameters regarding visceral fat have been studied to further understand the interactions between adipose tissue and the kidney. The Mayo Adhesive Probability (MAP) score is a 0 to 6 scoring system composed of perinephric fat thickness (PFT) and fat stranding quality.^{7,8} Although the MAP score was originally developed for preoperative prediction of partial nephrectomy, it has also been associated with malignant renal histology. However, there are reports that pure quantitative measurement of perinephric fat area (PFA) fails to predict the malignant pathology of renal tumours.^{7,8}

Compared with one-dimensional fat thickness or two-dimensional PFA, three-dimensional perinephric fat volume (PFV) may more accurately describe the amount of perinephric adipose tissue and its relationship with renal tumours. An increased PFV has been shown to influence the complexity of robotic-assisted partial nephrectomy with a significantly increased operation time, while MAP score was not a significant predictor.⁹

The aim of the present study was to focus on the relationship between PFV and RCC, which to the best of our knowledge, has not been previously investigated, and to compare other parameters derived from the quantity and quality of perinephric fat, between

benign and malignant tumours. Through these results, a further study aim was to evaluate the ability of perinephric fat to predict the malignant pathology of renal tumours.

Patients and methods

Study population

In this retrospective observational study, the medical records of all patients who had received a clinical or pathology diagnosis of renal tumour, either benign or malignant, from Mackay Memorial Hospital, Taipei, between April 2014 and December 2020, were reviewed. Patients without available abdominal computed tomography (CT) scan images, who had undergone haemodialysis, with history of any abdominal operation, with history of other malignancy, and/or with history of acute pyelonephritis of the same kidney were excluded. Patients having a solitary renal tumour with complete clinical and radiological data were enrolled, including those who underwent either partial or radical nephrectomy and patients who did not receive surgery but displayed a typical presentation of renal angiomyolipoma in a CT scan (< -10 HU). The clinical diagnosis of angiomyolipoma was unanimously agreed by two experienced radiologists (DCL and WMH). All participant data were deidentified for the study, and patients were grouped according to benign or malignant renal tumour for analyses.

The study protocol was reviewed and approved by the Institutional Review Board at Mackay Memorial Hospital, approval number 20MMHIS020e. Due to the retrospective study design and deidentification of patient data, the requirement of informed consent from study participants was waived by the same committee. The reporting of this study conforms to STROBE guidelines.¹⁰

CT scan and measurement of subcutaneous and visceral adipose tissue

All CT studies were performed using a 128-slice (Somatom definition AS; Siemens Healthcare, Forchheim, Germany) or a 256-slice (Somatom definition Flash; Siemens Healthcare) multidetector CT scanner. The settings for all examinations were identical and used the same scanning parameters, including: scan acquisition within a single breath-hold and obtained with a detector width of 128×0.6 or 256×0.6 mm, a tube voltage of 120 kVp, automatic exposure control for tube current, 0.5 s gantry rotation time, and 1.5 mm reconstructed slice thickness. The scan coverage was from the top of the hemi-diaphragm to the pelvic symphysis. All images were acquired with the patient in a supine position and at full inspiration status. The adipose tissue measure was quantified using a dedicated workstation (Aquarius iNtuition, version 4.4; TeraRecon, San Mateo, CA, USA). The region of interest was manually traced and the fat tissue was defined as pixels within a window of -190 to -30 HU and a window centre of -110 HU.¹¹ PFV was measured according to the visible boundaries of Gerota's fascia on the CT images. The adrenal glands, kidneys, and renal hilar structures were subtracted from the surrounding perinephric fat to obtain the calculated PFV (Figure 1). The axial image slice at the level of the renal vein was selected for measuring PFA and PFT. The distance between the posterior, lateral wall of the kidney and Gerota's fascia, and the area between the kidney and Gerota's fascia were measured. To measure the visceral fat area (VFA), and the subcutaneous fat area (SFA), axial view CT images at the L4–L5 level were selected. VFA and SFA were automatically quantified by the software to calculate the adipose tissue in the peritoneal cavity and the subcutaneous region. Subcutaneous fat thickness was measured as the largest

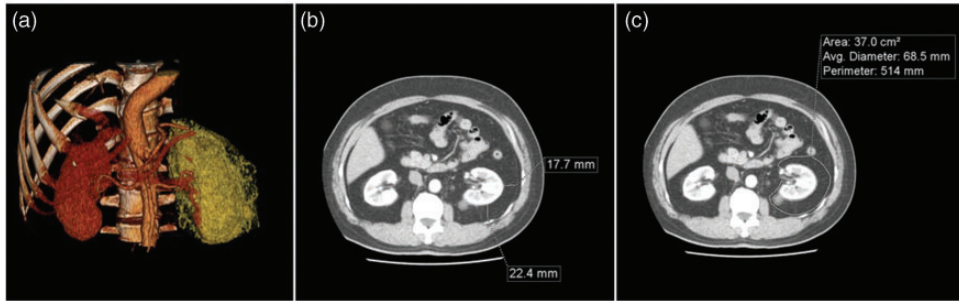


Figure 1. Representative multidetector computed tomography images demonstrating perinephric fat measures, including volume, thickness, and area. The perinephric fat volume was defined as the fat inside the boundaries of Gerota's fascia, as shown in (a) a 3D reconstruction (orange-coloured regions indicate visceral fat tissue). Axial view CT was used to measure (b) perinephric fat thickness and (c) area.

distance between the skin and the outer limit of the muscular wall of the abdomen at the level of the umbilicus.

The RENAL nephrometry score, based on five anatomical features of renal tumour, including (R)adius (maximal diameter), (E)xophytic/endophytic properties, (N)earness of tumour deepest portion to the collecting system, (A)nterior (a)/posterior (p) descriptor and the (L)ocation relative to the polar line, was calculated for each patient. Of the five components, four are scored on a 1, 2 or 3-point scale with the 5th indicating the anterior or posterior location of the mass relative to the coronal plane of the kidney.¹²

Statistical analyses

Continuous variables are presented as mean \pm SD and categorical data are presented as numbers and percentages. All statistical analyses were performed using IBM SPSS Statistics software, version 22 (IBM Corp. Armonk, NY, USA). Between-group differences were assessed using analysis of variance and χ^2 -test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the performance of perinephric fat parameters in diagnosing renal tumour malignancy. The cut-off value was calculated by the area under the ROC

curve (AUC) with optimal sensitivity and specificity. A P -value <0.05 was considered to indicate statistical significance.

Results

A total of 109 patients with a solitary renal tumour and complete clinical and radiological data were included (benign tumour group, $n = 54$; malignant tumour group, $n = 55$). Of those who underwent either partial or radical nephrectomy, 55 were diagnosed with RCC and 28 were found to have a benign renal tumour by pathological examination. The remaining 26 patients did not receive surgery, but displayed a typical presentation of renal angiomyolipoma in a CT scan (<-10 HU). The patients' demographic and pathological characteristics are summarised in Table 1. Most benign tumours were clinically or pathologically diagnosed as angiomyolipoma (47 cases [87%]), while oncocytoma was the second most common benign pathology (5 cases [9.3%]). There were no statistically significant between-group differences in patient age, or history of diabetes mellitus, hypertension or coronary artery disease.

Comparison of perinephric fat properties between the malignant and benign tumour groups (Table 2) revealed a significantly

Table 1. Demographic and pathological characteristics of 109 patients with renal tumour.

Parameter	Study group			Statistical significance
	Total (n = 109)	Benign (n = 54)	Malignant (n = 55)	
Age, years	55.4 ± 13.6	56.2 ± 13.9	54.6 ± 13.4	NS
Sex, male/female	53/56	11/43	42/13	P < 0.01
BMI, kg/m ²	25.5 ± 4.2	24.3 ± 3.9	26.4 ± 4.1	P = 0.01
Tumour size, cm	3.99 ± 2.39	4.56 ± 2.98	3.44 ± 1.46	P = 0.01
Medical history				
DM	27 (24)	12 (22)	15 (27)	NS
Hypertension	49 (45)	25 (46)	24 (43)	NS
CAD	10 (9)	6 (11)	4 (7)	NS
Smoking	20 (18)	4 (7)	16 (29)	P < 0.01
Pathology type		Angiomyolipoma 47 (87)	Clear cell RCC 42 (76.4)	
		Oncocytoma 5 (9.3)	Papillary RCC 9 (16.4)	
		Others 2 (3.7)	Chromophobe RCC 3 (5.4)	
			Xp11 translocation 1 (1.8)	
T Stage				
T1a			39 (70.9)	
T1b			15 (27.3)	
T2a			1 (1.8)	

Data presented as mean ± SD or n (%) prevalence.

BMI, body mass index; DM, diabetes mellitus; CAD, coronary artery disease; RCC, renal cell carcinoma.

NS, no statistically significant between-group difference ($P > 0.05$; analysis of variance or χ^2 -test).

increased MAP score, PFV, PFA, and PFT in the malignant group compared with the benign group. The VFA and SFA values were also significantly increased in patients with malignant renal tumour. After correction for BMI, the indexed PFV/BMI, PFA/BMI, and PFT/BMI values remained significantly higher in the malignant tumour group ($P < 0.05$). There was no statistically significant between-group difference in RENAL scores.

The ROC curve for perinephric fat parameters is presented in Figure 2. The AUC was 0.598 for MAP score, 0.733 for PFV, 0.748 for PFA, and 0.714 for PFT. The adjusted AUC after correction for BMI was 0.723 for PFV/BMI, 0.734 for PFA/BMI, and

0.709 for PFT/BMI. The optimal cut-off points, sensitivities, and specificities are summarised in Table 3. PFA displayed the highest sensitivity and PFT displayed the highest specificity.

Discussion

For patients diagnosed with a renal tumour by CT scan, it is feasible to evaluate features in the vicinity of the tumour and to conduct noninvasive measurements of fat with modern computer software. The information acquired from CT scans, including the existence of local invasion, the presence of enlarged collateral vessels, the amount and pattern of perinephric fat, and the

Table 2. Comparison of perinephric fat properties in 109 patients with renal tumour.

Parameter	Study group		Statistical significance
	Benign (n = 54)	Malignant (n = 55)	
PFV, cm ³	114.1 ± 106.2	222.7 ± 174.2	P < 0.01
PFA, cm ²	13.5 ± 9.4	26.8 ± 20.2	P < 0.01
PFT, cm	9.1 ± 6.1	18.4 ± 12.3	P < 0.01
VFA, cm ²	108.5 ± 59.7	142.1 ± 81.0	P = 0.015
SFA, cm ²	174.9 ± 71.9	206.0 ± 89.6	P = 0.048
RENAL score	7.8 ± 2.0	7.7 ± 1.6	NS
MAP score	1.5 ± 1.3	2.1 ± 1.6	P = 0.037
PFV/BMI	4.3 ± 2.7	8.2 ± 5.9	P < 0.01
PFA/BMI	0.55 ± 0.30	0.98 ± 0.65	P < 0.01
PFT/BMI	0.39 ± 0.22	0.69 ± 0.42	P < 0.01

Data presented as mean ± SD.

PFV, perinephric fat volume; PFA, perinephric fat area; PFT, perinephric fat thickness; VFA, visceral fat area; SFA, subcutaneous fat area; MAP, Mayo adhesive probability; BMI, body mass index.

RENAL score, nephrometry score based on tumour radius (maximal diameter), exophytic/endophytic properties, nearness of tumour deepest portion to the collecting system, anterior (a)/posterior (p) descriptor and location relative to the polar line. NS, no statistically significant between-group difference ($P > 0.05$; analysis of variance).

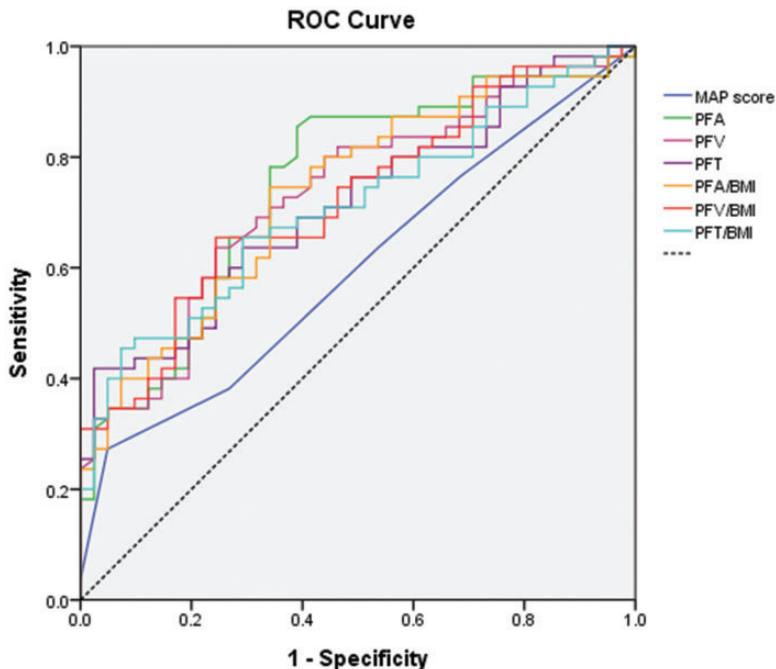


Figure 2. Receiver operating characteristic curves comparing parameters for measuring perinephric fat. The area under the curve (AUC) was 0.598 for Mayo adhesive probability (MAP) score, 0.733 for perinephric fat volume (PFV), 0.748 for perinephric fat area (PFA), and 0.714 for perinephric fat thickness (PFT). After correction for body mass index (BMI), the AUC was 0.723 for PFV/BMI, 0.734 for PFA/BMI, and 0.709 for PFT/BMI.

Table 3. Receiver operating characteristic (ROC) curve analysis of the ability of perinephric fat properties to predict malignancy in 109 patients with renal tumour.

Parameter	Cut-off value	Sensitivity	Specificity
PFV, cm ³	127.5	0.636	0.756
PFA, cm ²	11.6	0.855	0.61
PFT, cm	20.05	0.418	0.976
PFV/BMI	5.01	0.655	0.756
PFA/BMI	0.574	0.745	0.659
PFT/BMI	0.702	0.455	0.927

PFV, perinephric fat volume; PFA, perinephric fat area; PFT, perinephric fat thickness; BMI, body mass index.

amount of visceral fat, may provide a clinically significant estimate of RCC prognosis.^{7,13–17} An increased amount of visceral fat is indicated to be associated with poor oncologic outcomes, larger tumour size, and higher Furhman's grade of RCC.^{18,19} Additionally, an increase in fat thickness is shown to be a predictor of clear cell RCC (ccRCC) pathology, a risk factor of poor progression-free survival, and a predictor of tumour outward growth pattern.^{20–22} Interestingly, an increased amount of perinephric adipose tissue has also been found to be associated with poor outcomes for colorectal and ovarian cancer.^{23,24} However, to date, most available literature on perinephric fat addresses its effect on surgical difficulty and perioperative outcomes in partial nephrectomy.^{7,9,25–27}

Based on abundant evidence, the correlation between adiposity and malignancy is well-established, particularly in organs with close anatomical proximity to adipose tissue depots, such as the prostate and breast.^{28,29} Thus, it is reasonable to apply this concept to renal tumours, which are also embedded in rich adipose tissue, and to develop a noninvasive tool that may help predict malignant histology and prevent complications from unnecessary invasive procedures.

Bernstein et al.⁸ concluded that, instead of PFA, fat adhesiveness is predictive of malignant histology. However, the quantitative influence of adjacent adipose tissue

may not be fully elucidated, as studies regarding epicardial fat and coronary artery disease have suggested.^{30,31} An increased VFA has been demonstrated to be a potential parameter for distinguishing ccRCC from renal angiomyolipoma with minimal fat.³² In the present study, the parameters for measuring perinephric fat, including MAP score, PFT, PFA, PFV, and their BMI-corrected values, were all demonstrated to be significantly increased in patients with malignant renal tumour versus those with a benign tumour. The major outcome of the study, according to ROC curve analysis, was that perinephric fat measurements may potentially serve as a predictor of renal tumour malignancy. According to an academic points system, all perinephric fat parameters were categorized as fair accuracy, with an AUC between 0.7 to 0.8 both before and after being corrected for BMI. Among these parameters, PFA displayed the highest sensitivity and PFT had the highest specificity.

Investigation into the role of adipose tissue in tumorigenesis and metastasis is an emerging field of study. Hypertrophied adipose tissue depots in obese individuals are in a state of chronic low-grade inflammation, with macrophages and inflammatory cells comprising up to half of the adipose tissue cellularity compared with just 5–10% in lean subjects.^{31,33} Excessive reactive oxygen species, proinflammatory cytokines, and adipokines secreted by adipose tissue,

are considered to be tumour promoters.³⁴ Angiogenesis and alterations in the tumour microenvironment, promoted by regions of hypoxia caused by visceral adipose tissue, are hypothesized to be associated with the growth of RCC, and transcriptomic analyses have revealed a significant upregulation of hypoxia- and angiogenesis-related genes in obese patients with ccRCC compared with patients of normal weight.³⁵ The tumorigenesis role of adipose tissue in RCC may also vary between histological subtypes and different types of genetic mutation. An Italian research group demonstrated that, in comparison with control group, both ccRCC and non-clear cell RCC (nccRCC) groups have significantly increased VFA and VFA/SFA, yet the statistically significant increased SFA was only observed in the ccRCC group.^{36,37} An earlier Chinese study reported a significantly greater VFA in patients with ccRCC versus those with nccRCC by an average of 25 cm².³⁸ Even amongst the same ccRCC subtype, a significant difference in VFA has been measured between von Hippel–Lindau (VHL) gene mutation and lysine (K)-specific demethylase 5C (KDM5C) gene mutation groups.³⁹

The abovementioned hormonal and immune phenomena regarding adipose tissue were also observed in excessive perinephric fat with increased levels of tumour necrosis factor- α , and interleukin-6, as well as increased numbers of macrophages.⁴⁰ Previous molecular studies have reported the overexpression of uncoupling protein-1 and the under expression of homeobox protein 8 and 9 in the perinephric adipose tissue of patients with RCC.⁴¹ However, to date, the comprehensive molecular basis of perinephric fat involvement in carcinogenesis and tumour development remains unclear.

The results of the present study may be limited by its retrospective nature, small cohort size, lack of hormonal status, and use of single-centre data. In addition,

tumours of different pathology subtypes and stages were included in the same group, and this heterogeneous composition may lead to a within-group variation in adipose tissue amount.^{38,42} A proportion of patients with angiomyolipoma were diagnosed based on radiological examination, and the lack of pathology proof may have led to a bias. However, only lipid-rich angiomyolipomas (<−10 HU) are considered benign and left unoperated at Mackay Memorial Hospital in Taipei, and the radiological examination applied a region of interest (ROI) density measurement, which is reported to have a specificity of 100% with a threshold of <−10 HU for diagnosing angiomyolipoma.⁴³ Thus, we believe that the potential bias has been reduced to the lowest possible level. Different male to female ratios between the two groups should also be highlighted, as it is suggested that males have a greater amount of perinephric fat compared with females.^{7,8,44} Although small sample size was a limitation, an increased perinephric fat volume was not observed in male patients with benign renal tumours in the present study. Further investigations on a larger scale may be required to verify the present results. Of note, inter-interpretation variation in radiological diagnosis and measurement is an additional potential bias in studies that use such manually derived variables of perinephric fat.

In conclusion, an increased amount of perinephric fat is predictive of malignant pathology for renal tumours, regardless of whether it is measured in one, two, or three-dimensions, and the predictive accuracy for each perinephric fat parameter remained fair after correction for BMI. Further investigation is required to evaluate the diagnostic value of non-invasive radiological measurements of perinephric fat, as well as the underlying mechanism of adipose-tumour interaction.

Author contributions

YHC wrote the draft manuscript; JPT, DCL and WMH measured the CT scan-derived adipose tissue parameters; DCL performed the statistical analyses; MC supervised manuscript preparation and revision; and all authors read and approved the final manuscript.

Data accessibility

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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