Periprostatic Adiposity Measured on Magnetic Resonance Imaging Correlates with Prostate Cancer Aggressiveness

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Purpose: To evaluate the correlation between aggressiveness of prostate cancer (PCa) and obesity measuring the periprostatic fat on magnetic resonance imaging (MRI).

Materials and Methods: One hundred eighty-four patients who had undergone radical retropubic prostatectomy (RRP) were analyzed retrospectively. The different fat measurements (periprostatic fat area (PFA), the subcutaneous fat thickness, the anterior and posterior abdominal fat thicknesses and anteroposterior diameter) were performed on the slices of MRI and then compared with the clinical and pathologic characteristics.

Results: The PFA and ratio showed a statistically significant differences ($P = .019$ and $P = .025$, respectively) among three groups, that is to say, more adipose were distributed in periprostatic area of the high risk patients. Seventy-one patients in clinical stage and 82 patients in Gleason score have the significant differences between pre-operation and post-operation values. In the clinical stage, the PFA and ratio showed a statistically significant differences ($P = .014$ and $P = .037$, respectively). The difference group had more periprostatic adipose than the other one (65.26 ± 9.03 vs. 64.44 ± 9.62; 87.52 ± 3.97 vs. 87.30 ± 3.96). Nothing but the "PFA" was significantly different between two groups ($P = .017$). Logistic regression analysis adjusted for age revealed a statistically significant association between the PFA, the Ratio and the risk of having high-risk disease ($P = .031$ and $P = .024$, respectively).

Conclusion: The periprostatic adiposity not only affects the PCa aggressiveness, but also has effect in accurate assessment of the tumor stage and grade. We should predict the prognosis of patient with RRP by measuring periprostatic adiposity on pre-operative MRI.

Keywords: adipose tissue; body mass index; magnetic resonance imaging; obesity; prostatic neoplasms.

INTRODUCTION

Prostate cancer (PCa) is the second most common malignant tumor of men worldwide, the incidence of which has also risen gradually in China during recent decades.[1,2] Obesity has became a worldwide challenge in the 21st century. Many epidemiological studies have found that higher body mass index (BMI) and abdominal obesity were associated with increased risk of several cancers (kidney, colon, endometrium and breast) including prostate.[3-5] However, the relationship between obesity and PCa aggressiveness is still in controversial. Some studies have found positive correlation,[6-8] whereas others have drawn adverse results.[9,10] The difference of results is considered to be due to the method of measurement. The BMI doesn't effectively reflect the most metabolic active fat in body, whereas the visceral adipose is a more sophisticated measurement of abdominal obesity than BMI, because it is metabolically active and can produce a large number of hormones and cytokines such as tumor necrosis factor-α, interleukin-6, leptin and adiponectin.[11,12] Magnetic Resonance Imaging (MRI) is a direct, quantitative measurement method to characterize the distribution of abdominal adipose tissue in normal status or in pathologic conditions.[13] The aim of this study is to evaluate the correlation between aggressiveness of PCa and obesity by measuring the visceral fat (periprostatic fat) using MRI.

MATERIALS AND METHODS

From March 2006 to October 2012, one hundred eighty-four patients were histologically diagnosed as localized PCa by prostate needle biopsy at Xin Hua hospital affiliated to Shanghai Jiao Tong University School of Medicine before being given radical retropubic prostatectomy (RRP). In preoperative phase, all patients were evaluated with digital rectal examination (DRE), serum prostate-specific antigen (PSA), transrectal ultrasonography, radionuclide bone scan and X-ray chest film. Magnetic resonance imaging (MRI) was also performed to evaluate the local extent of disease and the possibility of nodal involvement for clinical staging. Pathologic stage is determined by histologic analysis of surgical samples including prostate, seminal vesicles and pelvic lymph nodes.

Measurements

Height and weight data were recorded before RRP. BMI (kg/m^2) was calculated and categorized according to the National Institutes of Health classification of normal weight (< 25 kg/m^2), overweight (25-29 kg/m^2) and obese (≥ 30 kg/m^2). Only two patients who had a BMI value of < 18.5 kg/m^2 were included in the normal weight group. The periprostatic fat area (PFA) (cm^2) and the subcutaneous fat thickness (SFT) measurements were performed on the slices of MRI at the transverse section, at the level of the femoral head and greater trochanter of the femur (**Figure 1**); the anterior abdominal fat thicknesses (AAT), posterior abdominal fat thicknesses (PAT) and anteroposterior diameter (APD) were measured on the slices of MRI (T2 weighted) of the midline section (**Figure 2**). The umbilicus, bladder, prostate and urethra were identified at the midline section. The ratio of visceral fat was calculated as the anterior plus posterior abdominal wall fat thickness subtracted from the APD divided by the APD and expressed as percentage. All measurements were performed in a blinded manner by a single observer (**Figure 1**). The SFT and the (PFA) were obtained from the images of MRI (T2 weighted) at the transverse section at the level of the femoral head and greater trochanter of the femur (**Figure 2**). The localization image is on the slice of MRI (T2 weighted) at the midline section. The anterior and posterior abdominal fat thicknesses, and APD were measured in 3 images around the midline and the results were averaged.

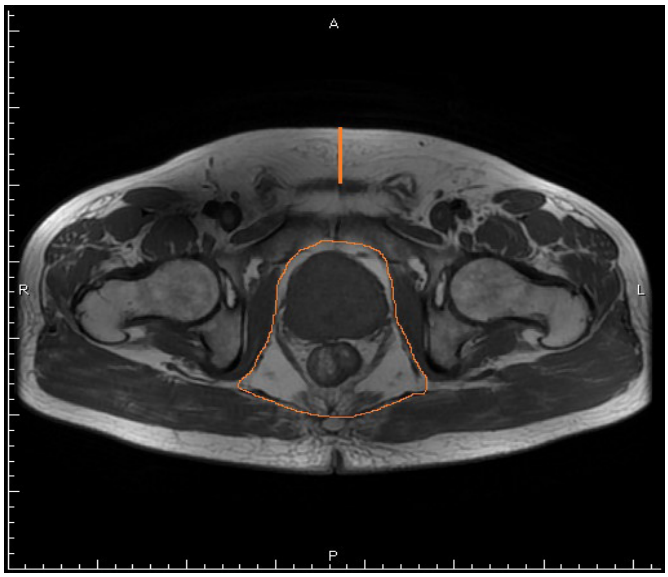

Figure 1. The periprostatic fat area and the subcutaneous fat thickness on the slices of magnetic resonance imaging at the transverse section, at the level of the femoral head and greater trochanter of the femur.

Statistical Analysis

Association between fat measurements and clinical/pathological characteristics were analyzed by chi-square test in case of categorical variables and Kruskal-wallis test in case of continuous variables. Logistic regression analysis was applied with adjustment of age to evaluate the independent effect of each variable on the risk of higher-risk disease.

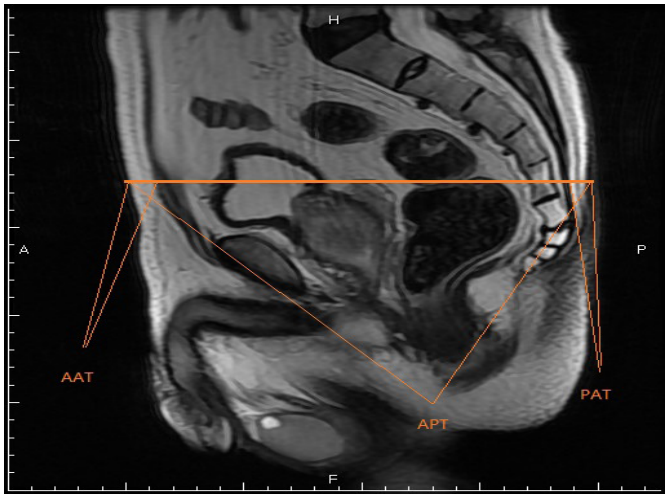

Figure 2. The anterior abdominal fat thicknesses, posterior abdominal fat thicknesses and anteroposterior diameter on the slices of magnetic resonance imaging (T2 weighted) at the midline section.

Table 1. Clinical characteristic of study subjects.*

Variables	Risk Groups			*P* Value
	Low	Intermediate	High	
No. of patients	47	80	57	
Age, years	70.10 ± 6.04	69.68 ± 6.39	68.07 ± 5.53	.177
Prostate volume, cm^3	40.40 ± 24.22	42.29 ± 22.55	48.02 ± 28.33	.250
T-zone volume, cm^3	18.76 ± 15.27	21.49 ± 19.10	25.02 ± 21.46	.242
Initial PSA, ng/mL	6.91 ± 2.87	12.47 ± 4.25	25.15 ± 11.49	.242
BMI, kg/m^2	25.51 ± 2.46	25.83 ± 2.16	25.74 ± 2.29	.142
SFT, cm	2.69 ± 0.83	2.78 ± 1.05	2.83 ± 1.03	.773
PFA, cm^2	64.44 ± 8.06	64.96 ± 9.75	65.69 ± 9.42	.019
AAT, cm	1.46 ± 0.55	1.42 ± 0.56	1.53 ± 0.67	.533
PAT, cm	0.98 ± 0.48	1.03 ± 0.43	1.03 ± 0.49	.800
APT, cm	19.54 ± 1.67	19.45 ± 1.76	19.87 ± 1.88	.387
Ratio (%)	87.31 ± 4.23	87.52 ± 3.84	87.65 ± 3.99	.025
Bleeding volume, mL	470.85 ± 289.64	452.62 ± 356.57	492.86 ± 463.92	.830
Duration of operation, min	214.77 ± 41.62	215.75 ± 40.09	219.65 ± 62.06	.853

The groups according to Kattan:[14] Low risk, ≤ T2a, Gleason score ≤ 6, iPSA < 10 ng/mL; Intermediate risk, T2b, Gleason score = 7, iPSA = 10-20 ng/mL; High risk, ≥ T2c, Gleason score ≥ 8, iPSA > 20 ng/mL.
Abbreviations: BMI, body mass index; SFT, subcutaneous fat thickness; PFA, periprostatic fat area; AAT, anterior abdominal fat thicknesses; PAT, posterior abdominal fat thicknesses; APT, anteroposterior diameter abdominal fat thicknesses; iPSA, initial prostate specific antigen.
Ratio was calculated as: the anterior plus posterior abdominal wall fat thickness subtracted from the anteroposterior diameter divided by the anteroposterior diameter.
* Data are presented as mean ± SD.

All statistic were performed by the Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 13.0 with statistical significance being defined as *P* values < .05.

RESULTS

Baseline Clinical Characteristics and Different Fat Measurements

According to Kattan[14] we stratified the patients into three groups. The clinical and pathologic characteristics were summarizes in **Table 1**. The median age, prostate volume, T-zone volume, bleeding volume and duration of operation had no significant differences among three groups (*P* > .05). BMI at the time of RRP was 25.51 ± 2.46, 25.83 ± 2.16 and 25.74 ± 2.29 kg/m^2, respectively (*P* = .142). The PFA and the ratio showed statistically significant difference between three groups (*P* = .019 and *P* = .025, respectively).

Table 2 demonstrates the difference of clinical stage and Gleason score between preoperative and postoperative phase. In clinical stage, the PFA and ratio showed a statistically significant difference (*P* = .014 and *P* = .037, respectively). In terms of Gleason score, nothing but PFA was found to have significant difference between two groups (*P* = .017). Moreover, the prostate volume and T-zone volume have statistically significant difference (*P* = .049 and *P* = .020, respectively).

The difference in bleeding volume and duration of operation are shown in **Table 3**. During operation, patients with bleeding volume over 450 mL were significantly older (*P* = .022) and had more dispose in periprostatic area (Ratio: 88.46 ± 3.00 vs. 86.95 ± 4.36, *P* = .013). The PAT, anteroposterior abdominal fat thickness (APT) and ratio was significantly higher in the group with operation time > 210 min (*P* = .015, *P* = .041 and *P* = .042, respectively).

Logistic regression analysis which adjusted for age (**Table 4**) revealed a statistically significant association between the PFA, the ratio and the risk of having higher-risk disease (*P* = 0.031 and *P* = 0.024, respectively).

DISCUSSION

In recent years, the relationship between obesity and cancer has drawn significant academic interests. Epidemiological studies have demonstrated that obesity is a risk factor of breast, endometrium, kidney and gallbladder cancers, but its role in PCA etiology remains elusive.[3,5,15]. Obesity is often assessed by BMI, which comes from physical measurement or self-reported height and weight. However, the BMI, which is a marker for overall obesity, cannot distinguish between adiposity and lean body mass, particularly in men with greater muscle mass, nor does it reflect fat distribution. Therefore, the link between BMI and PCa is controversial in many studies.[16-19] In our research, no association between BMI and PCa risk was revealed, and BMI was not an independent risk factor for PCa aggressiveness.

Abdominal adiposity or periprostatic adiposity has been found to precisely reflect the association between obesity and PCa in recent years.[20-22] Although abdominal fat make up only 10% of total body fat, it is metabolically more active than subcutaneous or peripheral fat. Furthermore, periprostatic fat is associated with fluctuation in levels of several hormones, including insulin, testosterone, estrogen, sex hormone binding globulin, and leptin which play a significant role in the biology of Pca.[23,24] The leptin, a cytokine produced by white adipose tissue, plays a critical role in the regulation of body weight by inhibit-

Table 2. The difference in clinical stage and Gleason score between preoperation and postoperation.*

	Clinical Stage			Gleason Score		
	Difference	No Difference	*P* Value	Difference	No Difference	*P* Value
No. of patients (%)	71 (38.59)	113 (61.41)	NS	82 (44.57)	102 (55.43)	NS
Age, years	68.39 ± 6.37	69.84 ± 5.77	.116	68.96 ± 6.37	68.55 ± 5.84	517
Prostate volume, cm^3	44.47 ± 27.02	43.69 ± 23.81	.839	46.83 ± 27.33	39.56 ± 21.08	.049
T-zone volume, cm^3	22.09 ± 17.40	22.20 ± 20.31	.971	24.81 ± 22.08	18.25 ± 13.69	.020
Initial PSA, ng/mL	15.22 ± 8.59	14.83 ± 10.97	.800	13.98 ± 9.41	15.78 ± 10.57	.231
BMI, kg/m^2	25.13 ± 2.62	24.92 ± 2.37	.451	25.36 ± 3.12	25.41 ± 2.78	.576
SFT, cm	2.77 ± 1.05	2.77 ± 0.96	.997	2.71 ± 0.99	2.82 ± 0.99	.46
PFA, cm^2	65.26 ± 9.03	64.44 ± 9.62	.014	65.29 ± 9.57	63.75 ± 8.78	.017
AAT, cm	1.50 ± 0.59	1.43 ± 0.60	.387	1.44 ± 0.58	1.48 ± 0.60	.626
PAT, cm	1.03 ± 0.51	1.03 ± 0.43	.951	0.99 ± 0.46	1.04 ± 0.46	.497
APT, cm	19.73 ± 1.69	19.36 ± 1.89	.169	19.39 ± 1.72	19.77 ± 1.81	.145
Ratio (%)	87.52 ± 3.97	87.30 ± 3.96	.037	87.59 ± 4.15	87.40 ± 3.86	.150

Abbreviations: BMI, body mass index; SFT, subcutaneous fat thickness; PFA, periprostatic fat area; AAT, anterior abdominal fat thicknesses; PAT, posterior abdominal fat thicknesses; APT, anteroposterior diameter abdominal fat thicknesses.
Ratio was calculated as: the anterior plus posterior abdominal wall fat thickness subtracted from the anteroposterior diameter divided by the anteroposterior diameter.
* Data are presented as mean ± SD.

ing food intake and stimulating energy expenditure. In addition, leptin influences cellular differentiation and progression in PCa cells, further increasing PCa risk and stage.[25] The waist circumference (WC) and waist-to-hip ratio (WHR) are commonly used to define the extent of abdominal obesity.[26,27] In a large cohort study among 129,502 men[28] waist circumference and waist-to-hip ratio were positively association with advanced disease among men with a lower BMI.

Although WC can be measured easily, it estimates abdominal adipose tissue imprecisely. MRI is an excellent technique to distinguish and quantify subcutaneous and periprostatic fat. The benefits of MRI over other adipose imaging methods are accelerated acquisition, quantitative reconstruction and physiologically based threshold, all of which are required for accurate adipose tissue measurements.[13,29] In addition, the patient with PCa should be undergo MRI before surgery in order to assess tumor stage, so fat measurement by MRI cannot increase the economic burden of patients. In our study, MRI is proved to be a precise way to measure the periprostatic adiposity. We could clearly distinguish the fat, muscle and bone. By measurement of abdominal adipose distribution, reflecting the periprostatic fat, we have found a close association between periprostatic adiposity (the PFA and ratio) and PCa aggressiveness as well as PCa risk. However, the SFT, PAT and AAT, reflecting the peripheral fat, have showed no statistically significant differences.

It is important to assess tumor stage and grade more accurately in the preoperative phase, because it would affect the selection of treatment of the localized PCa and evaluation of the patient's prognosis. The incidence of under staging was 38.6% in our study, which lies between 24% and 60% previously reported in large single institution studies.[30] The incidence of discordance in Gleason score between biopsy and RRP was 44.6%, which was similar to that reported by several researchers.[31] Previous studies have shown that preoperative serum PSA level, the percent of positive systematic prostate biopsies and the interval between biopsy and RRP are the most important predictors of under staging and under grading. In our study, the tumor volume affects the concordance in Gleason score between biopsy and RRP, probably owing to the association between the percentage of positive systematic biopsies and tumor volume.[30,32] Our study is to date only one that analyzed association between periprostatic adiposity and the discordance of staging or grading before and after surgery. These findings might be important and may indicate that obese patients require different treatment considerations. Several explanations could be given for the reason. First, the periprostatic fat tissue could affect the

Table 3. The difference in bleeding volume and duration of operation.*

	Bleeding Volume			Duration of Operation		
	≤ 450 mL	> 450 mL	*P* Value	≤ 210 min	> 210 min	*P* Value
No. of patients	118	66	NS	102	82	NS
Age, years	68.53 ± 6.31	70.65 ± 5.39	.022	69.29 ± 6.14	69.28 ± 6.02	.988
Prostate volume, cm^3	42.35 ± 24.09	45.80 ± 26.43	.368	42.23 ± 26.13	45.27 ± 23.44	.412
T-zone volume, cm^3	20.43 ± 17.67	24.50 ± 21.16	.165	20.03 ± 18.60	24.19 ± 19.45	.142
Initial PSA, ng/mL	15.22 ± 10.39	14.55 ± 9.56	.670	14.45 ± 9.62	15.63 ± 10.65	.432
BMI, kg/m^2	24.87 ± 2.61	25.08 ± 2.41	.098	25.28 ± 2.26	25.17 ± 2.19	.127
SFT, cm	2.80 ± 1.08	2.73 ± 0.79	.668	2.69 ± 0.91	2.87 ± 1.07	.214
PFA, cm^2	65.04 ± 9.61	65.06 ± 8.51	.998	65.12 ± 9.39	64.97 ± 9.03	.916
AAT, cm	1.51 ± 0.67	1.38 ± 0.41	.163	1.40 ± 0.50	1.53 ± 0.68	.125
PAT, cm	1.07 ± 0.48	0.93 ± 0.40	.055	0.94 ± 0.42	1.11 ± 0.50	.015
APT, cm	19.43 ± 1.80	19.90 ± 1.70	.085	19.36 ± 1.77	19.89 ± 1.75	.041
Ratio (%)	86.95 ± 4.36	88.46 ± 3.00	.013	86.82 ± 4.54	88.02 ± 3.40	.042

Abbreviations: BMI, body mass index; SFT, subcutaneous fat thickness; PFA, periprostatic fat area; AAT, anterior abdominal fat thicknesses; PAT, posterior abdominal fat thicknesses; APT, anteroposterior diameter abdominal fat thicknesses; NS, not significant.
Ratio was calculated as: the anterior plus posterior abdominal wall fat thickness subtracted from the anteroposterior diameter divided by the anteroposterior diameter.
* Data are presented as mean ± SD.

judgment of extracapsular disease extension, seminal vesicle invasion or lymph node metastasis on MRI. Second, the periprostatic fat tissue could influence the positive outcome of systematic prostate biopsies. Finally, the periprostatic fat tissue producing cytokine might change the level of preoperative serum PSA, which has been proved to be associated with under staging and under grading in preoperative phase. In addition, our study has showed that the periprostatic fat could increase the difficulty and risk of operation (bleeding volume and duration of operation), probably because the periprostatic fat is rich in vascular.

The limitations of our study are as follow: first, this is a retrospective review of prospectively maintained database, secondly, our study did not perform other anthropometric measurements such as waist circumference, waist-to-hip ratio and percentage of body fat. Thirdly, different risk group definition could lead to different outcome. The reason why we choose the Kattan,[14] is the treatment and prognosis of the localized PCa assessed according to it in China. Finally, the direct measurement of fat area and thickness on preoperative MRI could result in the very small observed difference in the percentage of periprostate fat, because it includes muscle, spinal fluid and bowel as well as periprostatic fat within the calculation. Despite these limitations,

Table 4. Logistic regression analysis of factors predicting high-risk disease.*

Variables	Odds Ratio (95% CI)	*P* Value
Prostate volume, cm^3	1.01 (0.97-1.05)	.599
T-zone volume, cm^3	1.01 (0.96-1.06)	.800
BMI, kg/m^2	0.98 (0.63-1.58)	.485
SFT, cm	0.74 (0.44-1.22)	.234
PFA, cm^2	1.00 (0.96-1.04)	.024
AAT, cm	1.06 (0.96-1.15)	.287
PAT, cm	1.08 (1.02-1.21)	.261
APT, cm	1.14 (1.02-1.24)	.091
Ratio (%)	1.05 (1.03-1.08)	.031

Abbreviations: BMI, body mass index; SFT, subcutaneous fat thickness; PFA, periprostatic fat area; AAT, anterior abdominal fat thicknesses; PAT, posterior abdominal fat thicknesses; APT, anteroposterior diameter abdominal fat thicknesses; CI, confidence interval.
Ratio was calculated as: the anterior plus posterior abdominal wall fat thickness subtracted from the anteroposterior diameter divided by the anteroposterior diameter.
* Data are presented as mean (interquartile range).

the result still remained significance. In further study, we should apply quantitative method of MRI to measure the periprostatic fat, in order to precisely reveal the association between periprostatic adiposity and aggressiveness of PCa. In addition, we should perform animal experiment, in order to find the mechanism that the periprostate adiposity can influence aggressiveness of PCa.

CONCLUSION

The periprostatic adiposity can not only affects the aggressiveness, but also has effect in accurate evaluation of stage and grade of PCa. In addition, the periprostate fat could increase the difficulty and risk of RRP.

CONFLICT OF INTEREST

None declared.

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