ORIGINAL ARTICLE

Periprostatic fat measured on computed tomography as a marker for prostate cancer aggressiveness

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Abstract

Objective Several reports found that obesity was associated with prostate cancer (PC) aggressiveness among men treated with radical prostatectomy or radiotherapy. Studies concerning this issue have basically relied on body mass index (BMI), as a marker for general obesity. Because visceral fat is the most metabolic active fat, we sought to evaluate if periprostatic fat measured on a computed tomography (CT) is a better marker than BMI to predict PC aggressiveness in a Dutch population who underwent brachytherapy for localized PC.

Patients and methods Of the 902 patients who underwent brachytherapy, 725 CT scans were available. Subcutaneous fat thickness (CFT), periprostatic fat area (cm^2) and fat-density (%) were determined on the CT scan. Patients were stratified into three groups: <25, 25–75 and >75 percentile of the fat-density. Associations between the three fat-density subgroups and BMI and PC aggressiveness were examined.

Results 237 patients were classified as having normal weight (37.2%), 320 as overweight (50.2%) and 80 as obese (12.6%). There was a strong significant association between BMI and fat-density and CFT. The strongest correlation was seen between BMI and CFT (Pearson *r* coefficient = 0.71). Logistic regression analysis revealed no statistically significant association between the different fat measurements and the risk of having a high-risk disease.

Conclusions Periprostatic fat and fat-density as measured with CT were not correlated with PC aggressiveness in patients receiving brachytherapy. However, 31% of the patients with a normal BMI had a fat-density of >75 percentile of the periprostatic fat-density.

Keywords Obesity · Visceral fat · Prostate cancer · Body mass index (BMI) · Brachytherapy

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Introduction

Obesity and prostate cancer (PC) are two major health concerns. On one hand, obesity is a rapidly growing worldwide epidemic and it increases the risk of several chronic diseases and certain cancers [1, 2]. On the other hand, PC is diagnosed more often in the prostate-specific antigen (PSA) era and the disease is often diagnosed at a localized stage suitable for curative treatment [3].

The relationship between obesity and PC is debated, with studies finding an inverse, a linear correlation with PC, or no relation at all [4–6]. However, several studies found a link between obesity and disease aggressiveness [7–9].

Recently, the classical perception of adipose tissue as a storage place of fatty acids has been replaced by the notion that adipose tissue produces a large number of hormones and cytokines, e.g., tumour necrosis factor-α, interleukin-6,

leptin and adiponectin [10]. The exact role of these cytokines in prostate carcinogenesis, however, is not known. Most of the studies that investigated the role of obesity on PC used body mass index (BMI, the weight in kilograms divided by the squared height in meters) as a marker of general obesity. Although there is a strong correlation between BMI and waist-circumference (WCF), the most metabolic active fat is the abdominal visceral fat and a better way to measure this is by waist-hip ratio or WCF. Therefore, WCF as an indicator of abdominal fat may be a better predictor for PC risk than BMI alone, especially in men with a low BMI. Computed tomography (CT) is another technique which measures visceral fat even more accurately [11, 12].

The aim of this study was to investigate whether periprostatic fat, measured on a CT, is a better marker for PC aggressiveness in patients who underwent brachytherapy for localized PC compared to BMI. We also evaluated the relation between BMI and different fat measurements. To the best of our knowledge such a study has never been performed.

Patients and methods

Patients

Between April 2004 and August 2008, 902 patients with biopsy-proven localized PC (stage cT1 or cT2) were treated with transrectal ultrasonography guided transperineal permanent mono brachytherapy at the department of Radiotherapy, University Medical Center Utrecht, The Netherlands. Due to the very short follow-up of this cohort of men we only focused on PC baseline characteristics. Patients underwent clinical staging by medical history, digital rectal examination and serum PSA measurement. Bone scans were obtained and pelvic lymph node dissection was performed when clinically indicated. A CT was performed 1 day after the brachytherapy to determine specific dose constraints. The CT was not performed in 153 patients and in 24 patients the quality of the CT was poor due to hip prostheses. This resulted in a study population of 725 men.

Because different risk classifications are used in the literature we decided to use two different risk classifications, one according to Ash et al. [13] and the other according to D'Amico et al. [14]. Tumour stage was described according to the 2002, TNM, American Joint Committee on Cancer system.

Fat measurement

Preoperative height and weight data were collected retrospectively by reviewing anaesthesia records. The BMI
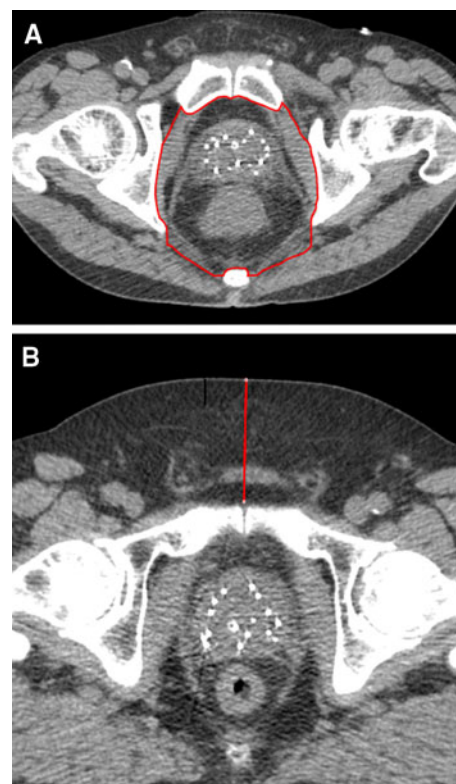

Fig. 1 Images demonstrate our method for determining visceral fat distribution and subcutaneous fat thickness on a CT scan. **a** Transverse section is made at the level of the caput femoris and greater trochanter of the femur. The *red line*, outlines the total contour area (cm^2), in which attenuation is measured. The line is drawn at the back side of the pubic bone, lateral border of obturatorius internus muscle, anterior side of the gluteus maximus muscle and coccyx bone. Within the region of interest the periprostatic fat area (cm^2) and the fat-density (%) was calculated. **b** Transverse section is made at the level of superior pubic ramus. The *red line* outlines the subcutaneous fat thickness by which the distance between the skin and pubic bone is measured. (cm)

(kg/m^2) was calculated and stratified into three groups according to the WHO, i.e. normal weight (<25), overweight (25–30) and obese (≥30). Only one patient had a BMI value of <18.5 kg/m^2, this patient was included in the normal weight group. The CT's were acquired on a single slice CT (Aura, Philips Medical Systems, Best, The Netherlands), and had an in-plane slice resolution of 0.49×0.49 mm with a slice thickness of 3 mm. We used an in-house developed software tool for delineation of the pelvic fat region and the measurement of the subcutaneous fat thickness (CFT, see Fig. 1) [15].

Because there are no comparable studies available we chose to delineate along established lines (see Fig. 1). The fat contained within the delineated contours of the CT, is segmented by thresholding on the Hounsfield Units (HU). We differentiated between fat (−190 to −30 HU), air (<−500 HU) and other soft tissue types [16]. Since the delineated contours did not contain bony structures, we did

not include a threshold for segmenting the bones separately. The total contour area (cm^2) was calculated by the total number of voxels within the contour minus the number of air voxels and the periprostatic fat area (cm^2) by just counting 'fat' voxels within the total contour area. The fat-density (%) was calculated by dividing periprostatic fat by the total contour area.

Patients were stratified into three groups: <25 percentile (group 1), between 25 and 75 percentile (group 2) and >75 percentile (group 3) of the fat-density.

Statistical analysis

Associations between the predefined three fat-density subgroups and clinical or pathological characteristics were examined by Chi-square tests in case of categorical characteristics and Kruskal–Wallis tests in case of continuous characteristics. The Pearson correlation coefficient was used to quantify correlations between BMI and the different fat measurements. Binary logistic regression analyses were performed to evaluate the independent effect of each variable on the risk of having high-risk disease versus low or intermediate risk (according to Ash et al. [13] and D'Amico et al. [14]).

Differences were considered to be statistically significant if $p < 0.05$. Data were analysed using SPSS for Windows (version 15.0).

Results

The median age (range), BMI and fat-density at the time of brachytherapy was 66 years (45–81), 25.8 kg/m^2 (17.6–56.8) and 31.8% (10.0–52.2), respectively. In 88 (12%) patients the BMI was not available. In all, 237 patients were classified as having normal weight (37.2%), 320 as overweight (50.2%) and 80 as obese (12.6%). Table 1 summarizes the clinical and pathological characteristics of the study population stratified by fat-density.

Patients in group 3 were significantly older. The median prostate volume was statistically different between the three groups but the differences were not clinically relevant. A clear significant association was seen between the fat-density groups and BMI, CFT and periprostatic fat. Figure 2 shows the correlation between BMI and the different fat measurements. The strongest correlation was seen between BMI and CFT (Pearson r coefficient = 0.71, $p < 0.001$).

Logistic regression analysis revealed no statistically significant association between the different fat measurements and the risk of having high-risk disease (Table 2). Only age was significantly associated with increased risk of having a high-risk disease, however in the multivariable analysis (data not shown) this significance disappeared.

Discussion

The urologist and radiation oncologist will be confronted more frequently with obese patients having a localized PC. Although the association between obesity and the risk of PC risk is controversial [4, 17, 18], a stronger link between obesity and increased risk for higher pathologic grade and higher rates of biochemical recurrence (BCR) compared with normal weight patients was seen in several studies [9, 19, 20]. Of note, all these studies were done in the USA. We conducted a study in The Netherlands where we evaluated 1,302 patients who underwent a radical prostatectomy. In that study BMI did not appear to have any prognostic value for BCR or worse pathologic features [21]. Same conclusions were drawn by another European study by Pfitzenmaier et al. [22]. In contrast with the USA, where 30% of the population is obese, only 9% to 14% of the European population was obese [23, 24]. Thereby, obese patients are less obese than the obese men in the USA and a relatively large proportion of the USA population consists of Afro-Americans who are more prone to be obese and more frequently have aggressive tumours compared with white men.

A question which may rise: are we measuring obesity on the right way? In most studies investigating obesity in relation to prostate aggressiveness and BCR, BMI is used as a criterion for general obesity. The most metabolic active fat however, is the abdominal visceral fat. WCF, as an indicator of abdominal obesity may be a better predictor of risk of more aggressive PC than BMI, especially in individuals with a lower BMI. Visceral fat is the most metabolic active fat and produce different kind of adipokines. Obesity is associated with increased levels of several adipokines and studies reported a link between the level of adipokines and aggressive PC [25–27].

A large study by the European Prospective Investigation into Cancer and Nutrition group concluded that once general obesity was adjusted for abdominal fat distribution it was positively associated with the risk of death. This association tended to be stronger among participants with a lower BMI [28]. In a large prospective cohort of 148,372 men, Pischon et al. [29] found that higher WCF was associated with increased risk of advanced PC and high-grade PC among individuals with lower BMI. The relative risk of advanced PC was 1.06 (95% CI 1.01–1.10) per 5-cm-larger WCF. Same conclusions were drawn in a prospective Swedish study [30]. These data suggest that especially abdominal adiposity may be associated with an increased risk of advanced PC and WCF is a better way to measure obesity.

Visceral fat can affect both the lean and obese and is more metabolically active than subcutaneous fat. By measuring the WCF the discrepancy between thin outside

Table 1 Baseline characteristics

	Group 1 N = 181 <25 percentile	Group 2 N = 363 25–75 percentile	Group 3 N = 181 >75 percentile	p value
Median (IQR)				
Age, years	64.0 (59.0–68.0)	66.0 (61.0–70.0)	68.0 (63.0–71.0)	<0.001[a]
Follow up, months	18.0 (11.0–30.5)	16.5 (11.0–28.8)	18.0 (11.0–29.0)	0.97[a]
Prostate volume, cm^3	37.0 (30.0–44.0)	34.3 (28.0–41.0)	34.0 (27.8–40.0)	0.02[a]
Initial PSA, ng/ml	8.4 (6.3–12.2)	8.5 (6.3–11.7)	9.0 (6.9–12.5)	0.20[a]
BMI, kg/m^2	24.5 (22.8–26.4)	26.0 (24.6–27.8)	26.8 (24.8–29.4)	<0.001[a]
Total periprostatic fat, cm^2	23.7 (19.3–25.9)	31.3 (28.0–34.5)	40.5 (36.9–43.5)	<0.001[a]
Fat density, %	24.0 (21.3–26.0)	31.8 (29.2–33.9)	38.5 (37.1–40.9)	
Subcutaneous fat, cm	3.9 (3.2–4.7)	4.7 (3.9–5.5)	5.1 (4.1–6.1)	<0.001[a]
N (%)				
WHO-classification				
Normal weight	88 (57.9)	109 (33.5)	40 (25.0)	<0.001[b]
Overweight	60 (39.5)	175 (53.8)	85 (47.0)	
Obesity	4 (2.6)	41 (12.6)	35 (19.3)	
Clinical stage				
T1	112 (61.9)	252 (69.4)	119 (66.1)	0.21[b]
T2	69 (38.1)	111 (30.6)	61 (33.9)	
Grade				
Low	111 (61.3)	231 (64.2)	114 (64.0)	0.46[b]
Intermediate	70 (38.7)	129 (35.8)	64 (36.0)	
Ash risk group				
Low	69 (38.1)	141 (39.2)	67 (37.4)	0.96[b]
Intermediate	76 (42.0)	154 (42.8)	75 (41.9)	
High	36 (19.9)	65 (18.1)	37 (20.7)	
D'Amico risk group				
Low	72 (39.8)	145 (39.9)	70 (38.7)	0.40[b]
Intermediate	99 (54.7)	200 (55.1)	95 (52.5)	
High	10 (5.5)	14 (3.9)	12 (6.6)	
Lymph node dissection				
Yes	7 (3.9)	5 (1.4)	3 (1.7)	0.14[b]
No	174 (96.1)	358 (98.6)	178 (98.3)	

Patients were stratified by fat density

IQR interquartile range

[a] Kruskal–Wallis-test

[b] χ^2-Test

(subcutaneous fat) and thick inside (visceral fat) cannot be made. A CT scan can distinguish between these two "layers". In our study we measured the visceral and subcutaneous fat on a CT to identify if one of these parameters is a better marker for tumour characteristics compared with BMI. Possible explanations for the lack of this correlation can be, first, there has been less enthusiasm for the use of brachytherapy in men with high-risk disease. These patients might be very well selected which can be an explanation for these negative findings. Second, the fat measurement was performed on one cross-sectional scan. Theoretically the accuracy of the fat measurement could be improved by measuring the fat content on more cross-sectional scans (volume measurement). However, in this study the selection bias of the brachytherapy patients is probable more important than the technique of fat measurement. Third, it is possible that the fat around the intra-abdominal organs are more metabolic active than the periprostatic fat. It would be interesting to measure the fat around the intra-abdominal organs. However, it was not possible to measure the intra-abdominal fat distribution and body circumference at the level of the umbilicus. Fourth, it would be very interesting to correlate the BMI and fat density with clinical outcome like BCR or disease specific survival instead of pre-treatment Gleason score, because these are better prognostic markers for PC aggressiveness. However, in this study the follow-up was much too short (mean < 20 months) to evaluate these outcomes.

Our analysis showed a correlation between BMI and CFT and periprostatic fat-density. The correlation between
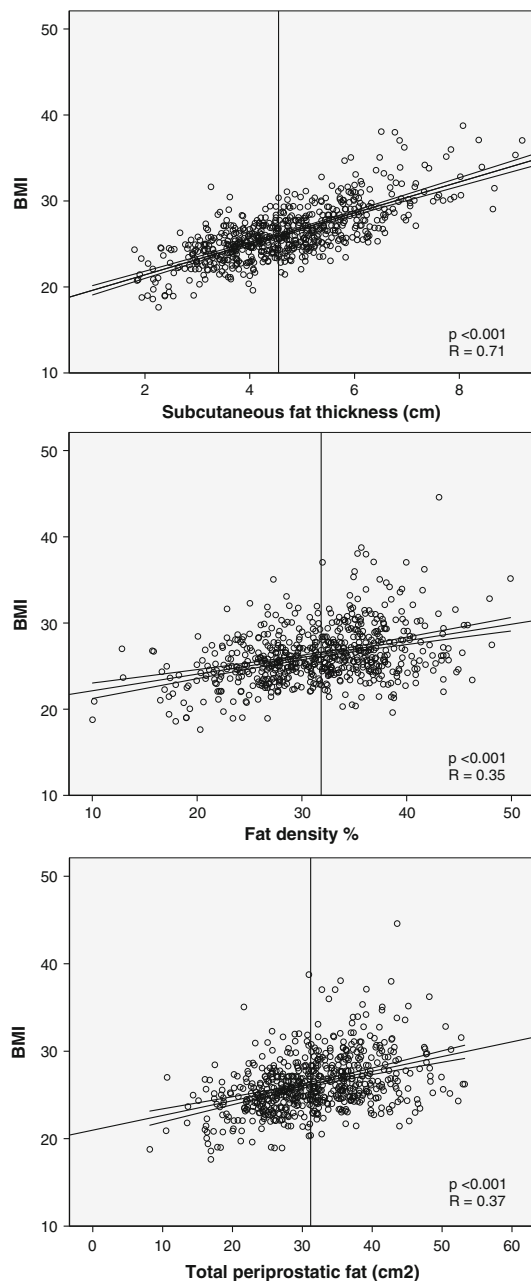
Fig. 2 Correlation between body mass index and different fat measurements. The linear regressive line is shown with 95% CI. The *vertical line* represents the median

Table 2 Univariable logistic regression analysis of factors predicting high-risk disease

Variable	Odds ratio (95% CI)	p value
According to ash		
Age	1.07 (1.03–1.11)	<0.001
Prostate volume	1.00 (0.98–1.02)	0.68
BMI (continuous)	0.97 (0.92–1.03)	0.37
BMI		
<25 kg/m^2	1	
25–30 kg/m^2	0.80 (0.53–1.21)	0.29
≥30 kg/m^2	0.51 (0.24–1.06)	0.07
Fat density (continuous)	1.00 (0.97–1.03)	0.94
Fat density		
Group 1	1	
Group 2	0.89 (0.56–1.40)	0.61
Group 3	1.05 (0.63–1.76)	0.85
Subcutaneous fat thickness	0.96 (0.85–1.10)	0.56
Periprostatic fat area	1.00 (0.976–1.02)	0.76
According to D'Amico		
Age	1.06 (1.00–1.13)	0.06
Prostate volume	1.01 (0.97–1.05)	0.57
BMI (continuous)	0.89 (0.79–1.01)	0.09
BMI		
<25 kg/m^2	1	
25–30 kg/m^2	0.63 (0.29–1.34)	0.23
≥30 kg/m^2	0.40 (0.86–1.73)	0.21
Fat density (continuous)	1.00 (0.95–1.06)	0.94
Fat density		
Group 1	1	
Group 2	0.69 (0.30–1.59)	0.39
Group 3	1.24 (0.52–2.96)	0.62
Subcutaneous fat thickness	0.80 (0.95–1.05)	0.11
Periprostatic fat area	1.00 (0.96–1.05)	0.93

BMI and CFT was much stronger than BMI and fat density. Interestingly, 31% of the patients with a normal BMI had a fat-density >75 percentile, compared with only 10% of the obese patients who had a fat-density <25 percentile of the fat-density. Thus, measurements on the outside of the body (BMI) do not always reflect the inner fat distribution measured on a CT scan. It is attractive to speculate that when this study was performed in a group of patients with more high-grade tumours, e.g. a group treated with external radiotherapy, these parameters could be a better prognostic marker for tumour characteristics than BMI, especially in patients with a low BMI. However, further studies are needed to identify the real value of these fat measurements on CT as correlates with PC aggressiveness.

Conclusion

Periprostatic fat and fat-density were not of any value to predict PC aggressiveness in patients receiving brachytherapy. However, 31% of the patients with a normal BMI had a fat-density of >75 percentile of the periprostatic fat-density. More studies, including patients who have more aggressive PC, are needed to identify the true value of fat measurement on a CT as a correlate of PC aggressiveness and/or predictor of treatment failure.

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