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Correlation of Periprostatic Fat Thickness Measured on Multiparametric MRI with Prostate Cancer Aggressiveness

Multiparametrik Manyetik Rezonans Görüntülemede Ölçülen Periprostatik Yağ Kalınlığının Prostat Kanseri Agresifliği ile Korelasyonu

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Abstract

Objective: In this study, the relationship between periprostatic and subcutaneous fat thickness on magnetic resonans imaging (MRI) and Gleason scores (GS) was retrospectively evaluated.
Materials and Methods: Fifty-one patients who underwent MRI before application of MRI fusion biyopsies were included 63,57±8,5 (45-88) years in this study. On midsagittal T2-weighted images, the thickness of subcutaneous and periprostatic fat was calculated as the vertical distance from the pubic symphysis both to the skin and to the prostate, respectively.
Results: The mean subcutaneous fat thickness (SCFT) and periprostatic fat thickness (PPFT) were 17.38±13.02 mm and 5.64±3.89 mm, respectively. A positive correlation was found between GS and PPFT (p<0.001), SCFT (p<0.001), body mass index (BMI) (p<0.001), prostate spesific antigen (PSA) (p=0.002) and PSA density (p<0.001). In multivariate analysis, only PPFT was found to be statistically significant in predicting GS ≥7 (p=0.005). It has been shown that the risk of detecting GS ≥7 prostate cancer increases 8.9 times with one mm increase in PPFT values.
Conclusion: Periprostatic fat tissue thickness can be used as an independent predictive factor in foreseeing prostate cancer aggressiveness before application of biopsy or radical prostatectomy.

Keywords: magnetic resonance imaging, periprostatic fat thickness, prostate cancer, Gleason score

Öz

Amaç: Bu çalışmanın amacı, prostat kanserinin manyetik rezonans görüntülemede (MRG) ölçülen periprostatik ve subkutan yağ kalınlığı ile Gleason skoru (GS) arasındaki ilişkiyi retrospektif olarak değerlendirmek.
Gereçler ve Yöntemler: Bu çalışmaya MRG füzyon biyopsisi öncesi MRG yapılan 51 hasta dahil edildi [63,57±8,51 (45 - 88) yıl)]. Midsagital T2 ağırlıklı görüntülerinde, subkutan ve periprostatik yağ kalınlığı, sırasıyla pubik simfizden cilde ve prostata olan dikey mesafe olarak hesaplandı.
Bulgular: Ortalama subkutanöz yağ kalınlığı (SCFT) ve periprostatik yağ kalınlıkları (PPFT) sırasıyla 17.38±13.02 mm ve 5.64±3.89 mm idi. Gleason skoru ile PPFT (p<0,001), SCFT (p<0,001), vücut kitle indeksi (VKİ) (p<0,001), prostat spesifik antijen (PSA) (p=0,002) ve PSA yoğunluğu arasında pozitif korelasyon bulundu (p<0.001). Çok değişkenli analizde GS ≥7'yi öngörmede sadece PPFT değeri istatistiksel olarak anlamlı bulundu (p=0,005). PPFT değerindeki 1 mm'lik artışla GS ≥7 prostat kanserini tespit etme riskinin 8,9 kat arttığı gösterilmiştir.
Sonuç: Periprostatik yağ dokusu kalınlığı, biyopsi veya radikal prostatektomi öncesi prostat kanseri agresifliğini tahmin etmede bağımsız bir prediktif faktör olarak kullanılabilir.

Anahtar kelimeler: manyetik rezonans görüntüleme, periprostatik yağ kalınlığı, prostat kanseri, Gleason skoru

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Introduction

In developed countries, prostate cancer (PCa) is the most commonly diagnosed cancer in men and is the second-most common cancer overall. Recent epidemiologic studies have found a correlation between obesity and a rise in the incidence of various cancers. Obesity is linked to aggressiveness of PCa, a poor response to treatment, and a high risk of cancer- specific mortality [1,2].

Increased periprostatic fat tissue contributes to the development and progression of PCa which may be due to the disruption of adipokines (such as adiponectin, leptin, CCL7, etc.) secreted from enlarged periprostatic fat tissue [3,4]. Furthermore, increased periprostatic fat thickness (PPFT) is related to a higher stage or grade of PCa [5,6]. Magnetic resonance imaging (MRI) measures PPFT and visceral fat at multiple levels of the body. As a result, we believe that the measurement of PPFT with MRI could be a useful diagnostic tool for PCa. However, few studies have been conducted on the utility of PPFT in detecting PCa or clinically significant PCa (Gleason score 3+4 or higher).

In this study, we aim to investigate the relationship between PPFT on MRI and GS.

Materials and Methods

Patients

Between July 2019 and July 2020, a total of 72 patients who underwent MRI-fusion prostate biopsy were investigated. Patients who had undergone an MRI screening using standards compatible with PI-RADSv2.1 (The Prostate Imaging Reporting and Data System), an MRI-guided biopsy and an appropriate post-biopsy pathology report were included in this study. A total of 21 patients without a high-resolution diffusion-weighted prostate MRI (n=5), and clinical and pathological information (n=6) who had previously undergone prostate biopsy (n=5), and adjuvant deprivation therapy (n=5) before biopsy were excluded from the study. As a result, a total of 51 patients were included in the study. Ethics approval was obtained for this study (Ethics Committee of University of Acibadem 2022-14/38).

Clinical and Pathological Data

Before the MRI-fusion biopsy, we investigated the patients' medical records to assess clinical and pathological information about parameters such as height, weight, BMI, PSA, PSA density, and GS. Patients were classified as low (GS=6) and high (GS ≥7) grade PCa.

MRI Protocol

A 3.0 T MRI scan Siemens Skyra system (Siemens Healthcare GmbH, Erlangen, Germany) with an abdominal eight-channel surface phased array coil was used for imaging. Transverse, sagittal, and coronal T2WI images, DWI images with multiple b-values, and corresponding ADC maps were obtained for analysis. DCE images were obtained after intravenous injection of gadoteric acid (Dotarem®; Guerbet, France) at a dose of 0.1 mmol/kg/bwt and at a rate of 3 mL/sec by using an automatic injector.

Image Analysis

The radiologist scored lesions in MRI using PIRADS v2.1 without knowing the patients' clinical information. Images were scored following the PI-RADS v2.1 standards with T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging. In addition, prostate volumes were also measured by MRI.

Sagittal T2-weighted images were used to calculate the SCFT and PPFT. The shortest perpendicular distances in the midsagittal plane between the pubic symphysis and the skin and between the pubic symphysis and the prostate, respectively, were used to calculate SCFT, and PPFT (**Figures 1 and 2**). To avoid overestimating these measurements, the shortest vertical distance was used. The current measurement technique we employed had good repeatability and stability, allowing us to reduce measurement errors from various planes and prevent interference from morphological changes of periprostatic organs, including the bladder and rectum.

Statistical Analysis

To determine fitness to normal distribution patterns, frequency histograms were examined. Continuous data were presented as mean ± standard deviation (SD) and subjected to either the nonparametric Mann-Whitney U test or the Student's t test for analysis. The Pearson or Spearman correlation analyses were used to calculate correlations between continuous variables. The $p<0.05$ was accepted as statistically significant. SPSS 22.0 program was used in the analysis. Age, PSA, PSA density, prostate volume, PIRADS, PPFT, SCFT and BMI values were assessed with univariate and multivariate regression analysis to predict high-grade PCa (GS ≥7).

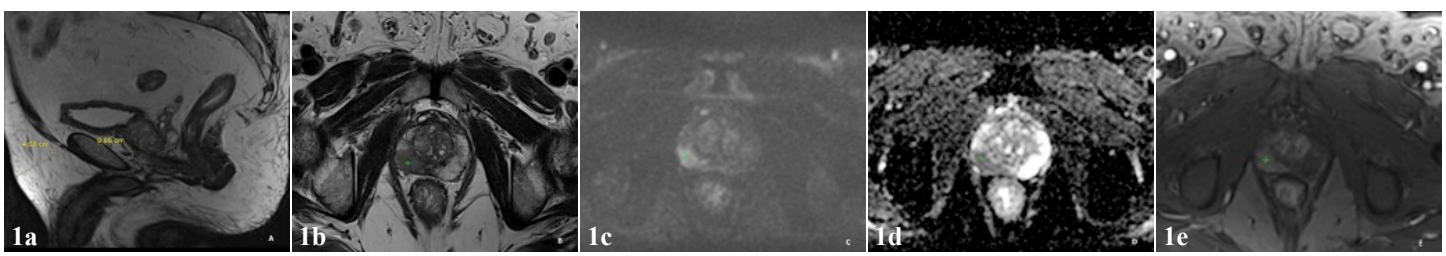

Figure 1. Multiparametric prostate MRI images of a 72-year-old patient with a PSA value of 8.53, prostate volume 33 cc and a Gleason score of 8 (4+4) by MRI fusion biopsy. **1a.** Periprostatic fat thickness (8.5 mm) and subcutaneous fat thickness measurements (46.8 mm) in the sagittal plane; **1b.** In axial T2W sequences, PIRADS 5 lesions with a diameter of 2 cm at the level of 9 at the level of the prostate midgland periferic zone; **1c.** Hyperintense appearance of the lesion on DWI; **1d.** Hypointense appearance in ADC mapping, **1e.** Contrast enhancement in the lesion in the arterial phase in perfusion dynamic contrast imaging

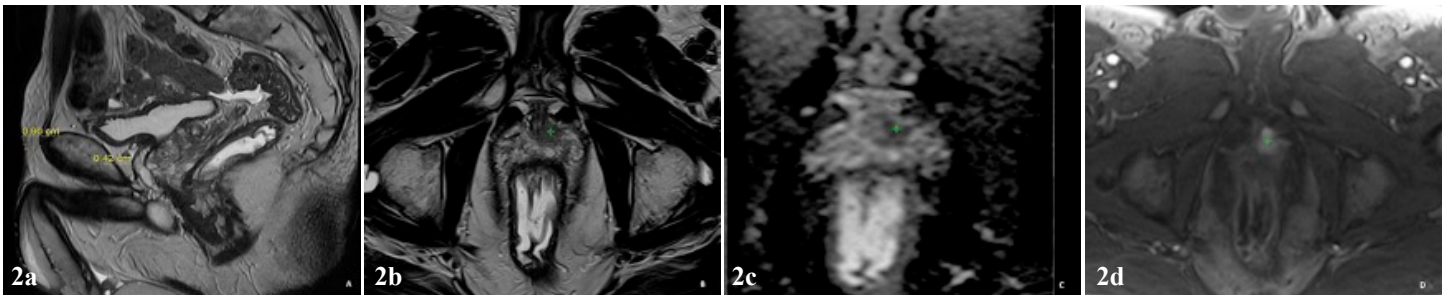

Figure 2. Multiparametric prostate MRI images of a 65-year-old patient with a PSA value of 4.4, prostate volume 28 cc and a Gleason score of 6 (3+3) by MRI fusion biopsy. **2a.** Periprostatic fat thickness (4.2 mm) and subcutaneous fat thickness (9 mm) measurements in the sagittal plane; **2b.** In axial T2W sequences, PIRADS 4 lesions with a diameter of 13 mm at the level of the prostate midgland; **2c.** Hypointense appearance in ADC mapping; **2d.** Contrast enhancement in the lesion in the arterial phase in perfusion dynamic contrast imaging

Results

Between July 2019 to July 2020, 51 patients (median age 63.57 years, range: 45-88) who underwent MRI-fusion biopsy were evaluated. The mean BMI of the patients was 25.00±4.649 kg/m^2 (range 19-38 kg/m^2). The mean PSA level was 10.65±14.461 ng/mL (range, 2–100 ng/mL). The mean PPFT and SCFT values were 5.64 ±3.89 (range 1-15 mm) and 17.38±13.02 mm (range 4-54 mm), respectively (**Table 1**).

Patients were classified as having low (GS=6: n=16: 31.4%) and high (GS ≥7: n=35: 68.6%) grade PCa. The patients' GSs were 3+3 (n=16), 3+4 (n=17), 4+3 (n=5), and ≥8 (n=13); 4+4 (n=7), 4+5 (n=4), 5+4 (n=1), and 5+5 (n=1). A significant difference was found between GS=6 and GS ≥7 patient groups in terms of PSA, PSA density, PIRADS score, BMI, PPFT, and SCFT values. There was no significant difference between the groups regarding age and prostate volume.

GS was found to be positively correlated with PPFT (p<0.001), SCFT (p<0.001), BMI (p<0.001), PSA (p=0.002), PSA density (p<0.001), and PIRADS (p<0.001). However, no significant correlation was found between age (p=0.065), prostate volume (p=0.426) and GS. Similarly, a positive correlation was detected between GS=6 and GS ≥7 groups, in terms of PPFT (p<0.001), SCFT (p<0.001), BMI (p<0.001), PSA (p=0.003), PSA density (p<0.001), and PIRADS (p=0.002) but any significant correlation was not found between groups in terms of age (p=0.204) and prostate volume (p=0.188).

In the univariate analysis, PSA, PSA density, PIRADS, PPFT, SCFT and BMI values were found to be statistically significant in predicting GS ≥7. However, in multivariate analysis, only PPFT value was found to be statistically significant in predicting GS ≥7 (p=0.005). It has been shown that the risk of detecting GS ≥7 PCa increases 8.9 times with 1 mm increase in PPFT values (**Table 2**).

Table 1. Clinical characteristics of study patients

	Gleason score (GS)		
	GS = 6 (n:16)	**GS ≥7 (n:35)**	**P**
	Mean ± std (min-max)	**Mean ± std (min-max)**	
Age (y)	61,31±5,199(51-70)	64,60±9,552(45-88)	0,204 *
PSA (ng/ml)	5,70±2,141(3-10)	12,91±16,992(2-100)	0,002**
PSA density	0,11±0,52(0-0,2)	0,25±0,218(0-1)	<0,001*
Prostate volume (cc)	54,81±18,071(26-90)	47,71±17,394(21-95)	0,188*
PIRADS	3,69± 0,704(3-5)	4,31 ± 0,591(3-5)	0,002**
PPFT (mm)	2,01±1,08(1-5)	7,31±3,566(3-15)	<0,001*
SCFT (mm)	7,54±2,231(4-12)	21,88±13,454(9-54)	<0,001*
BMI(kg/m^2)	21,19±1,136(19-23)	26,74±4,612(20-38)	<0,001*

PSA: prostate spesific antigen; PPFT: periprostatic fat thickness; SCFT: subcutaneous fat thickness; BMI: body mass index;
* Student's t test; ** Mann-Whitney U test

Table 2. Results of univariate and multivariate logistic regression analysis

		Univariate analysis	Multivariate analysis	
	Mean ± std	P value	Odds Ratio	P value
Age (y)	64,60±9,552	0,203		
PSA (ng/ml)	12,91±16,992	0,025		0,067
PSA density	0,25±0,218	0,013		0,069
Prostate volume (cc)	47,71±17,394	0,189		
PIRADS	4,31 ± 0,591	0,004		0,374
PPFT (mm)	7,31±3,566	0,005	8,941 (1,9-41)	0,005
SCFT (mm)	21,88±13,454	0,004		0,302
BMI(kg/m^2)	26,74±4,612	0,005		0,270

PSA: prostate spesific antigen; PPFT: periprostatic fat thickness; SCFT: subcutaneous fat thickness; BMI: body mass index

Discussion

The periprostatic fat tissue is thought to be a metabolically active capsule-shaped organ. The relationship between periprostatic adipose tissue and the development and progression of PCa has attracted attention because of its potential role in the tumor microenvironment. The majority of studies showed a correlation between periprostatic fat tissue and the aggressiveness of PCa [6–9].

Using various measurement methods in transrectal ultrasonography (TRUS), CT, and MRI, the relationship between periprostatic fat tissue and PCa aggressiveness has been confirmed in recent studies. Van Roermund et al. [8] evaluated periprostatic adipose tissue as a predictive marker for PCa aggressiveness using a single 3-mm thick CT section. They demonstrated that the periprostatic fat area and density, which is calculated as the ratio of the periprostatic fat to the total contour area (percent), were indicators of the aggressiveness of cancer. According to Woo et al., [6] PPFT assessed on a single preoperative mid-sagittal T1-w MRI from the symphysis pubis to the prostate, positively correlated with GS. Periprostatic adiposity has been demonstrated by Zhang et al. [9] as a useful parameter in accurately determining the tumor stage and grade in addition to having an impact on PCa aggressiveness. They emphasized the significance of measuring periprostatic adiposity in preoperative MRI as a predictive prognostic marker.

In this study, we have demonstrated that PPFT is an independent predictor of high-grade PCa on MRI. It was discovered that higher PPFT is a predictive risk factor for high-grade disease. We have found that retropubic PPFT measured on midsagittal images significantly correlated with GS and was able to distinguish PCa with GS ≥7 from PCa with GS=6. Our study raises the possibility that PPFT measurement, in line with previous studies, may have significant clinical implications in the preoperative evaluation of the prostate and will guide effective management in patients with PCa. GS is the best predictor of consequences of PCa among all clinical and pathological markers in patients with PCa [10]. Our study showed a substantial correlation between PPFT and histological scoring and demonstrated the critical function that periprostatic fat tissues play in the carcinogenesis of PCa.

PCa is one of many cancers for which obesity is a known risk factor. The imbalance between proinflammatory and antiinflammatory cytokines in the adipose tissue microenvironment and the differential expression of specific genes may play important roles in prostate carcinogenesis and the spread of the disease, even though the underlying mechanisms are not fully elucidated [11]. We hypothesize that visceral adipose tissue may play a substantial role in determining the severity of PCa based on the significant positive correlation between BMI, PPFT, and SCFT measures and GS that we have observed in our study.

We used MRI to measure the thickness of retropubic fat in the midsagittal plane, which is the technique used for determining the PPFT. We think that there are some advantages of using MRI over transrectal ultrasound (TRUS) and CT, which had been used in previous studies [7,8,12]. TRUS mainly depends on the operator. Additionally, the PPFT may change depending on how much pressure is placed on the prostate during the TRUS examination. Although CT is an important diagnostic tool for identifying and measuring visceral and subcutaneous fat, it is rarely used in patients with PCa unless they are also going to receive radiotherapy. Although estimating the amount of fat using CT yields quite accurate results, calculating the total PPF volume and peri-prostatic fat (PPF) density (%) requires use of a special software. In addition, it is essential to consider radiation exposure. However, because it is frequently used in preoperative evaluation in terms of risk stratification for patients with PCa, MRI is regularly used for the diagnosis, localization, and elimination of an additional imaging method. Additionally, it doesn't expose the patients to the adverse effects of ionizing radiation. The MRI method is fairly easy to use and doesn't call for specialized measurement or interpretation knowledge.

In our study, patients diagnosed with PCa by MRI-fusion

biopsy, which is a new point-and-shoot technological diagnostic method in PCa, were included in the study. There are many studies in the literature showing that MR-fusion biopsy is more successful than transrectal prostate biopsy, which is a systematically used diagnostic tool for PCa. Xei et al. [13] found that MRI-fusion biopsy detected greater number of clinically significant and high-risk PCa cases and fewer clinically insignificant cases of PCa compared to systematic protocols. The results of the measurements made with the MRI parameters of the patients diagnosed with PCa by MRI-fusion biopsy make our study different from other studies.

Cao et al. [14] showed that PPFT measured on MRI is an independent diagnostic marker for PCa and high-grade PCa. Increased PPFT was detected to be a risk factor indicating the diagnosis of PCa as well as for detecting high-grade PCa by biopsy. They found that each millimeter increase in PPFT had a 55% and 46% increase in the odds of detecting PCa and high-grade PCa, respectively. In our study, we showed that the risk of detecting PCa with GS ≥7 increased 8.9 times with one mm increase in PPFT values.

Also, in a similar study, Bhindi et al., [12] found that PPFT may be a risk factor for the detection of PCa and high-grade PCa in patients who had undergone prostate biopsy. This study is one of the first studies using TRUS biopsy, and our study was performed with a more advanced and new technique, ie. MRI-fusion biopsy.

There are several limitations to our study. Indeed, our study was a retrospective analysis, and PPFT was only measured in one plane on the MRI. Establishing a consistent procedure can call for a more precise technique, like volumetric measurement. The findings of our investigation still indicated that PPFT is a viable predictor indicating the need (if any) to perform prostate biopsy. Also the results of the radical prostatectomy were not taken into consideration and the pathology findings of our patients were verified by MR-fusion biopsy. The biological markers (adipokines) quantified from radical prostatectomy samples of PPFT, which is a sign of biological activity, will be correlated with the GS in subsequent studies in order to better understand the cause-and-effect relationship between periprostatic fat tissue and GS.

Conclusion

As an easily quantifiable estimate of visceral adipose tissue PPFT, is a reliable biological marker for predicting PCa aggressiveness. According to the results of our study, measuring PPFT on MRI may be able to help determine a patient's GS prior to biopsy or surgery to be performed for PCa.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Acibadem (Approval date, and registration number: 02.09.2022-14/38).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – B.K.S., D.S.; Design – B.K.S., D.S.; Supervision –D.S.; Resources – B.K.S., D.S.; Materials – B.K.S., D.S.; Data Collection and/or Processing – B.K.S., Analysis and/or Interpretation – B.K.S., D.S.; Literature Search – B.K.S., D.S.; Writing Manuscript – B.K.S., D.S.; Critical Review – B.K.S., D.S.
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