RESEARCH ARTICLE

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Impact of Subcutaneous Fat Thickness on Biochemical Recurrence and Recurrence-Free Survival in Patients Undergoing Radical Prostatectomy

ABSTRACT

Objective: Aim of this study is to evaluate the association between subcutaneous fat thickness (SCFT) and biochemical recurrence (BCR) in patients who have undergone radical prostatectomy (RP).

Methods: Study included 52 patients who had non-metastatic prostate cancer (PCa), underwent RP at our center between April 2015 and January 2020. All patients had a full abdomen computed tomography (CT) scan within six months prior to surgery. Measurements of fat, muscle, and tissue were evaluated by two radiologists, and binary logistic regression analysis was performed to determine factors influencing BCR. SCFT was identified as the only radiological factor influencing recurrence. A cut-off value (25.6) was determined using an ROC curve, and patients were divided into two groups based on this value.

Results: In Group 1 (SCFT < 25.6), the median recurrence time was 39 (3-65) months, and the median follow-up time was 40.5 (17-65) months. In Group 2 (SCFT ≥ 25.6), the median recurrence time was 20.5 (3-58) months, and the median follow-up time was 43 (12-69) months. The one-year and three-year recurrence-free survival rates were 82.1% and 78.4% for Group 1, respectively, while they were 62.5% and 52.2% for Group 2, respectively (p=0.047).

Conclusions: The ability to predict recurrence in PCa is crucial for the management and treatment of the disease. Our study, which demonstrates a significant relationship between SCFT and BCR, suggests that radiological evaluation and measurements will be further utilized in the diagnosis, treatment, and follow-up of the disease.

Keywords: Biochemical Recurrence, Prostate Cancer, Subcutaneous Fat Thickness.

Radikal Prostatektomi Uygulanan Hastalarda Deri Altı Yağ Kalınlığının Biyokimyasal Nüks ve Nükssüz Sağkalım Üzerine Etkisi

ÖZET

Amaç: Bu çalışmanın amacı radikal prostatektomi (RP) uygulanan hastalarda deri altı yağ kalınlığı (DAYK) ile biyokimyasal nüks (BKN) arasındaki ilişkiyi değerlendirmektir.

Yöntem: Çalışmaya Nisan 2015 ile Ocak 2020 tarihleri arasında merkezimizde RP uygulanan toplam 52 metastatik olmayan prostat kanseri tanılı hasta dahil edildi. Tüm hastalara ameliyattan önceki altı ay içinde tüm batın bilgisayarlı tomografi (BT) taraması yapıldı. Yağ, kas ve doku ölçümleri iki radyolog tarafından yapıldı ve BKN'yi etkileyen faktörleri belirlemek için ikili lojistik regresyon analizi uygulandı. DAYK, nüksü etkileyen tek radyolojik faktör olarak tanımlandı. ROC eğrisi kullanılarak kesme değeri (25,6) belirlendi ve hastalar bu değere göre iki gruba ayrıldı.

Bulgular: Grup 1'de (DAYK < 25,6) ortanca nüks süresi 39 (3-65) ay, ortanca takip süresi ise 40,5 (17-65) ay idi. Grup 2'de (DAYK ≥ 25,6) ortanca nüks süresi 20,5 (3-58) ay, ortanca takip süresi ise 43 (12-69) ay idi. Bir yıllık ve üç yıllık nükssüz sağkalım oranları Grup 1'de sırasıyla %82,1 ve %78,4 iken Grup 2'de sırasıyla %62,5 ve %52,2 idi (p=0,047).

Sonuç: Prostat kanserinde nüksü tahmin edebilmek hastalığın yönetimi için çok önemlidir. DAYK ile BKN arasında anlamlı bir ilişki olduğunu ortaya koyan çalışmamız; hastalığın tanı, tedavi ve takibinde radyolojik değerlendirme ve ölçümlerden daha fazla yararlanılacağını düşündürmektedir.

Anahtar Kelimeler: Biyokimyasal Nüks, Prostat Kanseri, Deri Altı Yağ Kalınlığı.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the fifth leading cause of cancer-related deaths among men globally, with around 1.4 million new cases and 375,000 deaths in 2020 (1).

Patients with biochemical recurrence (BCR) are known to be at an increased risk of developing distant metastases, experiencing death from PCa, and having higher overall mortality rates (2). Nomograms have been developed to predict the likelihood of BCR following local treatment of PCa. Some nomograms are based solely on pre-treatment factors, while others incorporate histopathological examination (3-5). Due to the growing use of multiparametric prostate magnetic resonance imaging (mpMRI), recent nomograms have begun to include variables like maximum tumor diameter. mpMRI provides a detailed assessment of PCa and facilitates a more accurate tumour classification. It enables the determination of precise measurements regarding the size, location, margins and invasiveness of tumors (6).

There are hypotheses which propose potential protective effects of subcutaneous adiposity in cancer patients. Possible explanations include energy metabolism, signaling from adipose tissue, and a higher frequency of medical visits among obese individuals (7).

This study aims to examine the correlation between subcutaneous fat thickness before surgery and BCR in patients who undergo radical prostatectomy (RP).

MATERIAL AND METHODS

The study was conducted according to the regulations of the institutional research ethics board. The study was approved by Ethics Committee of University (Approval No: 2022/0067, Date: 09/02/2022) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients participating in study.

Our center evaluated 230 patients who underwent preoperative mpMRI followed by RP between April 2015 and January 2020. Our study included 52 PCa patients who received primary RP and underwent an additional abdominal computed tomography (CT) scan within 6 months before surgery, meeting the criteria of non-metastatic disease, no androgen deprivation therapy, and no other malignancies. Exclusions from the analyses encompassed patients with insufficient imaging data or those who were lost to follow-up.

The definition for biochemical recurrence (BCR) was characterized by two consecutive postoperative PSA values exceeding 0.2 ng/ml. Metastases were considered as any lesions detected on postoperative systemic imaging. PSA surveillance was conducted every three months during the initial two years, followed by biannual monitoring in the subsequent year, and subsequently on an annual basis during the follow-up period. The frequency of PSA measurements was adjusted based on the patient's risk group and the adjuvant treatments received.

Two experienced radiologists assessed the patients' fat, muscle, and tissue measurements, and performed binary logistic regression analysis to determine the factors that influence BCR. The study concluded that subcutaneous fat thickness (SCFT) is the only radiological factor that influences recurrence. Using ROC curve analysis, a prediction value of 25.6 mm was determined. Patients were categorized into two groups according to this predictive value.

The average cross-sectional area of muscle and fat tissue was obtained from two axial images in the same series at the third lumbar vertebra (L3) using Horos v4.0 (Nimble Co LLC d/b/a Purview, Annapolis, MD, USA) and OsiriX v5.0 (Pixmeo, Geneva, Switzerland). Manual outlining was done to trace different tissue compartments, and the tissue of interest was segmented based on Hounsfield Unit (HU) thresholds. Selected areas were manually adjusted if necessary, and the total cross-sectional area of the segmented tissue was automatically calculated (Figure 1).

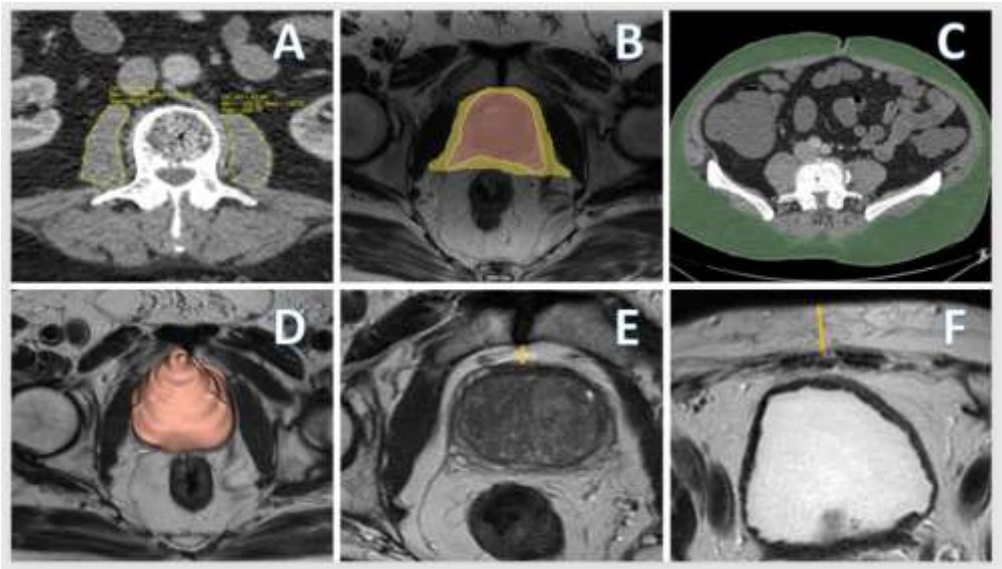

Figure 1. Parameters via MRI (A- Prostate volume, B- Periprostatic fat tissue area, C- Periprostatic fat tissue thickness, D- Psoas muscle density, E- Subcutaneous fat area, F- Subcutaneous fat thickness)

Statistics Analysis: The data were analyzed using SPSS version 22 (IBM, NY, USA). Binary logistic regression identified factors influencing BCR. An ROC curve assessed predictive value. Patients were grouped below and above the threshold. Categorical variables were compared using Pearson chi-square or Fisher's exact tests for non-normally distributed data. Kolmogorov-Smirnov tested distribution normality. Student's t-test analyzed normally distributed variables, while Mann-Whitney U test assessed others. Kaplan-Meier calculated survival rates; differences were log-rank tested. Statistical significance: $p<0.05$.

RESULTS

Tables 1 and 2 show the demographic, clinical, pathological, and radiological characteristics of the groups. Group 1 (SCFT <25.6) had a median time to recurrence of 39 months (range: 3-65) and a median follow-up time of 40.5 months (range: 17-65).

Table 1. Demographic, clinical and radiological characteristics of the groups

	Group 1 (n=28)	Group 2 (n=24)	p value
Age at diagnosis (years)	66 ± 5.7	63.8 ± 6.7	0.188
Body mass index (kg/m^2)	26.5 ± 3.2	28.1 ± 3.7	0.087
Charlson Comorbidity Index	4.96 ± 0.2	5.33 ± 0.39	0.842
Prostate-specific antigen (ng/ml)	11.9 ± 2.9	24.1 ± 8.2	0.139
Periprostatic adipose tissue area (cm^2)	14.6 ± 5.9	14.3 ± 5	0.821
Subcutaneous fat thickness (mm)	18.9 ± 3.8	30.1 ± 4.7	**<0.001**
Subcutaneous area of adipose tissue (cm^2)	196.9 ± 65.8	244.1 ± 52.6	**0.007**
Visceral adipose tissue area (cm^2)	172.8 ± 71.4	178.8 ± 44	0.726
Periprostatic adipose tissue thickness (mm)	7.6 ± 3.5	7.6 ± 2.9	0.964
Periprostatic adipose tissue area / Prostate volume	33 ± 30.8	31.5 ± 16	0.830
Periprostatic adipose tissue thickness / Subcutaneous fat thickness	0.41 ± 0.25	0.25 ± 0.13	**0.007**
Psoas muscle density (HU)	46 ± 8.3	51.8 ± 6.8	**0.010**
Skeletal muscle density (L3 vertebra level) (HU)	31.1 ± 9.3	34.8 ± 9.1	0.163
Prostate volume on mpMRI (cm^3)	56.8 ± 28.3	52.2 ± 22.6	0.529

Table 2. Preoperative patient history, pathology evaluation and postoperative clinical features

	Group 1 (n=28)	**Group 2 (n=24)**	**p value**
Family history of prostate cancer, n (%)	4 (% 14.3)	4 (%16.7)	0.556
pT			0.187
2	15	9	
3	13	15	
RRP-ISUP Grade			0.218
1	6	1	
2	5	10	
3	7	1	
4	7	4	
5	3	8	
EPE +, n (%)	13 (% 46.4)	15 (% 62.5)	0.246
LNI +, n (%)	0	0	
Biochemical recurrence, n (%)	6 (% 21.4)	11 (% 45.8)	0.061
Progression, n (%)	1 (% 3.6)	2 (% 8.3)	0.590

RRP: retropubic radical prostatectomy, ISUP: The International Society of Urological Pathology, EPE: extraprostatic extension, LNI: lymph node invasion

Group 2 (SCFT ≥25.6) had a median time to recurrence of 20.5 months (range: 3-58) and a median follow-up time of 43 months (range: 12-69). Group 1 had one-year and three-year recurrence-free survival rates of 82.1% and 78.4%, respectively, while for Group 2, they were 62.5% and 52.2%, respectively (p=0.047) (Figure 2).

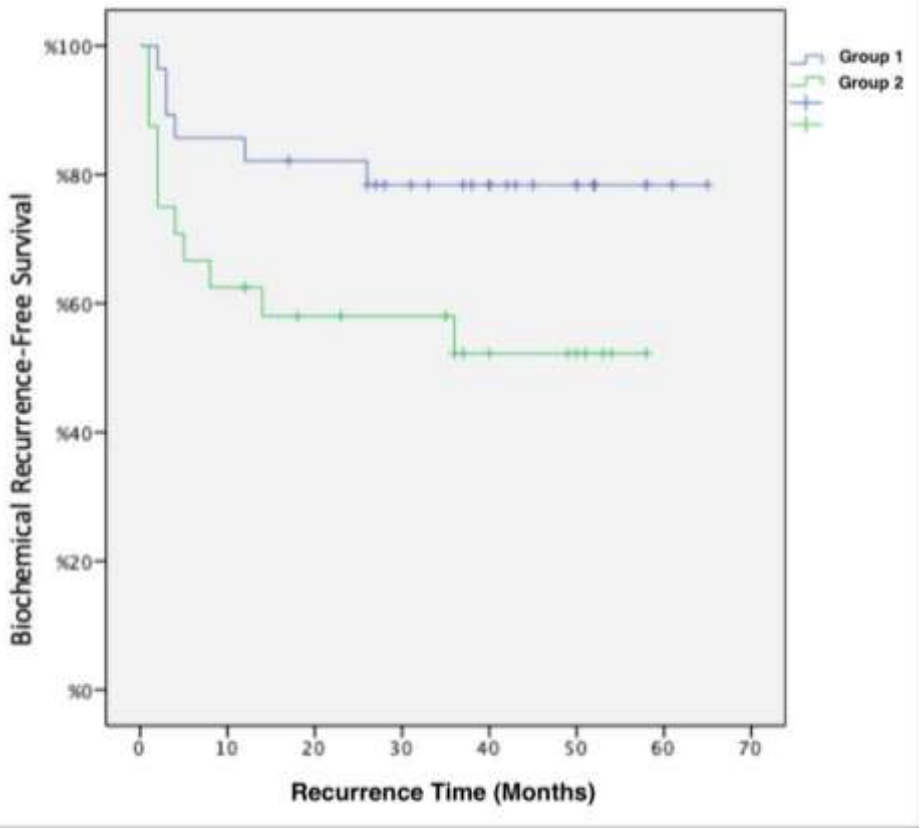

Figure 2. Kaplan-Meier curve for biochemical recurrence-free survival

In terms of RP ISUP grades, pathologic stages, extraprostatic extension, and lymph node involvement, there was no significant difference between the two groups. Regarding BCR, although there was no significant difference, Group 2 showed a higher rate of BCR that was almost statistically significant (p=0.061) (Table 2). In univariate analysis, subcutaneous fat thickness, TRUS biopsy ISUP grade, pT, RRP ISUP grade, and extraprostatic extension were all associated with BCR risk. In multivariate analysis, the presence of extraprostatic extension was the only factor that remained significantly associated with BCR risk (HR: 30.667; 95% CI: 3.617-259.986; p<0.002) (Table 3).

Table 3. Univariate and multivariate regression analysis of biochemical recurrence.

	Univariate Model					**Multivariate Model**				
	HR	(95% CI)			p value	HR	(95% CI)			p value
Age	0.938	0.850	-	1.036	0.206					
Body Mass Index	1.125	0.948	-	1.336	0.178					
Family history of prostate cancer	0.644	0.116	-	3.590	0.616					
CCI	1.480	0.986	-	2.220	0.058					
Diagnosis PSA	1.015	0.993	-	1.037	0.195					
Periprostatic adipose tissue area	1.001	1.000	-	1.002	0.206					
Subcutaneous fat thickness	1.100	1.004	-	1.206	0.042					
Subcutaneous adipose tissue area	1.000	1.000	-	1.000	0.180					
Visceral adipose tissue area	1.000	1.000	-	1.000	0.484					
Periprostatic fat thickness	0.988	0.821	-	1.189	0.900					
Skeletal muscle area	1.000	1.000	-	1.000	0.131					
Psoas muscle area	1.000	0.998	-	1.001	0.687					
Prostate volume MRI	0.997	0.974	-	1.020	0.792					
TRUS biopsy ISUP Grade	2.662	1.563	-	4.533	0.001					
pT	11.572	2.274	-	58.883	0.003					
RRP ISUP Grade	3.439	1.741	-	6.793	0.001					
EPE	30.667	3.617	-	259.986	0.002	30.667	3.617	-	259.986	0.002

HR: hazard raito, CI: confidence interval, CCI: Charlson Comorbidity Index, PSA: prostate-specific antigen, MRI: magnetic resonance imaging, TRUS: transrectal ultrasound, ISUP: The International Society of Urological Pathology, RRP: retropubic radical prostatectomy, EPE: extraprostatic extension

DISCUSSION

The association between body composition and PCa prognosis has been extensively studied, particularly concerning the obesity paradox. Numerous literature studies suggest that obesity (BMI ≥30 kg/m²) is linked to higher risks of high-grade PCa and recurrence following prostatectomy (8,9). In patients with advanced disease, some articles suggest that obesity may have a protective effect. Observations have shown that men with metastatic hormone-sensitive PCa who are obese tend to demonstrate improved progression-free survival and overall survival (10). The role of BMI as a prognostic marker for adiposity remains uncertain. A meta-analysis of 16 studies, which monitored 26,479 PCa patients post primary treatment, indicated that a 5 kg/m² increase in BMI was associated with a 21% higher risk of BCR (11). Multiple studies in the literature do not conclusively establish a connection between high BMI and the risk of BCR. The correlation between BMI and PCa outcomes may exhibit variations among studies, leading to contradictory findings. These differences in results could be attributed to factors such as study design, patient characteristics, duration of follow-up, and statistical adjustments. As a result, the relationship between high BMI and the risk of BCR in PCa remains a subject of continuous research and discussion (12-14). Thus, researchers are examining adiposity-related parameters other than BMI, which are linked to prognosis.

Studies have demonstrated that visceral fat is linked inversely to bioavailable testosterone and displays a more pronounced correlation with insulin resistance and pro-inflammatory cytokines compared to subcutaneous fat (15,16). In contrast to subcutaneous depots, visceral adipose tissue presents greater expression of glucocorticoid and androgen receptors, possesses a higher metabolic activity, and demonstrates elevated levels of lipolysis (15). In the regression analysis, the study did not discover a link between visceral fat area and BCR. However, subcutaneous fat thickness was identified as the only radiological parameter that influenced BCR. Identifying adiposity phenotypes with the greatest risk of developing aggressive PCa can contribute to uncovering the mechanisms connecting obesity to the onset of aggressive disease. Additionally, this identification can assist in targeting appropriate intervention strategies (17).

In vitro research has established a correlation between periprostatic adipose tissue and the development of an aggressive phenotype in PCa cells (18). Multiple clinical studies have confirmed a connection between periprostatic adipose tissue and the degree of aggressiveness displayed by PCa (19). A retrospective analysis of pelvic MRI was carried out by Woo et al. in 190 patients prior to RP (20). The study revealed a significant correlation between the Gleason score in RP specimens and periprostatic fat thickness. In a study conducted by Qiang et al., involving 184 men who underwent RP, a positive correlation was discovered between periprostatic fat area and the aggressiveness of PCa (21). Our study did not find any association between periprostatic fat area and BCR in the regression analysis. Obesity and its associated metabolic alterations play a substantial role in the occurrence of BCR, metastatic progression, and mortality among men with PCa. As per a study by Lopez et al., a link between overall survival in PCa patients and total adiposity is absent (22). Nonetheless, the study indicated that elevated levels of subcutaneous adipose tissue are linked to enhanced survival (HR 0.68, 95% CI: 0.54-0.84, p=0.001). There is a strong correlation between the area of fat tissue measured in a single axial abdominal image and the total volume of body fat tissue (23). The radiodensity of adipose tissue has recently been identified as a novel imaging biomarker that is closely associated with various adipokines (24). McDonald et al. conducted a study that involved 171 radiotherapy patients with high-risk PCa (25). Their findings indicate no statistically significant correlation between the area of subcutaneous fat tissue and BCR. Qiang et al. conducted a retrospective study and found no significant differences in subcutaneous fat thickness between clinical stages, Gleason scores, or risk groups (21). Similarly, our study did not find any significant association between subcutaneous fat tissue area and BCR in the regression analysis.

Study Limitations: The study has limitations. The study's retrospective design may have introduced biases and limitations in data collection. The study results may not be applicable to other ethnic groups as there may be variations in body composition attributed to ethnicity and race. Variations in the results may occur among patients with different PCa stages. It is crucial to consider the limitations when interpreting and applying the findings of the study. Prospective studies with diverse populations are necessary to validate and generalize the results.

CONCLUSION

Predicting recurrence in prostate cancer (PCa) is crucial for disease monitoring and treatment. Our study data demonstrated a significant correlation between subcutaneous fat thickness and BCR, indicating that radiological evaluation and measurements may become more common in the diagnosis, treatment, and follow-up of PCa in the future. The morphometric examination of mpMRI imaging can aid in pinpointing patients who are at an elevated risk of experiencing an unfavorable prognosis. In the future, body composition parameters determined by mpMRI data could offer objective prognostic factors to guide personalized treatment decisions. Supporting existing data with multicenter prospective studies is crucial.

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