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The Added-value of Staging ^{18}F-FDG PET/CT in the Prediction of Overall Survival in the Patients with Bladder Cancer

Mesane Kanseri Hastalarında Evreleme ^{18}F-FDG PET/BT'nin Genel Sağkalımı Öngörmeye Katkısı

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Abstract

Objectives: This retrospective study aimed to evaluate the prognostic importance of ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-positive pelvic lymph nodes (LNs) and extra-pelvic disease on staging ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) in patients with bladder cancer.

Methods: Bladder cancer patients who underwent staging ^{18}F-FDG PET/CT were included in the study. Histopathologic features of tumors, therapy histories, presence of distinguishable tumors on CT and PET images, sizes and maximum standardized uptake value (SUV_{max}) of primary tumors, total numbers, sizes, and SUV_{max} of ^{18}F-FDG-positive pelvic and extra-pelvic LNs, and total numbers and SUV_{max} of distant metastases (M1a/1b) were recorded. Patients were followed up until death or the last medical visit. Factors predicting overall survival were determined using Cox regression analysis.

Results: Fifty-five patients [median age: 70 (53-84), 48 (87.3%) male, 7 (12.7%) female] with bladder cancer were included in this study. Twenty-nine (52.7%) patients had ^{18}F-FDG positive pelvic LNs, while 24 (43.7%) patients had ^{18}F-FDG positive extra-pelvic disease. Patients with ^{18}F-FDG-positive pelvic LNs had a higher rate of extra-pelvic disease (p=0.003). The median follow-up duration was 13.5 months. The median overall survival was 16.3 months [95% confidence interval (CI) 8.9-23.7]. The primary tumor distinguishability on PET (p=0.011) and CT (p=0.009) images, the presence of ^{18}F-FDG-positive pelvic LNs (p<0.001) and ^{18}F-FDG-positive extra-pelvic disease/distant metastases (M1a/M1b) (p<0.001), and the number of distant metastases (p=0.034) were associated with mortality. The ^{18}F-FDG-positive extra-pelvic disease/distant metastases [p=0.029, odds ratio: 4.15 (95% CI 1.16-14.86)] was found to be an independent predictor of mortality in patients with bladder cancer.

Conclusion: The presence of ^{18}F-FDG-positive extra-pelvic disease in pretreatment ^{18}F-FDG PET/CT is an important prognostic factor in bladder cancer patients.

Keywords: Bladder cancer, ^{18}F-FDG PET/CT, overall survival

Öz

Amaç: Bu çalışmanın amacı mesane kanseri hastalarında evreleme ^{18}F-florodeoksiglikoz (^{18}F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografide (PET/BT) ^{18}F-FDG pozitif pelvik lenf nodlarının ve ekstra-pelvik hastalığın prognostik önemini değerlendirmektir.

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Yöntem: Evreleme ^{18}F-FDG PET/BT çalışması yapılan mesane kanseri tanılı hastalar çalışmaya dahil edildi. Tümörlerin histopatolojik özellikleri, BT ve PET görüntülerinde ayırt edilebilir tümör varlığı, primer tümörün boyut ve maksimum standartlaştırılmış tutulum değeri (SUV_{maks}), ^{18}F-FDG pozitif pelvik ve ekstra-pelvik lenf nodlarının sayı, boyut ve SUV_{maks} değerleri, uzak metastaz sayısı ve SUV_{maks} değerleri kaydedildi. Hastalar ölüme veya son hastane vizitine kadar takip edildi. Genel sağkalımı öngören faktörleri belirlemek amacıyla Cox regresyon analizi yapıldı.

Bulgular: Elli beş [medyan yaş: 70 (53-84), 48 (%87,3) erkek, 7 (%12,7) kadın] mesane kanseri tanılı hasta çalışmaya dahil edildi. Yirmi dokuz (%52,7) hastada ^{18}F-FDG pozitif pelvik lenf nodu, 24 (%43,7) hastada ekstra-pelvik hastalık mevcuttu. ^{18}F-FDG pozitif pelvik lenf nodu olan hastalar daha sık ekstra-pelvik hastalığa sahipti (p=0,003). Medyan izlem süresi 13,5 ay, medyan genel sağkalım 16,3 ay [%95 güven aralığı (GA) 8,9-23,7] bulundu. Univariant analizde PET (p=0,011) ve BT'de (p=0,009) primer tümör ayırt edilebilirliği, ^{18}F-FDG pozitif pelvik lenf nodu varlığı (p<0,001), ^{18}F-FDG pozitif ekstra-pelvik hastalık/uzak metastaz varlığı (M1a/M1b) (p<0,001) ve metastaz sayısı (p=0,034) mortalite ile ilişkili bulundu. Multivariant analizde ^{18}F-FDG pozitif ekstra-pelvik hastalık/uzak metastaz varlığı [p=0,029, olasılık oranı: 4,15 (%95 GA 1,16-14,86)] mesane kanseri hastalarında mortaliteyi öngörmede bağımsız risk faktörü olarak bulundu.

Sonuç: Evreleme ^{18}F-FDG PET/BT çalışmasında ^{18}F-FDG pozitif ekstra-pelvik hastalık varlığı önemli bir prognostik faktördür.

Anahtar kelimeler: Mesane kanseri, ^{18}F-FDG PET/BT, genel sağkalım

Introduction

Bladder cancer (BC) is the tenth most common cancer and the thirteenth leading cause of cancer-related deaths worldwide according to the World Health Organization GLOBOCAN 2020 database (1). It is approximately 4 times more common in men than in women (1). Tobacco smoking is the most critical cause of BC, with an attributable risk of approximately 50% (2). The global geographic and temporal distribution patterns of BC reflect the prevalence of tobacco use (1,3).

Urothelial BC is the most common histopathological subtype. BC is a heterogeneous clinical spectrum that includes non-muscle-invasive and muscle-invasive diseases. Approximately 75% of patients have a non-muscle-invasive disease confined to the bladder mucosa/submucosa, whereas the remaining 25% have a muscle-invasive disease at the time of diagnosis (4). Therapy management and prognosis differ substantially from each other.

Early diagnosis and accurate staging, and individualized treatment and follow-up, are crucial for a successful outcome in BC (5). Computed tomography (CT) and magnetic resonance imaging (MRI) are widely used for local staging, imaging of lymph nodes (LNs), and distant metastases despite some limitations. For instance, the assessment of LN metastases in CT and MRI is based on size; therefore, the identification of metastases in normal-sized or minimally enlarged nodes is limited in these imaging modalities (6). ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/CT (PET/CT) is widely used for staging, restaging, and treatment response evaluation in various cancers. Initially, its use was limited in patients with BC due to the high urinary excretion activity of the ureters and bladder (7). Nevertheless, several studies have shown that PET/CT has a higher sensitivity in the determination of LN and distant metastases than CT and MRI, and it has caused a therapy management alteration in 19-68% of BC patients (8,9,10). Therefore, ^{18}F-FDG PET/CT is increasingly being used in clinical practice, and its exact role continues to be evaluated (6). Recommendations of guidelines on the use of ^{18}F-FDG PET/CT in BC increase over time. The National Comprehensive Cancer Network (NCCN) suggests that ^{18}F-FDG PET/CT may be beneficial in selected patients with T2 (muscle-invasive disease) and in patients with ≥cT3 disease (11). Moreover, PET/CT should be included in oligometastatic disease staging when considering radical surgery according to consensus statements of the European Association of Urology and European Society of Medical Oncology (12).

In the era of precision oncology, early prediction of prognosis is important in patient management and personalized therapy. Identification of prognostic factors for malignancies is an important research topic in oncology. Several studies have demonstrated various clinicopathological prognostic factors in patients with BC. In addition to these factors, the findings of ^{18}F-FDG PET/CT may have prognostic importance in terms of overall survival (OS). ^{18}F-FDG PET/CT has been shown to be highly sensitive in detecting extravesical tumor deposits in BC patients. However, it is critical to know whether the findings detected in ^{18}F-FDG PET impact prognosis in patients with BC. A limited number of studies have investigated its prognostic value (13). Therefore, our hypothesis was that the presence of ^{18}F-FDG-positive pelvic LNs and extra-pelvic diseases may predict patients with a poorer OS. Treatment management and intensification can be modified in these patients accordingly. This study aimed to evaluate the prognostic importance of the presence of ^{18}F-FDG-positive pelvic LNs and extra-pelvic disease on ^{18}F-FDG PET/CT in patients with BC.

Materials and Methods

Patient Population

This retrospective study was approved by the University of Health Sciences Türkiye, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Non-invasive Clinical Research Ethics Committee (no: 2022-09/167, date: 22.09.2022), and the requirement for informed consent was waived. Patients with histologically proven BC were included in this study. Patients who underwent a staging ^{18}F-FDG PET/CT due to the presence of muscle-invasive BC, high-risk histopathologic subtype, and/or radiological equivocal findings (lung nodules, bone lesions, etc. on CT or MR images that were evaluated as an equivocal for metastasis by clinicians) were included in the study. However, patients who underwent surgery or received chemotherapy (CTx) and/or radiotherapy (RT) before ^{18}F-FDG PET/CT imaging were excluded from the study. Furthermore, patients with secondary primary cancers were not included in the study.

Clinicopathological Features

Demographic characteristics were evaluated using the hospital information system. Tumor histopathologic subtypes and the presence of muscularis propria invasion were recorded from pathology reports. Therapy histories [CTx, RT, chemoradiotherapy (CRT), and surgery] after PET/CT were recorded. Patients were followed until death or the last medical visit. Follow-up time was calculated from the date of PET/CT to the date of death, lost to follow-up, or the last medical visit.

PET/CT Acquisition

All patients had fasted for at least 6 h before ^{18}F-FDG PET/CT studies. The serum glucose levels measured at the time of ^{18}F-FDG injections were 150 mg/dL. ^{18}F-FDG was intravenously administered at a dose of 5.5 MBq/kg body weight. PET/CT images were obtained using a three-dimensional Siemens Biograph True Point 6 PET/CT device 60 min after ^{18}F-FDG injection. A PET scanner and a 3-mm sliced multidetector CT scanner obtained simultaneous images in the same session. Low-dose CT images without intravenous iodinated contrast were used for attenuation correction and anatomical correlation. If nuclear medicine physicians required, some patients underwent dual-phase ^{18}F-FDG PET/CT with/without intravenous diuretic administration. Patients who underwent dual-phase pelvic imaging and their findings were recorded.

Image Analysis

Primary bladder tumors were assessed using PET/CT images. The presence of irregular wall thickening or mass formation was accepted as a distinguishable tumor on CT images. Primary tumors with distinguishable ^{18}F-FDG uptake from background activity were recorded as distinguishable tumors on PET images. The sizes and maximum standardized uptake value (SUV_{max}) of the primary tumors were recorded. The patients were evaluated for a synchronous tumor in the genitourinary tract on ^{18}F-FDG PET/CT images.

LNs with distinguishable ^{18}F-FDG uptake from background activity were accepted as ^{18}F-FDG positive. The presence, total number, and SUV_{max} of ^{18}F-FDG-positive pelvic and extra-pelvic LNs were recorded. Short-axis sizes of the largest ^{18}F-FDG-positive pelvic and extra-pelvic LNs were measured.

Extra-pelvic ^{18}F-FDG positive disease was accepted as distant metastases. M1a is the presence of ^{18}F-FDG positive extra-pelvic LNs, whereas M1b is other distant metastases according to the 8th TNM staging system (14). The locations, total numbers, and SUV_{max} of distant metastases (M1a/1b) were recorded.

Statistical Analysis

Statistical analyses were performed using SPSS software version 21. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were performed using frequencies for ordinal/nominal variables, medians, minimum, and maximum values for non-normally distributed variables, and mean ± standard deviation for normally distributed variables. The chi-square test was used to analyze the association between primary tumor distinguishability on PET/CT images, the presence and number of pelvic LNs, and the presence of extra-pelvic ^{18}F-FDG-positive disease (M0/M1a/M1b). The Kruskal-Wallis test was used to compare the features of primary tumors and pelvic LNs between the groups. Cox regression analyses were performed to determine the predictors of mortality in univariate and multivariate analyses. Regression analyses were performed using forward-conditional selection. Survival analysis was performed using the Kaplan-Meier method. An overall 5% type-1 error level was used to infer statistical significance.

Results

Fifty-five patients with BC were included in this study. The median age of the patients was 70 (53-84). In 55 patients, 48 (87.3%) were male and 7 (12.7%) were female. The indication for ^{18}F-FDG PET/CT imaging was the presence of muscle-invasive (muscularis propria) BC in 39 (70.9%) patients, whereas it was radiologically equivocal in 12

(21.8%) patients. Moreover, 4 (7.3%) patients had high-risk pathologic subtypes. Of these 4 patients, 1 had sarcoid subtype, 2 had small cell neuroendocrine carcinoma, and 1 of whom was adenocarcinoma + small cell neuroendocrine carcinoma.

The findings of ^{18}F-FDG PET/CT are summarized in Table 1. The median size of the primary tumor was 25.0 (13.0-168.0) mm. The mean SUV_{max} of the primary tumor was 16.1±6.2. The total number of patients with a distinguishable primary tumor on CT (an irregular wall thickening or a mass formation) was 38 (69.1%). The total number of patients with a distinguishable primary tumor on PET images (higher ^{18}F-FDG uptakes from the background) was 32 (58.2%). Eight (14.5%) patients had dual-phase pelvic PET/CT scans, and three of them had a distinguishable primary tumor on late-phase PET scan. Five patients had a suspicion of synchronous tumors in the genitourinary tract on PET/CT images.

Twenty-nine (52.7%) patients had ^{18}F-FDG-positive pelvic LNs, whereas 24 (43.7%) patients had ^{18}F-FDG-positive extra-pelvic disease (n=9 non-regional LNs, n=15 the other distant metastases). The total number of patients with bone, lung, and liver metastases was 9 (16.4%), 11 (20.0%), and 3 (5.4%), respectively.

There was a significant association between the presence of ^{18}F-FDG-positive pelvic LNs and extra-pelvic disease/distant metastases (M1a/M1b) (p=0.003). While 5 (19.2%) of 26 patients without ^{18}F-FDG positive pelvic LNs, 19 (65.5%) of 29 patients with ^{18}F-FDG positive pelvic LNs had ^{18}F-FDG-positive extra-pelvic disease. Patients with ^{18}F-FDG-positive pelvic LNs had a significantly higher rate of extra-pelvic disease.

There was no significant association between the presence of ^{18}F-FDG positive extra-pelvic disease and patient age (p=0.146), size (p=0.228) and SUV_{max} (p=0.520) of primary tumor, or size (p=0.289) and SUV_{max} (p=0.438) of pelvic LNs. Moreover, there was no significant difference between the presence of ^{18}F-FDG-positive extra-pelvic disease/distant metastases, primary tumor distinguishability on PET (p=0.145) and CT (p=0.225), and the number of ^{18}F-FDG-positive pelvic LNs (p=0.096).

The median follow-up duration was 13.5 months (3.2-78.8, interquartile range: 23.1 months). Four patients underwent cystectomy. The total numbers of patients who

Table 1. The findings of ^{18}F-FDG PET/CT

Features			Median or mean ± SD (min-max) or number (%)
The median size of primary tumor (mm)			25.0 (13.0-168.0)
The mean SUV_{max} of primary tumor (g/dL)			16.1±6.2 (5.4-29.0)
The presence of ^{18}F-FDG positive pelvic lymph node			29 (52.7%)
The number of ^{18}F-FDG positive pelvic lymph node		<5	19 (34.5%)
		5-9	2 (3.6%)
		>9	8 (14.5%)
The median size of ^{18}F-FDG positive pelvic lymph nodes (mm)			9.0 (5.0-42.0)
The median SUV_{max} of pelvic lymph nodes (g/dL)			5.4 (1.7-23.6)
The number of ^{18}F-FDG positive extra-pelvic lymph node		<5	11 (20.0%)
		5-9	4 (7.3%)
		>9	6 (10.9%)
The median size of extra-pelvic lymph nodes (mm)			9.0 (4.0-66.0)
^{18}F-FDG positive extra-pelvic disease/distant metastases (n=24)	Non-regional lymph node metastases (M1a)		9 (16.4%)
	Others distant metastases (M1b)		15 (27.3%)
The number of distant metastases		<5	8 (14.5%)
		5-9	5 (9.1%)
		>9	11 (20.0%)
The median SUV_{max} of distant metastases (g/dL)			7.0 (1.7-27.4)

SUV_{max}: Maximum standardized uptake value, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, SD: Standard deviation, min-max: Minimum-maximum

received CTx, RT, and CRT were 17 (30.9%), 8 (14.6%), 18 (32.7%), respectively. Twelve (21.8%) patients have no treatment. The patients received CTx and/or RT and/or immunotherapy according to the clinician's decisions. In the follow-up, 36 (65.5%) of 55 patients died. The median OS was 16.3 months [95% confidence interval (CI) 8.9-23.7]. OS was 59.7% at 1 year, 42.4% at 2 years, and 30.8% at 3 years.

The results of the univariate and multivariate analyses are shown in Table 2. In the univariate analyses, primary tumor distinguishability on PET (p=0.011) and CT (p=0.009) images, the presence of ^{18}F-FDG-positive pelvic LNs (p<0.001) and ^{18}F-FDG-positive extra-pelvic disease/distant metastases (M0/M1a/M1b) (p<0.001), and the number of distant metastases (p=0.034) were significantly associated with mortality. Consequently, the presence of ^{18}F-FDG-positive extra-pelvic disease/distant metastases [p=0.029, odds ratio: 4.15 (95% CI 1.16-14.86)] was found to be an independent predictor of mortality in patients with BC in the multivariate analysis.

The median OS was significantly lower in patients with ^{18}F-FDG-positive extra-pelvic disease than in those without ^{18}F-FDG-positive extra-pelvic disease (Figure 1). The median OS of M0, M1a, and M1b patients was 32.9, 30.6, and 5.1 months, respectively (p<0.001).

Discussion

In the era of precision medicine, accurate pretreatment staging is essential for better outcomes in patients with BC, similar to other malignancies. Despite the initial hesitation due to the high urinary ^{18}F-FDG activity, ^{18}F-FDG PET/CT is increasingly used in clinical practice in BC patients with growing evidence-based data (7). In this study, we found that the presence of ^{18}F-FDG-positive extra-pelvic disease/distant metastases is an independent predictor of poorer OS in patients with BC.

Table 2. The results of the univariate and multivariate analyses

Parameters	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Patient age	-	-	p=0.988	-	-	-
Patient gender	-	-	p=0.582	-	-	-
High-risk pathologic subtype	-	-	p=0.909	-	-	-
Muscularis propria invasion	-	-	p=0.728	-	-	-
The distinguishability of primary tumor on CT	4.03	(1.41-11.51)	p=0.009*	-	-	-
The distinguishability of primary tumor on PET	2.87	(1.28-6.44)	p=0.011*	-	-	-
Primary tumor size	-	-	p=0.242	-	-	-
The SUV_{max} of primary tumor	-	-	p=0.369	-	-	-
The presence of ^{18}F-FDG positive pelvic LN	4.00	(1.87-8.57)	p<0.001*	-	-	-
The number of ^{18}F-FDG positive pelvic LN	-	-	p=0.256	-	-	-
The size of ^{18}F-FDG positive pelvic LN	-	-	p=0.363	-	-	-
The SUV_{max} of ^{18}F-FDG positive pelvic LN	-	-	p=0.721	-	-	-
The number of ^{18}F-FDG positive extra-pelvic LN	-	-	p=0.140	-	-	-
The size of ^{18}F-FDG positive extra-pelvic LN	-	-	p=0.259	-	-	-
The presence of ^{18}F-FDG positive extra-pelvic disease/distant metastases (M)	-	-	p<0.001*	4.15	(1.16-14.86)	p=0.029*
• M1a (extra-pelvic lymph node)	1.99	(0.75-5.24)	p=0.165	-	-	-
• M1b (others distant metastases)	6.18	(2.70-14.14)	p<0.001	-	-	-
The SUV_{max} of distant metastases	-	-	p=0.092	-	-	-
The number of distant metastases	-	-	p=0.034*	-	-	-
Surgery	-	-	p=0.110	-	-	-
CTx/RT/CRT	-	-	p=0.288	-	-	-

*Statistically significant parameters. OR: Odds ratio, CI: Confidence interval, CT: Computed tomography, PET: Positron emission tomography, SUV_{max}: Maximum standardized uptake value, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose, LN: Lymph node, CTx: Chemotherapy, RT: Radiotherapy, CRT: Chemoradiotherapy

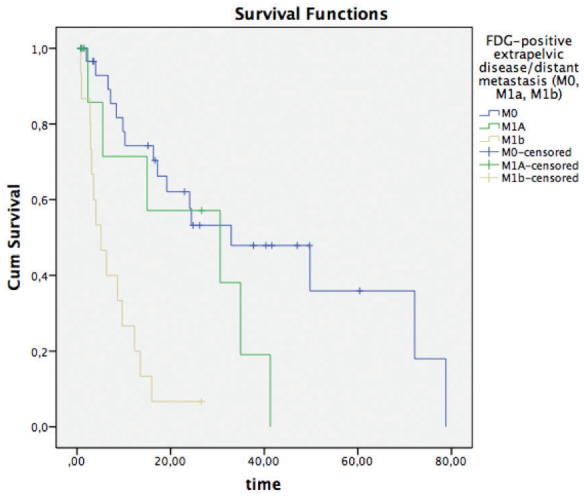

Figure 1. Kaplan-Meier survival analysis according to the presence of extra-pelvic [18]F-FDG positive disease in BC patients
[18]F-FDG: [18]F-fluorodeoxyglucose, BC: Bladder cancer

In this study, it was shown that patients with [18]F-FDG-positive pelvic LNs had a significantly higher rate of [18]F-FDG-positive extra-pelvic disease/distant metastases. LN involvement in BC has a prognostic implication (15). The presence, location, and number of involved LNs can help predict the prognosis of patients with BC This finding could be due to the prognostic importance of pelvic LNs, and the presence of these might be related to a more advanced disease. A prospective study to assess primary lymphatic landing sites from the bladder by Roth et al. (16) showed that the major lymphatic landing sites are pelvic (regional and common iliac) LNs, whereas only 4% of cases showed drainage initially to more distal LNs-para-aortic regions. All patients with para-aortic LNs had additional LNs in the pelvis (external iliac, internal iliac, or obturator fossa regions) (16). Based on this study, our findings may be due to lymphatic drainage pathways for extra-pelvic LNs (M1a) and the prognostic significance of pelvic LNs. Considering this finding of our study, patients with suspected pelvic LN positivity in conventional imaging modalities should be carefully evaluated for the presence of extra-pelvic disease in clinical practice. Consequently, these patients may be staged by [18]F-FDG PET/CT because of their higher sensitivity in the evaluation of LNs and distant metastases. In addition, [18]F-FDG PET/CT has an advantage in determining metastatic LNs regardless of the size.

In our study, the presence of [18]F-FDG positive pelvic LNs and [18]F-FDG positive extra-pelvic disease were associated with mortality in univariate analysis; however, only the presence of [18]F-FDG-positive extra-pelvic disease was found to be an independent predictor of mortality in BC patients in multivariate analysis. The median OS was significantly poorer in patients with [18]F-FDG-positive extra-pelvic disease than in those without [18]F-FDG-positive extra-pelvic disease. In parallel to our study, although their study designs and patient populations were somewhat different, a study on the prognostic value of [18]F-FDG PET/CT in muscle-invasive BC by Mertens et al. (13) found that extravesical [18]F-FDG-positive disease was an independent indicator of mortality in multivariate analysis. Furthermore, the studies demonstrated that OS was significantly poorer in patients with positive [18]F-FDG PET/CT than in those with negative [18]F-FDG PET/CT (17,18). According to the findings, the presence of [18]F-FDG-positive disease, especially in extra-pelvic regions, is an important prognostic factor in BC patients. In addition, patients with [18]F-FDG-positive extra-pelvic LNs had significantly better outcomes than patients with distant metastases, consistent with the literature (19). Contrary to the belief in clinical practice regarding the limitation of [18]F-FDG PET in BC, it is a valuable tool for the determination of pretreatment prognosis and stage, especially in selected BC patients. The presence and location of [18]F-FDG-positive disease has a critical prognostic value for patients with BC. [18]F-FDG PET/CT may contribute to treatment management and personalized therapy decisions by early determination of extra-pelvic disease in patients with BC.

The primary tumor distinguishability on PET and CT was associated with mortality in patients with BC in univariate analysis. It is known that the size of the primary tumor in BC is a prognostic factor (20,21). Patients with larger primary tumors might have more distinguishable tumors on PET and/or CT; therefore, their prognosis might be poorer than others. Moreover, aggressive tumors have a higher [18]F-FDG uptake (22,23), which may contribute to the distinction of primary tumors from urinary activity in PET images.

In our study, there was no association between the presence of [18]F-FDG-positive extra-pelvic disease, OS, and the sizes and SUV_{max} of primary tumors and pelvic LNs. These findings might be due to various factors such as a heterogeneous study population, difficulties such as high bladder activity in interpretation of primary tumor and pelvic LNs on PET/CT, and aggressive tumor behaviors independent of tumor sizes. However, to the best of our knowledge, metabolic prognostic factors such as SUV_{max} have not been reported in BC patients (24).

Study Limitations

This study has some main limitations. First, this was a retrospective study with a limited number of patients. Because of the nature of the study, some clinical information

such as clinical T-stages could not be obtained. Moreover, our patient population was heterogeneous in terms of clinicopathological features and therapies. Although it has been shown that ^{18}F-FDG PET/CT identifies more pelvic and extra-pelvic diseases, the number of studies investigating its prognostic value is limited. Therefore, our study has provided valuable information. Multicenter randomized prospective studies with more patients are needed on this topic.

Conclusion

^{18}F-FDG PET/CT is a valuable tool for staging and determining pretreatment prognosis in selected BC patients. The presence of ^{18}F-FDG-positive extra-pelvic disease in pretreatment ^{18}F-FDG PET/CT is an important prognostic factor in BC patients.

Ethics

Ethics Committee Approval: This retrospective study was approved by the University of Health Sciences Türkiye, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Non-invasive Clinical Research Ethics Committee (no: 2022-09/167, date: 22.09.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: H.B., Concept: S.G.A., B.B.D., H.B., G.U., Design: S.G.A., B.B.D., H.B., G.U., Data Collection or Processing: S.G.A., B.B.D., Analysis or Interpretation: S.G.A., B.B.D., G.U., Literature Search: S.G.A., Writing: S.G.A., B.B.D., G.U.

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