The impact of IV contrast enhanced ^{18}F-FDG PET/CT on the staging of bladder cancer

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Keywords: ^{18}F-FDG - Contrast enhanced - PET/CT - Bladder cancer

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Received:
16 March2021
Accepted revised:
23 April 2021

Abstract

Objective: The aim of this retrospective study was to compare the diagnostic accuracies of conventional radiological imaging (CI) methods magnetic resonance imaging or computed tomography (MRI or CT) and intravenous (IV) contrast enhanced (CE) fluorine-18-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) for the staging of bladder cancer (BC). **Materials and Methods:** The ^{18}F-FDG CE-PET/CT results of 35 consecutive patients with BC were analyzed. Diagnostic value of CE-PET/CT and CI are compared for their accuracy in revealing primary tumors, nodal-distant metastasis, and the final tumor staging. The imaging results were compared with the gold standard, including of histopathology and clinical follow-up. We also investigated the effect of maximum standardize uptake value(SUVmax) and lymph node metastasis on survival. **Results:** The CE-PET/CT had a diagnostic accuracy of 89% (31/35), compared to 57% (19/35) for CI. The results of CE-PET/CT imaging lead to upstaging in 37% (13/35) patients compared to CI staging. For primary tumor detection, the sensitivity of CE-PET/CT was 97% (34/35). Contrast enhanced-PET/CT detected nodal metastases in 19 (54%) patients, whereas CI detected in 9 (26%) patients. Contrast enhanced-PET/CT detected distant metastases in 14 (40%) patients, while conventional methods showed distant metastases in 9 (26%) patients. Maximum SUV of primary tumor does not have a significant effect on survival, whereas the median survival time of patients without lymph node metastasis is longer than patients who have lymph node metastasis (P=0.038). **Conclusion:** These data suggest that ^{18}F-FDG CE-PET/CT had good diagnostic performance compared to conventional imaging for detecting primary tumor, nodal and distant metastasis in BC. Upstaging by CE-PET/CT changed the management of patients.

Hell J Nucl Med 2021; 24(1): 75-82 *Published online: 30 April 2021*

Introduction

Bladder cancer (BC) is the most common form of urinary system malignancy. It is responsible for 3% of new cancer cases and 2.1% of cancer-related deaths worldwide, and it is seen four times more frequently in men than women [1]. For invasive BC, radical cystectomy (RC) with bilateral pelvic lymph node dissection is recommended as the standard treatment method [2].

Conventional imaging techniques, such as non-enhanced or contrast-enhanced (CE) abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI), are usually preferred for pre-treatment staging. Because CT and MRI function as a morphological evaluation, they may be inadequate for detecting metastatic lymph nodes smaller than 1cm [3]. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) urinary excretion and high uptake in the bladder due to urine create challenges in detecting bladder-wall invasion and thereby limit the use of positron emission tomography (PET)/CT in BC. However, some studies have indicated that ^{18}F-FDG PET/CT has 50%-70% sensitivity and high specificity in detecting metastatic lymph nodes and can also reveal sub-centimetric nodes [4-7]. Accurate lymph node mapping and the detection of distant metastases are important for preoperatively determining surgical margins and for disease management in general. A recent multicentre retrospective study showed that ^{18}F-FDG PET/CT findings were associated with increased survival in urothelial carcinomas [8].

In this retrospective study, we aim to compare conventional imaging methods with intravenous CE ^{18}F-FDG PET/CT in tumour node metastasis (TNM) staging of BC and to investigate the association of PET/CT findings with patient survival.

Materials and Methods

Patients

Thirty-five patients who received a histopathological diagnosis of bladder cancer underwent routine conventional imaging and ^{18}F-FDG CE-PET/CT for staging were included in our study. All patients were followed for 3 years with minimum 1 year after diagnosis. Pathological evaluation and imaging modalities were used for disease staging. Patients with a known secondary tumor before imaging, patients with radiocontrast media allergy and patients lost to follow-up were excluded. Time between ^{18}F-FDG CE-PET/CT imaging and disease-related death was calculated as survival time. In survivors, the last date of follow-up was used to calculate survival time. This study was conducted in concordance with good clinical practice guidelines and the current laws. The present study protocol was reviewed and approved by the Institutional Review Board Ethics Committee (Decision no: 14-A-29).

^{18}F-FDG PET/CT protocol

Positron emission tomography/CT images were acquired using Siemens mCT 20 excel LSO PET/ CT scanner (Siemens Molecular Imaging, Hoffmann Estates, Illinois, USA). Overall, 3.7-5.2MBq/kg of ^{18}F-FDG was injected intravenously after minimum 6 hours of fasting, with a serum glucose level under 140mg/dL. The patients were provided with 1.5 liters of water during the time between injection and imaging. All patients underwent early whole-body imaging for 50-70 minutes after injection, while 29 patients underwent pelvic late imaging (2 hour) with full bladder. Computed tomography imaging for PET/CT was performed using a multidetector scanner with 20 slices, at 80-140kV, 20-266mAs, 0.8 pitch, and 512×512 matrix auto-matically defined by the software. Computed tomography images were taken 50 seconds after injecting 75-100mL (300 mg/mL) of non-ionic contrast materials intravenously through forearm veins using an automated injection system (Ulrich medical system; Ulrich Medical, Ulm, Germany). Computed tomography imaging was performed between vertex and upper thigh in craniocaudal direction with 5mm of slice thickness and 0.5s of rotation time. Then, PET imaging was performed in the same range through craniocaudal direction at 8-9 bed positions, 1.5min for each PET bed. Ultra HD images were acquired using time-offlight +True X algorithm for PET/CT at iteration 2 and subset 16 values for reconstruction.

Interpretation of PET/CT images

Images acquired from all patients were evaluated by two nuclear medicine attending physicians with a 10-year experience in PET/CT, at the workstation both visually and semi-quantitatively at axial, coronal, and sagittal planes. Positron emission tomography/CT image evaluation was done unaware of the previous imaging results of patients. For visual evaluation, foci of increased ^{18}F-FDG uptake compared with the background and CT findings were evaluated in conjunction. For semi-quantitative analysis, maximum standardized uptake value (SUVmax) was measured in foci with increased ^{18}F-FDG uptake in visual evaluation and considered to be a lesion. Maximum SUV was calculated by placing the volume-of-interest (VOI) at 1-2cm diameter on the most active-looking slice of ^{18}F-FDG positive lesions. Maximum SUV of the primary tumor and detected lymph nodes were measured on both early and late images. Focal ^{18}F-FDG uptake with an abnormal soft tissue mass or a lymph node on CT counterpart was considered significant for malignancy. Standardized uptake values were considered in semi-quantitative evaluation, but interpretation was based on visual evaluation. Maximum tumor diameter was measured from the axial CE-CT scan of the PET/CT imaging.

Computed tomography

Computed tomography imaging with intravenous non-ionic contrast material at portal venous phase (delayed 70s, slice width 2mm) was performed on 24 patients using a 128-slice Phillips Brilliance multidetector CT (Philips Medical Systems, Cleveland, Ohio, USA). Computed tomography images were acquired with 128×0.625mm collimation, 0.5s of rotation time, 1 pitch, 300-450mAs (personalized settings determined by automatic exposure control system), and 120 kV parameters. Overall, 75mL of non-ionic contrast material was injected at 3mL/s injection velocity through the forearm veins using an automatic injector (Covidien OptiVantage DH, Mallinkrodt, Cincinnati, Ohio, USA).

Morphological criteria regarding size and shape were used for discrimination between benign and malignant lymph nodes. The parameters observed on CT included the size (we just evaluated the lymph nodes with maximum short-axis diameter ≥10mm) and morphologic characteristics (including the presence of the fatty hilum of lymph nodes, the ratio of short-axis/long-axis diameter of lymph nodes, and the margin) of the lymph nodes; the inhomogeneous tumor like enhancement and the presence of necrosis inside lymph nodes were considered as metastatic.

Magnetic resonance imaging

Magnetic resonance imaging was performed on 11 patients included in our study by using a superconducting magnetic resonance scanner with a 1.5T main magnetic field (Signa HDxt; GE Healtcare, Milwaukee, Wisconsin, USA). Gadolinium-containing contrast material was administered by manual intravenous bolus injection at 0.2mL/kg dose. We evaluated the following characteristics of MR images of lymph nodes: the presence of lymph nodes only with maximum short-axis diameter of at least 10mm and morphology; enhancement degree of lymph nodes (an enhancement degree similar to that of the bladder muscle layer indicates remarkable enhancement and a lower degree indicates mild–moderate enhancement); and necrosis in lymph nodes. The maximum tumor diameter was measured at the site of the maximum tumor area on axial T2-weighted images.

Statistical analysis

Mean, standard deviation, median, minimum, maximum, frequency and ratio were used as descriptive statistics, where applicable. The distribution of variables was analyzed using Kolmogorov-Smirnov test. Kappa reliability test was used for reliability analysis. LogRank test was used to evaluate the effect of categorical parameters on survival time. Cox regression analysis was preferred for evaluating continuous variables including SUVmax. Critical value for significance was set as 0.05. All analyses were performed by using MedCalc Statistical Software version 12.7.7 (MedCalc Software

bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

Among 35 patients included in the study, 2 (5.7%) patients were female and 33 (94.3%) were male. Their mean age was 67.5±9.2 years (range: 48-81). Fifteen patients underwent cystectomy and pelvic lymph node dissection. Later histopathological examination revealed that one (3%) of these patients had sarcomatoid urothelial carcinoma and 14 (40%) had invasive urothelial carcinoma. Twenty patients (57%) who were not operated underwent transurethral resection (TUR) biopsy and were revealed to have invasive papillary/urothelial carcinoma. Four patients received radiation therapy (RTx), 4 patients received chemotherapy (CTx), and 10 patients received both RTx and CTx (CRTx). Among operated patients, 1 received RTx and 3 received CTx. One patient with stage 4 disease was lost before initiating therapy.

The sensitivity of ^{18}F-FDG CE-PET/CT imaging for primary tumor was 97% (34/35) and it only failed to show the primary tumor in one patient who were diagnosed with superficial carcinoma via TUR biopsy. Twenty-nine patients underwent lower-abdominal pelvic late imaging with full bladder 1 hour after routine PET/CT image acquisition, aiming to better evaluate the margins of primary tumor with the help of contrast media in the bladder (Figure 1). As a result, primary tumor mean SUVmax was 15.8±5.3 in early imaging while it was 21.3± 7.5 in delayed imaging and the increase in delayed imaging was found to be statistically significant (P< 0.001). Maximum SUV of patients are summarized in Table 1.

Table 1. *Comparison of primary tumor SUVmax in early and delayed imaging.*

	Min-Max	Median	Ort.±s.s.	P
T SUVmax1	7.2-27.5	15.3	15.8±5.2	**< 0.001^{w}**
T SUVmax2	10.0-37.6	21.7	21.3±7.5	
LNSUVmax1	2.4-27	6.5	8.5±5.6	**< 0.001^{w}**
LNSUVmax2	2.8-39.9	10.9	12±7.9	

Wilcoxon Signed Ranks Test

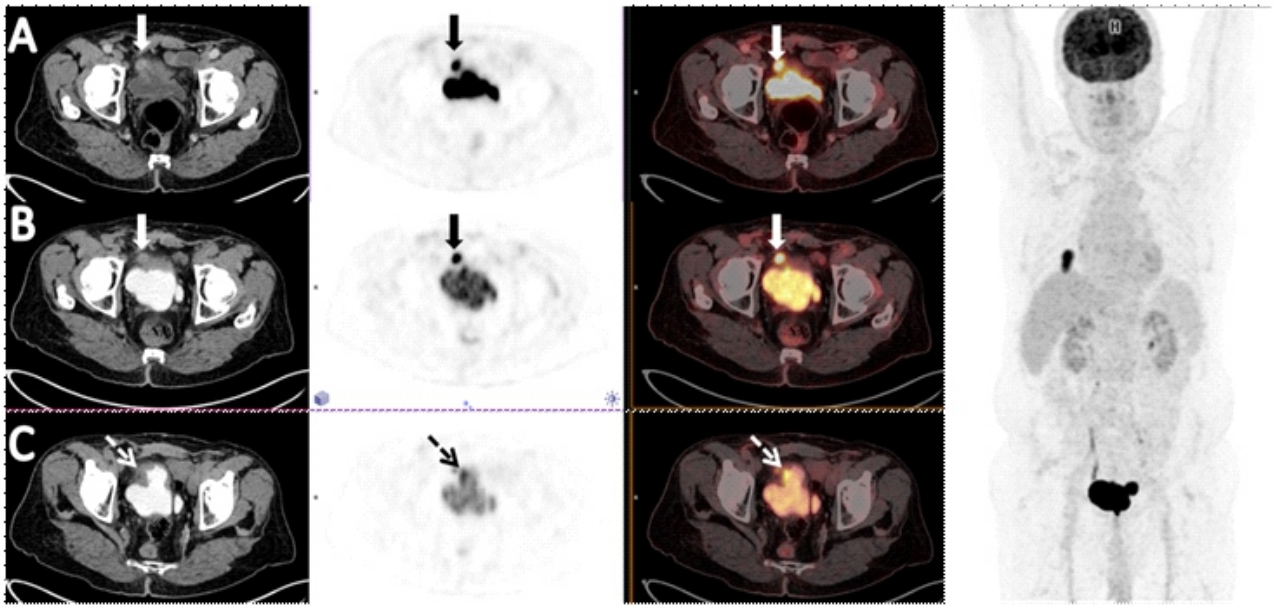

Figure 1. A 72-years-old man, who was diagnosed with urothelial carcinoma after TUR, underwent PET/CT imaging. While prevesical metastatic lymph node (arrows) is not clearly differentiated from the bladder walls in the first hour (early) images (A:CT-PET-Fusion images), it is clearly distinguished in the second hour (delayed) images (SUVmax:39.9) (B:CT-PET-Fusion images). While the primary tumor is not clearly differentiated in the early image, residual tumor tissue (dashed arrows) in the right anterolateral wall is clearly distinguished in the delayed images (C: CT-PET-Fusion images). Biopsy of the hypermetabolic nodular lesion (SUVmax:17.3) observed in the posterobasal segment of the right lung in the MIP image was reported as bladder cancer metastasis.

Fluorine-18-FDG CE-PET/CT evaluation for nodal staging showed 3 cases with N1, 5 cases with N2, and 11 cases with N3 disease, whereas CI revealed 4 patients with N1, 2 with N2, and 3 with N3 disease.

Fluorine-18-FDG CE-PET/CT showed distant metastases in 14 patients (40%), 8 (23%) of which were lung, 5 (14%) of which were bone, 2 (6%) of which were non-pelvic lymph node and 1 (3%) of which were adrenal metastases. On the other hand, conventional modalities detected distant metastases in 9 patients (26%).

As for clinicopathological stage, 8 patients (23%) were evaluated to have stage 1, 3 (9%) patients to have stage 2, 4 (11%) patients to have stage 3, and 20 (57%) to have stage 4 disease. However, 5 (14%) patients had stage 1, 4 (11%) patients had stage 2, 4 (11%) patients had stage 3, and 22 (63%) patients had stage 4 disease according to CE-PET/CT imaging whereas 11 (31%) patients had stage 1, 7 (20%) patients had stage 2, 3 (9%) patients had stage 3, and 14 (40%) patients had stage 4 disease according to conventional imaging modalities. The results of CE-PET/CT imaging lead to upstaging in 37% (13/35) patients compared to CI staging.

Patients' clinicopathological stage showed 57% concordance with radiological stage (P=0.001, Kappa= 0.314), while it showed 89% concordance with CE-PET/CT stage (P< 0.001, Kappa= 0.770). The stage reliability analyses are summarized in Table 2.

A 71-years-old male patient who had a bladder tumor staged as T4N2M1 on CE-PET/CT was also found to have high ^{18}F-FDG uptake in 1.2cm wall thickness on sigmoid colon, interpreted as synchronous colon tumor. Colonoscopic biopsy revealed adenocarcinoma. The patient underwent radical cystoprostatectomy, pelvic lymph node dissection and rectosigmoidectomy. The pathological examination showed pT2a adenocarcinoma for colon and pT4N2 invasive urothelial carcinoma for bladder. This synchronous tumor in rectosigmoid colon and metastatic lymph nodes did not appear in abdominal CT obtained prior to CE-PET/CT imaging (Figure 2).

Another patient who had a bladder tumor staged as T2N0M0 with conventional imaging was found to have an 8x10cm mass in anterior mediastina with SUVmax:18.5 (late SUVmax:23.9) in CE-PET/CT imaging. Contrast enhanced-PET/CT evaluated the bladder tumor as T2N0M0 and the mass in the anterior mediastinum as thymus-derived synchronous tumor. The true-cut biopsy of the mass revealed type 2b thymoma. Three patients who underwent cystoprostatectomy were also found to have T1 prostate adenocarcinoma (Gleason score 3+3), however, both CE-PET/CT and CI failed to show these tumors.

After approximately 3 years of follow-up, overall median survival was found to be 9 months and 26 patients (74%) were lost due to bladder cancer. Univariate analyses found that the presence of lymph node metastases (Figure 3), lymph node stage and clinicopathological stage were associated with overall survival (OS) (P=0.002, P<0.001, and P=0.001, respectively). Yet, multivariate analyses failed to show this association (P>0.05). Primary tumor SUVmax and lymph node SUVmax values had no significant association with OS in univariate analyses (P>0.05) (Table 3).

Table 2. *Comparison of clinicopathological stage with conventional imaging and Ce-PET/CT staging.*

		Clinicopathological Stage (CPS)					
		I	II	III	IV	Reliability %	Kappa/P
CI Stage	I	6	2	0	3		
	II	1	1	3	2	CI.Stage = CPS n=20 / 57%	**Kappa= 0.314**
	III	1	0	0	2	CI.Stage = CPS n=3 / 9%	**P=0.001**
	IV	0	0	1	13	CI.Stage = CPS n=12 / 34%	
PET/CT Stage	I	5	0	0	0		
	II	1	3	0	0	PET.Stage = CPS n=31 / 89%	**Kappa= 0.770**
	III	1	0	3	0	PET.Stage = CPS n=4 / 11%	**P<0.001**
	IV	1	0	1	20	PET.Stage = CPS n=0 / 0%	

Kappa reliability analysis, CI: conventional imaging

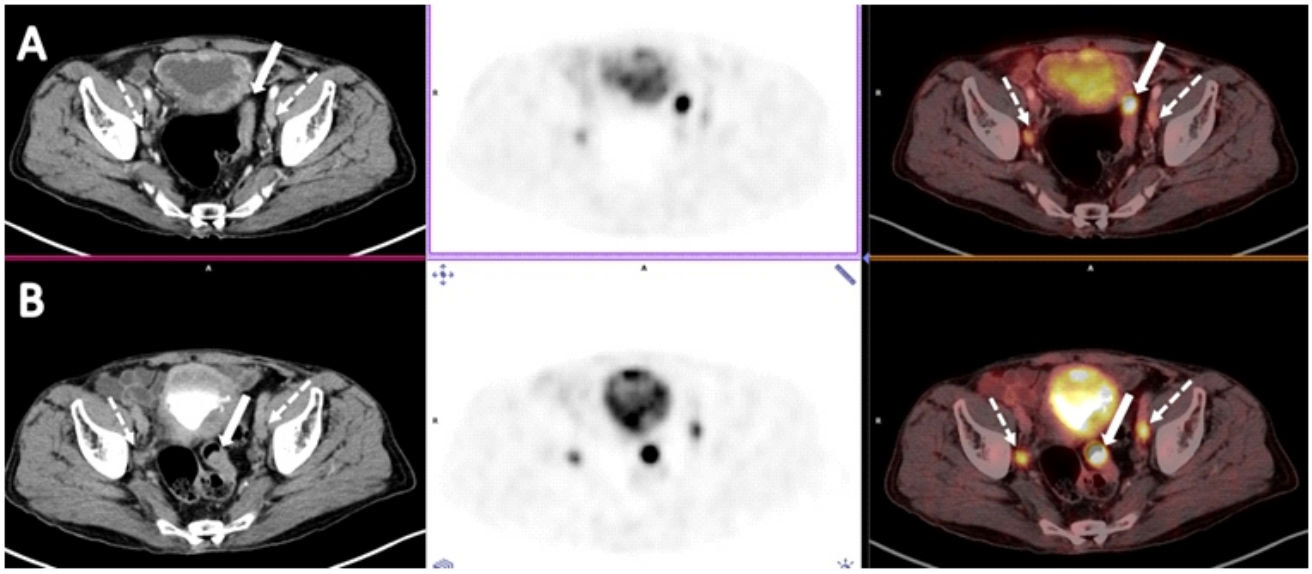

Figure 2. A 71-years-old man who had a bladder tumor underwent PET/CT. In the first hour (early) images (A: CT, PET, Fusion images), the increased ^{18}F-FDG uptake (SUVmax: 11) observed in the bladder walls became prominent in the second hour (late) images (B: CT, PET, Fusion images) (SUVmax: 15.7)and the tumor invades the rectum and prostate gland (not shown). In the late images (B) of the lymph nodes observed in the bilateral parailiac area(dashed arrows), a significant increase in ^{18}F-FDG uptake is observed, and the early-late SUVmax values were 4.36 and 11.1, respectively. Intense ^{18}F-FDG uptake (SUVmax: 16.8) is observed in early and late images in the sigmoid colon (arrows). The pathological examination showed pT2a adenocarcinoma for colon and pT4N2 invasive urothelial carcinoma for bladder.

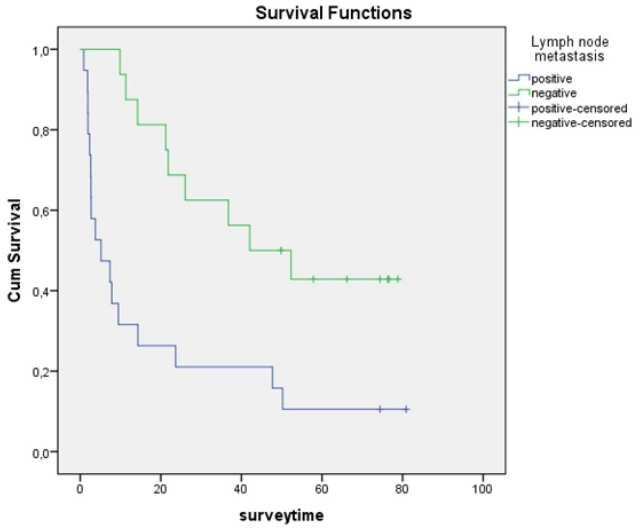

Figure 3. Association of the presence of lymph node metastasis with survival (Kaplan-Meier).

Discussion

Bladder cancer is the most common cancer of the urinary system, with 75% superficial and 25% invasion to muscle tissue [9]. Muscle invasion increases the risk of distant metastases, which are most encountered in lymph nodes, bone, lung and liver [10]. Standard staging of bladder cancer is performed using TNM staging based on primary tumor (T), lymph node (N), and distant metastasis (M) [11].

In a study that evaluated 34 patients for initial staging after transurethral biopsy, ^{18}F-FDG PET/CT was found to have 87.5% sensitivity, 80% specificity, and 82% accuracy while these rates were 66%, 57%, and 60% for CT, respectively. Among 43 evaluated for re-staging, ^{18}F-FDG PET/CT was found to have 85% sensitivity, 60% specificity, and 70% accuracy while these rates were 80%, 50%, and 58% for CT, respectively. Maximum SUV for primary tumor, ranged from 5.7 to 30.4 and for lymph node metastases ranged from 3.5 to 13.8. The rate of detecting primary tumor with histopathological confirmation was 88% for both PET/CT and CT [12]. In their study with 54 patients who have locally advanced bladder cancer, Aljabery et al. (2015) reported 86% specificity, 58% positive predictive value (PPV), and 76% negative predictive value (NPV) for PET/CT while only reporting 89% specificity, 64% PPV, and 77% NPV for CT [13]. In our study, the sensitivity of ^{18}F-FDG CE-PET/CT for localizing primary tumor was 97% (34/35) and the primary tumor could not be shown in one

Table 3. *Impact of SUVmax, stage and lymph node metastasis variables on survival.*

		Median survival (months)	Odds ratio	95% CI Lower -upper	P
Clinicopathological stage					**0.001**[2]
	1	62.7 (:mean)		47.7-77.6	
	2	41		8.9-73.0	
	3	11		-	
	4	7		6.1-33.9	
Lymph Node Metastasis					**0.002**[2]
	Yok	41.0		13.6-70.6	
	Var	5.0		0.0-11.8	
Lymph Node Stage					**<0.001**[2]
	0	41.0		13.6-70.6	
	1	47.0		0.0-112.0	
	2	5.0		0.0-11.4	
	3	2.0		2.08-3.3	
Lymph node SUVmax		-	0,986	0.904-1.076	0.753[1]
Tumor SUVmax		-	0,991	0.810-1.074	0.834[1]

[1]*Log Rank test, CI: Confidence Interval,* [2]*Cox Regression Analysis*

patient with superficial carcinoma diagnosed with TUR before imaging.

Jeong et al. (2015) compared ^{18}F-FDG PET/CT with CT for lymph node (LN) staging in patients with T1 (n=9) and muscle invasive bladder cancer (MIBC) (n=52). In patient-based analyses, they found that PET/CT had 47.1% sensitivity, 93.2% specificity, 72.7% PPV, and 82.0% NPV while CT had 29.4% sensitivity, 97.7% specificity, 78.2% PPV, and 78.2% NPV. The authors reported that PET/CT had low sensitivity for LN staging of MIBC and it did not increase the diagnostic accuracy of CT for LN metastasis. This can be affected by various factors, such as the patient population included, extent of LN dissection, and cut-off value of SUV [14].

In 78 patients with bladder cancer who had histopathological confirmation with radical cystectomy, Soubra et al. (2016) found the sensitivity and specificity of ^{18}F-FDG PET/CT to be 56% and 98%, respectively, for nodal metastasis [15]. In another study, CT scan had 46% sensitivity and 98% specificity and PET/CT scan had 68% sensitivity and 95% specificity for pelvic LN involvement (n = 93) [16]. In our study, ^{18}F-FDG CE-PET/CT evaluation for nodal staging showed 3 cases with N1 disease, 5 cases with N2 disease, and 11 cases with, whereas conventional modalities revealed this numbers to be 4, 2, and 3, respectively, indicating a significant superiority for CE-PET/CT.

In their study with 207 high-risk bladder cancer with or without muscle invasion, Goodfellow et al. (2014) compared the roles of PET/CT and CT in distant metastases and found the sensitivity of PET/CT and CT to be 54 and 41%, respectively. Both modalities had similar specificities of 97 and 98% (16). In our study, CE-PET/CT showed distant metastases in 14 patients (40%) while conventional modalities detected distant metastases in only 9 patients (26%).

In a previous study, preoperative ^{18}F-FDG PET/CT imaging detected 47% more malignant lesions than CT in patients with high-risk MIBC and changed the treatment plans of 27% of patients [17]. A recent study has reported 28% upstaging and 1% downstaging with PET/CT [18]. In our study, the results of CE-PET/CT imaging lead to upstaging in 37% (13/35) patients compared to CI staging. We also found a significant concordance with CE-PET/CT stage and clinicopathological stage. Patients' clinicopathological stage showed 57% concordance with radiological stage, while it showed 89% concordance with CE-PET/CT stage. This may be due to

CE-PET/CT imaging and evaluation according to additional image acquisition. There is no similar study in the literature regarding CE-PET/CT in bladder cancer to compare with our findings. However, studies that investigate the role of CE-PET/CT in renal, larynx and ovarian malignant neoplasms showed ^{18}F-FDG CE-PET/CT to be superior to conventional imaging modalities [19-21].

Yoon et al. (2017) reported the sensitivities of early dynamic (ED), whole-body (WB, 60minutes after injection), and additional delayed (AD, 120 minutes after injection) PET imaging for bladder cancer to be 84.6%, 57.7%, and 61.2%, respectively. The sensitivity of ED PET was significantly higher than that of WB (P= 0.002), and AD PET (P=0.008) [22]. In our study, 29 patients underwent lower-abdominal pelvic late imaging with full bladder 1 hour after routine PET/CT image acquisition, achieving better evaluation of the margins of primary tumor with the help of contrast media in the bladder.

The use of IV contrast media increases the CT Hounsfield units in contrasting area. These areas in turn were transformed to artifactually high PET attenuation factors and ultimately led to an overestimation of SUV values. An approximately 8.4% increase in SUVmax has been reported in malignancies [23]. Because of IV contrast there is an increase in SUV values compared to other studies that use low-dose CT and this is the reason that our SUV values are higher than those of previous studies.

Contrast enhanced-PET/CT revealed type 2b thymoma in one patient and adenocarcinoma of sigmoid colon in another patient in our study. Similar studies also found synchronous tumors in 3% of patients [16].

Several studies have shown that nodal involvement in BC is significantly associated with a higher risk of recurrence and worse cancer-specific mortality after radical cystectomy [24]. Extravesical ^{18}F-FDG avid lesions, suspicious for malignancy on PET/CT, were correlated with mortality in 211 patients with MIBC and the data suggested that ^{18}F-FDG may be an independent prognostic indicator of mortality [25].

Alongi et al. (2017) reported that, nodal and metastatic PET-defined involvement predicted increased risk of disease progression only at univariate analysis (nodal involvement HR=3.7, P=0.006; distant metastases HR=2.7, P= 0.038). By evaluating semi-quantitative PET parameters in those patients with positive findings (n=21), SUVmax>6 and total lesion glycolysis (TLG)>8.5 were found to be the optimal thresholds to predict progression-free survival (PFS) (2-year PFS 62% for SUVmax<6 vs. 15% for SUVmax>6; 2-year PFS 66% for TLG<8.5 vs. 18% for TLG>8.5). Cox regression analysis showed significant results only for SUVmax >6 (univariate HR=4; P=0.018; multivariate HR=5.08; P=0.045) and for SUVmean >4.5 (univariate HR=2.3; P=0.012) [26]. In our study, univariate analyses found that the presence of lymph node metastases, lymph node stage and clinicopathological stage were associated with overall survival (P= 0.002, P<0.001, and P=0.001, respectively), yet, multivariate analyses failed to show this association. Primary tumor SUVmax and metastatic lymph node SUVmax values had no significant association with OS in univariate analyses.

Study limitations

Our study's limitations include its relatively low sample size, all patients undergoing radical cystectomy + pelvic lymph node dissection, evaluating OS rather than PFS and including patients receiving different treatment modalities.

In conclusion, these data suggest that ^{18}F-FDG CE-PET/CT had much more diagnostic accuracy compared to conventional imaging methods for detecting primary tumor, and also nodal and distant metastasis in BC. More effective tumor staging used with CE-PET/CT can lead to changes in patient management, contribute to predicting prognosis, and may have a positive impact on survival rates.

The authors declare that they have no conflicts of interest.

Ethics

The present study protocol was reviewed and approved by the Institutional Review Board of İstanbul university, Cerrahpaşa Medical School Ethics Committee. (Decision no: 14-A-29). Informed consent was obtained by all subjects when they were enrolled.

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