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ORIGINAL ARTICLE

Recurrent bladder carcinoma: clinical and prognostic role of 18 F-FDG PET/CT

Pierpaolo Alongi[1] · Federico Caobelli[2] · Roberta Gentile[3] · Alessandro Stefano[4] · Giorgio Russo[4] · Domenico Albano[5] · Sergio Baldari[3] · Maria Carla Gilardi[4] · Massimo Midiri[1,5]

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Abstract
Aim A small number of studies evaluated the detection rate of lesions from bladder carcinoma (BC) of 18 F-FDG PET/CT in the restaging process. However, the prognostic role of FDG PET/CT still remains unclear. The aim of the present study was to evaluate the accuracy, the effect upon treatment decision, and the prognostic value of FDG PET/CT in patients with suspected recurrent BC.
Materials and Methods Forty-one patients affected by BC underwent FDG PET/CT for restaging purpose. The diagnostic accuracy of visually interpreted FDG PET/CT was assessed compared to histology (n = 8), other diagnostic imaging modalities (contrast-enhanced CT in 38/41 patients and MRI in 15/41) and clinical follow-up (n = 41). Semiquantitative PET values (SUVmax, SUVmean, SUL, MTV, TLG) were calculated using a graph-based method. Progression-free survival (PFS) and overall survival (OS) were assessed by using Kaplan-Meier curves. The risk of progression (hazard ratio, HR) was computed by Cox regression analysis by considering all the available variables.
Results PET was considered positive in 21 of 41 patients. Of these, recurrent BC was confirmed in 20 (95 %). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FDG PET/CT were 87 %, 94 %, 95 %, 85 %, 90 %. AUC was 0.9 (95 %IC 0.8-1). Bayesian positive and negative likelihood ratios were 14.5 and 0.13, respectively. FDG PET/CT findings modified the therapeutic approach in 16 patients (modified therapy in 10 PET-positive patients, watch-and-wait in six PET-negative patients). PFS was significantly longer in patients with negative scan vs. those with pathological findings (85 % vs. 24 %, $p < 0.05$; HR = 12.4; $p = 0.001$). Moreover, an unremarkable study was associated with a longer OS (88 % vs. 47 % after 2 years and 87 % vs. 25 % after 3 years, respectively, $p < 0.05$). Standardized uptake value (SUV)max > 6 and total lesion glycolysis (TLG) > 8.5 were recognized as the most accurate thresholds to predict PFS (2-year PFS 62 % for SUVmax < 6 vs. 15 % for SUVmax > 6, $p = 0.018$; 2-year PFS 66 % for TLG < 8.5 vs. 18 % for TLG > 8.5, $p = 0.09$).
Conclusion A very good diagnostic performance for FDG PET/CT was confirmed in patients with suspected recurrent BC. FDG PET/CT allowed for a change in treatment decision in about 40 % of cases and showed an important prognostic value in assessing PFS and OS.

Keywords Bladder cancer · 18 F-FDG-PET/CT · Restaging · Prognostic role · Clinical role

✉ Pierpaolo Alongi
alongi.pierpaolo@gmail.com

[1] Department of Radiological Sciences, Nuclear Medicine Unit, San Raffaele G. Giglio Institute, Contrada Pietrapollastra-Pisciotto, 90015 Cefalù, Italy

[2] Department of Nuclear Medicine, Basel University Hospital, Basel, Switzerland

[3] Nuclear Medicine Unit, Department of Biomedical Sciences and Morphological and Functional Images, University of Messina, Messina, Italy

[4] IBFM-CNR, Cefalù, Italy

[5] DIBIMEF - Sezione di Scienze Radiologiche, Università degli Studi di Palermo, Palermo, Italy

Introduction

Bladder cancer (BC) is the ninth most common tumor, with 380,000 new cases annually. The ratio of male/female patients

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is 3.8/1 [1]. According to data from the US, BC prevalence has been increasing substantially with about 70,000 new cases annually [2]. Despite the recent therapy advances, it has been reported that 15,250 deaths occurred from BC in 2013 [3]. Ten to 15 % of the patients present with metastatic disease at diagnosis and despite radical treatments, even those patients with initial local disease develop metastatic involvement in approximately 50 % of cases within 2 years from the diagnosis [4].

Failure of clinical staging is the biggest barrier to predict survival and plan additional treatment protocols. Computed tomography (CT) and magnetic resonance imaging (MRI) have suboptimal sensitivity (48–87 %) for the detection of lymph node metastases due to the widely adopted morphologic criteria mainly based on node size [5], thus underestimating metastases occurring in normal-sized lymph nodes [6].

Recently, a number of studies have investigated the diagnostic value of ^{18}F-fluorodeoxyglucose (FDG) PET, eventually fused with CT in the staging of BC [7, 8]. Despite the widespread use of FDG PET/CT in the clinical setting for restaging of BC, there are only a few reports in the literature on its performance in detecting recurrent lesions. Even more importantly, its impact during the restaging process on prognosis and therapy planning still needs to be elucidated. As such, it would be important to investigate the impact of FDG PET/CT on both treatment management and prognosis in patients with recurrent BC. The aims of the present study were: 1) to evaluate the diagnostic performance of FDG PET/CT for suspected recurrent BC, 2) to assess the impact on treatment decision, and 3) to investigate the prognostic value of FDG PET/CT in the restaging process.

Materials and methods

We retrospectively evaluated 41 patients affected by BC from the FDG PET/CT database of San Raffaele G. Giglio Hospital in Cefalù, Italy. All patients underwent ^{18}F-FDG PET/CT for restaging purpose.

Inclusion criteria were as follows: (a) pathology confirmed diagnosis of BC after primary treatment; (b) FDG PET/CT performed as second-stage examination to detect locally recurrent lesions and/or metastatic involvement. These were suspected based on conventional imaging and/or clinical data; (c) FDG PET/CT findings confirmed pathologically and/or by means of other imaging modalities (contrast enhanced computed tomography [CE-CT], magnetic resonance imaging [MR], and bone scan). (d) PET/CT performed within 3 months from conventional imaging; (e) clinical and instrumental follow-up data available (clinical case notes, multidisciplinary meeting reports coupled with evaluation of further available CE-CT, MR, FDG PET/CT, and bone scan). Minimum follow-up duration was set at 24 months after primary treatment. At follow-up, data about disease-free status or presence of local and/or metastatic progression were recorded. Additionally, treatment decision-making guided by FDG PET/CT results was evaluated.

FDG PET/CT imaging

FDG PET/CT scans were performed in accordance with the standard whole-body oncological protocol in use in our institution, following international guidelines published on behalf of the European Association of Nuclear Medicine (EANM) [9, 10]. Written informed consent was obtained by each patient before the examination and the study was performed in compliance with the Declaration of Helsinki. FDG PET/CT was performed in the fasting state for at least 6 h and the glucose level was always lower than 160 mg/dL. Images were acquired on a PET/CT Discovery™ scanner (GE Healthcare, Haifa, Israel) from the vertex to the mid-thigh, with inclusion of the upper extremities. Acquisition was started 60 min after the intravenous administration of 3.7 MBq/Kg FDG (6-8 beds, 2-4 min per bed position). A low-dose CT (90–120 mA, 140 kV, 0.8 s per tube rotation) was also acquired to perform non-uniform attenuation correction. FDG PET/CT images were reconstructed to a 256×256 matrix and qualitatively evaluated by two experienced nuclear medicine physicians. The readers were always kept blind to the results of other imaging modalities and to clinical data. PET/CT was rated positive if the metabolic activity in the lesion was moderately or markedly increased relative to comparable normal structures or surrounding soft tissues (e.g., blood pool in the case of pulmonary nodules). A lesion with no or faint FDG uptake (less or equal to the surrounding soft tissues) was defined as negative. The co-registered low dose CT was used to allow for more accurate tumor delineation if a local recurrence was suspected. If CT scan was not considered sufficient to discriminate between tumor and urinary activity, delayed PET/CT images of the pelvis were acquired starting 30-60 min after completing the first scan.

Semi-quantitative PET values (standardized uptake value [SUV]max, SUVmean, SUV normalized to lean body mass [SUL], metabolic tumor volume [MTV], total lesion glycolysis [TLG]) were calculated on hypermetabolic lesions using a graph-based method, which has been previously described [11]. The difference in segmentation between the conventional approach and this graph-based method consists in that the conventional approach, although widely used for its ready availability and simplicity, is somewhat influenced by PET image noise and heterogeneity. Conversely, the graph-based method used in the present paper considers the segmentation as the solution to a linear system with an exact solution; as such, it is very accurate in noisy and low contrast images, such as PET images. SUL value has been calculated as

increasingly used in the latest years for quantitative assessment of clinical PET, owing to its ability to remove inter-operator variability [12].

Disease progression and survival rate were assessed using post-therapy follow-up data, including routine conventional diagnostic procedures such as CE-CT, MRI, bone scan, and eventually biopsy on suspicious residual disease. Subsequent FDG PET/CT scans, performed after the restaging scan during the follow-up period were also used to assess disease status.

According to the corresponding state of disease at the time of the PET examination, as recorded in the clinicians' or multidisciplinary team's case notes at follow-up, PET results were then rated as true/false positive and true/false negative.

Statistical analysis

Using final diagnosis as a reference, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), accuracy, and likelihood ratios were calculated based on Bayes's law, with 95 % confidence intervals (CIs). ROC curves were used both to assess for sensitivity and specificity and to determine the most accurate thresholds of semiquantitative values. OS was defined as the time interval between primary surgery and death. Progression-free survival (PFS) was determined considering the time interval between the latest treatment and the appearance of clinical or radiological progression. PFS and OS were computed using Kaplan-Meier curves. Univariate and multivariate Cox proportional hazards models were fitted in the whole sample. The independent prognostic value of PET/CT was tested against different variables (e.g. nodal or organ metastasis, muscle invasive primary tumor, type of treatment) in a subgroup of 35 out of 41 patients. Cox regression model was built using a stepwise selection procedure with significant p value set to <0.05. The relationship between outcome and the variables included was summarized by hazard ratios (HR) with 95 % confidence intervals (95 %CI). All statistical analyses were performed using the IBM SPSS Statistics software (version 20.0). $p < 0.05$ was considered significant.

Results

Forty-one patients scanned between January 2010 and December 2015 met the inclusion criteria. Primary histological subtypes were distributed as follows: transitional cell carcinoma, n = 33 (80 %); papillary transitional cell carcinoma, n = 6 (15 %); squamous cell carcinoma, n = 2 (5 %). T status on TNM staging was available in 35/41 subjects (85.3 %: T1, n = 10; T2, n = 8; T3, n = 9; T4, n = 8). Differentiation grading data were available in 24/41 patients (58.5 %: G1, n = 3;G2, n = 3; G3, n = 19). Mean age of study population was 67 ± 10 years, 36/41 patients were male (87.8 %). Twenty-three patients (56.1 %) underwent radical cystectomy, 10 (24.4 %) trans-urethral resection (TURB), eight (19.5 %) received intravescical immunotherapy with Calmette-Guerin Bacillus (CGB) as primary treatment. Patients' data are summarized in Table 1.

PET Performance in detecting recurrences

FDG PET/CT was rated positive in 21 patients and negative in 20. Among patients with available staging-TNM data, six patients with primary stage T1, four patients with T2, four patients with T3, and four with T4 had evidence of FDG-avid relapsed disease (Table 1). Hypermetabolic lesions were found in two patients with differentiation grading G1, in one patient with G2, and 13 patients with G3.

Table 1 Characteristics of patients

n	41
Age, years (mean ± SD)	67 ± 10
Primary tumor treatment	
Radical cystectomy, no. (%)	23 (56)
Trans-urethral resection, no. (%)	10 (24)
Intravesical immunotherapy BCG, no. (%)	8 (20)
Histology, no. (%)	
Transitional cell carcinoma	33(80)
Papillary transitional cell carcinoma	6 (15)
Squamous carcinoma	2 (5)
T status-TNM staging, no. (%)*	
T1	10 (29)
T2	8 (23)
T3	9 (25)
T4	8 (23)
Differentiation grading, no. (%)**	
G1	3 (12)
G3	3 (12)
G3	19 (76)
PET/CT, no. (%)	
Negative	20 (49)
Positive	21 (51)
True positive	20 (48)
True negative	17 (41)
PET findings, no.(%)	
Abdominopelvic lymph node	16 (39 %)
Supra-renal lymph node	3 (7 %)
Bone lesion	5 (12 %)
Lung	5 (12 %)
Confirmed recurrent disease, no. (%)	
No	21 (51)
Yes	20 (49)

*available in 35 patients; **available in 25 patients

PET/CT findings were compared to CE-CT in all subjects, to MR in six and to bone scan in four. Histopathology was available in 11 patients. Furthermore, 29 patients underwent a second FDG PET/CT examination during follow-up.

Suspected recurrence of BC was confirmed in 20/21 patients with a positive FDG-PET scan (as reference, other imaging and/or follow-up clinical data were used in 13 patients and histopathology in eight). In one patient, FDG PET/CT showed a false positive finding, later diagnosed as lymph nodal chronic inflammatory disease. In 17/20 patients with negative FDG-PET scan, other imaging and/or follow-up clinical data confirmed absence of recurrent disease. In 3/41 patients FDG PET/CT failed to detect recurrences, due to the presence of small lesions under the spatial resolution of PET scanner.

Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FDG-PET were 87 %, 94 %, 95 %, 85 %, 90 %, respectively. Area under the curve (AUC) was 0.9 (95 % CI 0.8-1; $p < 0.05$). Positive and negative likelihood ratios were 14.5 and 0.13, respectively. Odds ratio pretest was 1.44.

Change in treatment decision

FDG PET/CT findings had a significant impact on therapeutic approach in 16 patients (39 %). Specifically, six (15 %) PET-negative patients remained in "watch-and-wait" and did not undergo further therapies, while therapeutic regimen was modified in 10 patients (24 %) with a positive scan. Specifically, the treatment switched from palliative to salvage (i.e. surgery) in three patients (7 %), new chemotherapy or immunotherapy was started in five patients (12 %) with advanced BC and two patients (5 %) underwent targeted radiotherapy.

FDG PET/CT and prognosis

After a mean follow-up period of 27 months (± SD 10.9), 17 (41 %) patients had progressive recurrence of disease, and six (14 %) had died. Of 24 (58 %) patients without progressive disease, nine (22 %) had stable disease and 15 (36 %) were disease-free.

Unremarkable FDG PET/CT scan was associated with a significantly longer survival rate over 2 and 3 years compared to a positive examination (88 % vs. 47 % after 2 years and 87 % vs. 25 % after 3 years, respectively, $p < 0.05$; Fig. 1; Table 2). Similarly, the absence of hypermetabolic, suspected lesions on FDG PET correlated with a longer 2-year PFS compared to a pathology scan (85 % vs. 24 %, $p < 0.05$; Fig. 2; Table 2).

A positive PET scan was strongly associated with an increased risk of disease progression (HR = 12.4; $p = 0.001$) both at univariate and at multivariate Cox regression analysis. 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, $p = 0.038$). However, at multivariate analysis, PET positivity was confirmed as the only variable with independent prognostic value (Table 3).

In addition, in a subgroup of 35 patients in which staging data were available, univariate and multivariate Cox regression analysis showed increased risk for PET positivity in PFS ($p = 0.03$ and 0.02, respectively) and OS ($p = 0.006$ and 0.04, respectively). The presence of muscle-invasive tumor at staging significant was significantly correlated with shorter PFS and OS at univariate analysis ($p = 0.005$ and 0.01, respectively). In a multivariate analysis, however, the significance was only approached with regard to PFS ($p = 0.05$) and not demonstrated concerning OS ($p = 0.2$). Finally, T at staging and the therapeutic regimen (surgery and/or chemotherapy) failed to predict a difference in outcome (Table 4).

By evaluating semiquantitative PET parameters in those patients with positive findings (n = 21, Table 3), SUVmax > 6 and TLG > 8.5 were found to be the optimal thresholds to predict 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; $p = 0.012$). The other semiquantitative parameters, including SUL, failed to show a significant predictive value.

Discussion

Evaluation of recurrence and metastatic involvement plays a pivotal role in planning the optimal therapy in patients with BC. In fact, the survival rate decreases parallel to the stage of the disease and survival time decreases by more than half in the presence of metastatic disease. The 5-year recurrence-free survival in node-positive patients who underwent cystectomy is estimated to be 34-43 %, which is considerably lower than that in patients without nodal involvement [5]. In a surgery-only study, the 5-year recurrence-free survival has been reported to be 76, 74, 52, and 36 % in patients with pT1, pT2, pT3, and pT4 tumors, respectively [4].

Detection and local staging in BC using FDG PET/CT has not been widely undertaken to date due to physiologic FDG activity excreted through the urinary system, thus hampering the visualisation of primary BC and regional nodes. However, a paper by Drieskens et al showed that metabolism-based anatomical information gathered by adding 18 F-FDG-PET to CT provided high diagnostic accuracy in the pre-operative staging of invasive transitional cancers, particularly invasive BC [13]. Moreover, a recent meta-analysis reported optimal

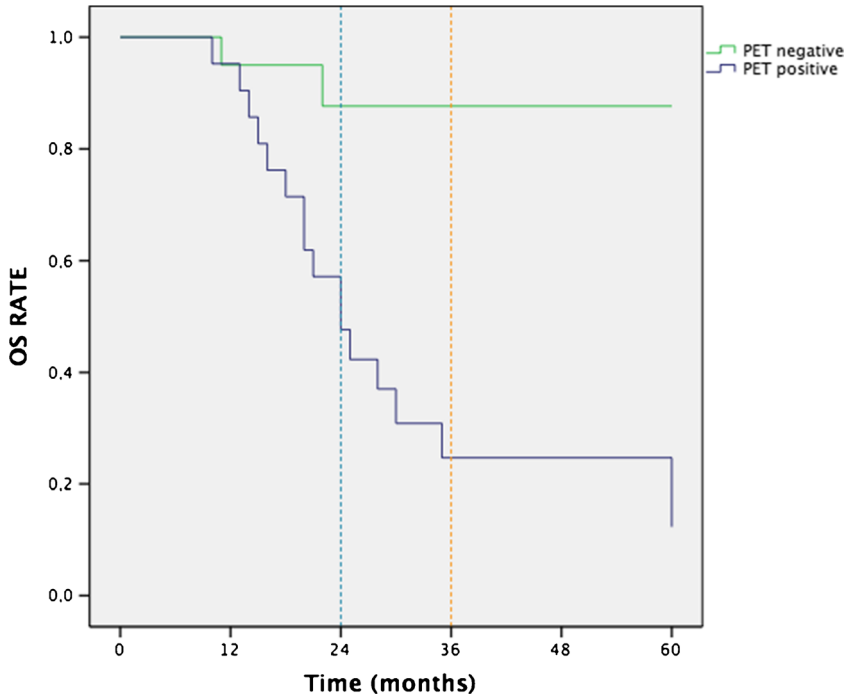

Fig. 1 Overall survival (OS) calculated by means of Kaplan-Meier survival analysis depending on the FDG-PET

performance of FDG PET or PET/CT in detection of metastatic lesions of urinary bladder cancer (pooled sensitivity 82 %, pooled specificity 89 %, diagnostic accuracy 92 %) [14]. However, as suggested by Maurer et al. in evaluation of current staging procedures in BC, although promising results could be obtained for these PET/CT examinations in smaller series, their true value cannot be determined at present [15].

Such favourable performances in the staging process were demonstrated to pertain also to the restaging, making FDG PET/CT an important tool in rendering decisions regarding radiotherapy, chemotherapy, and post-operative follow-up [16]. Our work also demonstrates that FDG PET/CT, performed in the restaging process, has optimal diagnostic performances, similar to those yielded by staging FDG PET/CT. In fact, the pooled sensitivity and specificity in our study were 87 % and 94 %, respectively, while diagnostic accuracy was 90 %.

Table 2 Kaplan Meir analysis of 2-year progression-free survival (PFS) and 3-year overall survival (OS)

	2-year PFS	3-year OS	*p* value
FDG PET/CT findings (n = 41)			
Positive	24 %	25 %	<0.05
Negative	85 %	87 %	<0.05
PET semi-quantitative values			
SUVmax > 6	15 %	12 %	<0.05
SUVmax < 6	62 %	50 %	<0.05
TLG > 8.5	18 %	9 %	0.06
TLG < 8.5	66 %	60 %	0.06

It still remains unclear whether FDG PET/CT may also play an important role in the prognostic assessment of patients affected by BC. To date, the prognostic value of PET/CT, using ^{11}C-choline as radiotracer, has been studied in a single instance by Maurer et al [17], wherein an unsatisfactory predictive value concerning predict OS or cancer-specific death in BC patients was reported. However, the prognostic assessment was investigated only pre-operatively and PET/CT was performed using another radiopharmaceutical, able to trace different metabolic pathways than FDG.

In this regard, the present study provides major novelty in two aspects. First, to the best of our knowledge, this is the first paper investigating the prognostic role of FDG PET/CT in restaging patients affected by BC. This may lead to a broader applicability of this technique in selected centers. And second, it confirms the ability of this technique to change therapeutic approach in a significant proportion of patients. This may provide robust evidence that decisions regarding therapeutic approach can effectively rely on FDG PET/CT findings.

FDG PET/CT, as performed in the restaging process, has recently been demonstrated to play a pivotal role in the prognostic assessment in other types of cancer [18, 19]. We here demonstrate that a similar prognostic value also pertains to BC. In fact, from our results obtained applying Cox regression and Kaplan-Meyer analysis, a positive PET/CT is significantly associated with a higher rate of progression and a significantly reduced overall survival, regardless of nodal or metastatic involvement (Fig. 3). Conversely, a negative scan allows for predicting a more favourable outcome (Fig. 4). PET positivity also proved to yield the highest significance compared to other

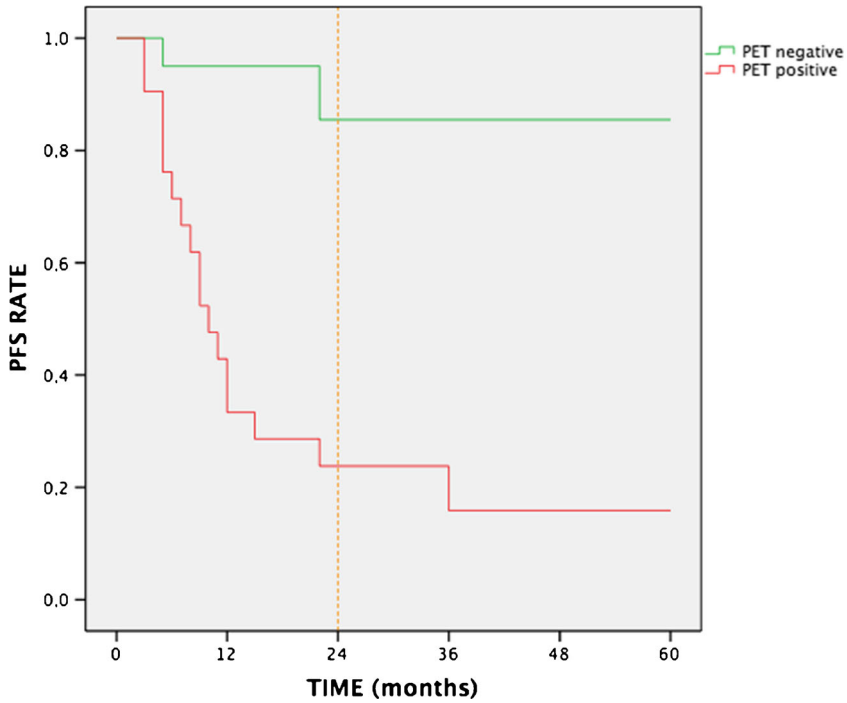

Fig. 2 Progression-free survival (PFS) calculated by means of Kaplan-Meier survival analysis depending on the FDG-PET

recognized variables that may affect the outcome such as presence of muscle invasive tumor and therapeutic approach. From our multivariate analysis, only PET positivity has been identified as independent predictor, while the presence of muscle-invasive tumor only approached significance and other variables such as T at staging and therapeutic regimen failed to show a prognostic value. This is apparently in contrast to what reported in the literature, recognizing an important prognostic role for T at staging [20]. We may hypothesize that this discrepancy rely on the small number of patients in each subgroup (i.e. max 11 subjects); if the same hypothesis was tested with multivariate analysis in a larger population, results would probably be more consistent with those in literature.

Of note, we also identified thresholds in semiquantitative parameters, able to identify patients at increased risk of disease progression. From the analysis of ROC curves, values of SUVmax above 6 and of TLG above 8.5 were able to predict a poorer outcome. Conversely, other semiquantitative parameters such as SUVmean, SUL, and MTV failed to prove relevant for the prognostic assessment. Similar contentious results when using semiquantitative parameters for the prognostic assessments have already been reported in literature in other types of cancer: while a recent paper reported an important role for TLG

Table 3 FDG PET/TC value on Cox regression (univariate and multivariate) analysis for the prediction of progression disease

Variable	Univariate analysis		Multivariate analysis	
	HR (95 % IC)	*p*	HR (95 % IC)	*p*
FDG PET/CT findings (n = 41)				
Positive	12.4 (2.8-23)	*<0.01*	16.3	*0.001*
Negative	*	*	*	*
Lymph-nodal disease	3.76 (1.4-9.6)	*0.006*	0.72 (0.2-2-1)	*0.5*
Organ metastatic lesions	2.7 (1.05-6.8)	*0.038*	0.91 (0.3-2.4)	*0.8*
PET Semi-quantitative values (n = 21)				
SUVmax > 6	4 (1.2-12)	*0.018*	5.08 (0.8-26)	*0.045*
SUL > 3.5	2.1 (0.7-5.8)	*0.1*	0.44 (0.09-2.4)	*0.3*
SUVmean > 4.5	2.3 (08-5.9)	*0.012*	1.2 (0.2-5.7)	*0.7*
MTV > 3.5	1.7 (0.6-4.6)	*0.281*	0.7 (0.2-14)	*0.7*
TLG > 8.5	3 (0.8-10)	*0.09*	1.7 (0.2-14)	*0.61*

Table 4 Cox regression (univariate and multivariate) analysis for the prediction of progression disease and overall survival

Variable (n = 35)	Univariate PFS		Multivariate PFS		Univariate OS		Multivariate OS	
	HR (95 % IC)	*p value*	HR (95 % CI)	*p value*	HR (95 % CI)	*p value*	HR (95 % CI)	*p value*
FDG PET/TC positive	9.3(2.1-28)	0.03	7.5 (1.3-30.1)	0.021	8.2 (1.8-34)	0.006	5.02 (1.9-24)	0.04
T1	0.6 (0.97-1.4)	0.1	0.9 (0.07.8)	0.7	0.4 (0.09-1.7)	0.2	0.8 (0.03-21)	0.9
T2	1.14 (0.3-3.5)	0.8	1.6 (0.27-12)	0.6	1.19 (0.3-3-4)	0.8	1.5 (0.08-30)	0.7
T3	1.3 (04-3.8)	0.5	2.07 (0.25-26	0.3	0.9 (0.3-2-7)	0.9	1.7 (0.07-35)	0.7
T4	1.8 (0.6-5.2)	0.2	2.83 (0.2-17)	0.5	2.2 (0.7-6-6)	0.1	2.5 (0.1-43)	0.5
Primary muscle-invasive tumor	4.1 (1.8-36)	0.005	3.1 (1.02-36)	0.05	2.8 (1.4-27)	0.01	2.3 (0.5-15.1)	0.2
Radical surgery	0.8 (0.3-2-4)	0.7	0.56 (0.1-2)	0.4	0.9 (0.3-2.2)	0.8	0.7 (0.2-2.5)	0.5
Chemotherapy	0.9 (0.3-2.7)	0.9	0.82 (0.1-6.7)	0.8	0.7 (0.2-2.3)	0.6	0.3 (0.04-2.4)	0.27

The comparison between FDG PET/CT general positivity and other variables was performed in a subgroup of 35/41 patients

changes over time in patients affected by ovarian carcinoma [21], other studies demonstrated no predictive values for SUVmax in a similar population [22]. The results of the present study may be explained by the different underlying disease, but also by the fact that a completely different and innovative approach was used for the semiquantitative analysis.

In fact, to date various segmentation algorithms have been suggested [23], but the choice of a standard method is a very challenging and yet unresolved step. Semiquantitative parameters calculation varies substantially depending on the algorithm used to delineate metabolic lesions, due to the low spatial resolution, high statistical uncertainty, and noise of PET images. In this study, lesion delineation was obtained using an automatic random walk algorithm [10], able to yield an accurate segmentation with consequent accurate calculation of parameters such as SUV, SUL, MTV, and TLG.

The ability to change therapeutic approach in patients affected by BC has been investigated in a few papers. In a study comprising 57 patients, among which 72 % underwent PET/

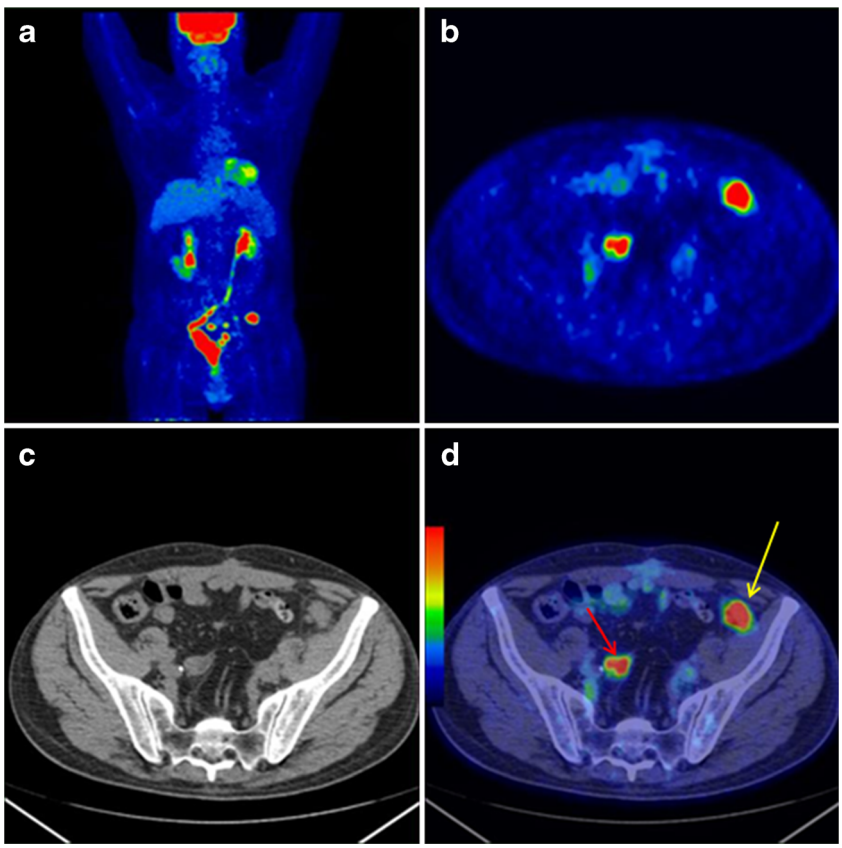

Fig. 3 Representative image showing PET/CT findings in a 62-year-old man who was treated with radical cystectomy and neobladder reconstruction for muscle-invasive bladder cancer. FDG PET/CT showed hypermetabolic pelvic lymph nodes (SUVmax = 11;TLG = 36). During the follow-up period, the patient showed disease progression with disseminated metastases; progression-free survival = 8 months; overall survival = 14 months. **A** = maximum intensity projection (MIP); **B** = axial FDG PET; **C** = axial CT; **D** = axial fused FDG PET/CT; *red arrow* indicates urinary activity in the neobladder; *yellow arrow* indicates the most FDG avid lymph node in left external iliac region

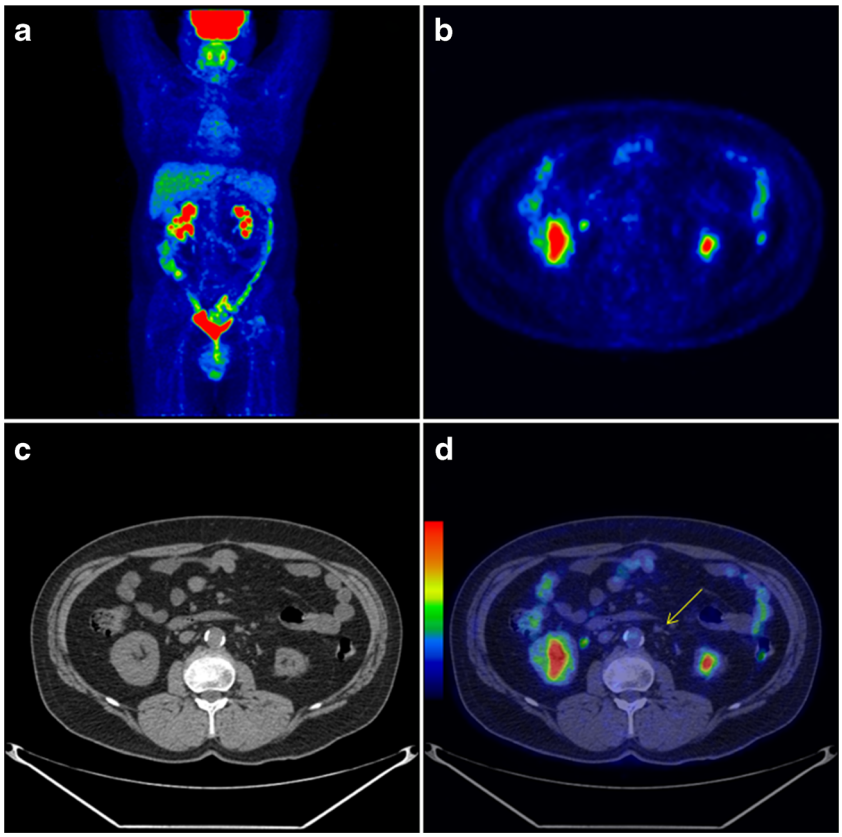

Fig. 4 Representative image showing PET/CT findings in a 58-year-old man who was treated with radical cystectomy for muscle-invasive bladder cancer. FDG PET/CT did not show any nodal or metastatic involvement. After 4-year follow-up, the patient was still alive and disease-free. *A* = maximum intensity projection (MIP); *B* = axial FDG PET; *C* = axial CT; *D* = axial fused FDG PET/CT; *yellow arrow* indicates a non FDG-avid lymph node

CT during restaging, the management was changed in 68 % of cases after PET [24], thus showing a substantial impact of FDG PET/CT in the suspicion of recurrence. Conversely, Mertens et al. retrospectively evaluated 96 patients undergoing FDG PET/CT at staging, reporting a modification of the management in 13.5 %, mostly due to disease upstaging [25]. In our study, PET/CT allowed for a change in therapy management in about 40 % of the patients, thus demonstrating an important impact. As such, we may speculate that FDG PET/CT, performed in the restaging process, plays an important role in modifying the therapeutic approach, while a similar value cannot be demonstrated at staging. This bears also importance to assess the cost-effectiveness of PET/CT. In fact, a recent study showed that the advantage of FDG PET/CT in preoperative staging of BC is not significant enough to justify the additional cost [26]. But our results suggest that the impact of FDG PET in the restaging process may justify the relatively high costs of this procedure. It should be considered, however, that clinical and cost effectiveness of FDG PET/CT in terms of outcome should be confirmed in prospective trials featuring larger cohorts of patients [7, 8].

Some limitations should be acknowledged. First, due to the retrospective nature of the present study, data concerning primary tumor extension and grading at diagnosis were not available for all the patients. While a subgroup analysis was feasible with regard to T extension at diagnosis, many missing data about N and M at staging prevented meaningful statistics on the impact on nodal and metastatic involvement on the outcome. As such, we cannot rule out that the different conditions at staging may have affected our results. For the same reason, there is lack of information regarding presence or absence of residual tumour after surgery. Furthermore, we were not able to select patients with a balanced proportion of local recurrence, nodal involvement, and distant metastases. Indeed, none of our patients had local recurrences. This may have led to less significant differences between positive and negative PET examinations, due to a probably better PFS and longer OS in patients with only local recurrences. Despite this limitation, a significant prognostic role in patients with lymph-nodal and/or metastatic involvement could be demonstrated and PET results allowed for modifying the therapeutic approach in a large proportion of patients. Including patients with only local recurrences may theoretically permit identifying a subgroup of patients with intermediate risk, but this needs to be clarified in future studies. The present paper constitutes a fundamental base for future works.

Second, delayed PET acquisition of the pelvis was not routinely performed, as CT images were rated in most cases adequate to delineate tumor extension. Delayed images are indeed very useful in the clinical practice to limit the incidence of false positives, but firm conclusions on their impact in our population cannot be drawn. It should be considered,

however, that the diagnostic performance seems to indicate that the use of CT was sufficient to reliably define the presence of recurrent lesions. Third, patient sample is relatively small (n = 41), but is the most comprehensive to date and was sufficient to perform an adequate pooled statistic. Finally, the variable treatment regimens performed after the restaging scan may have affected outcome.

Conclusion

FDG PET/CT has a very good diagnostic performance in patients with suspected recurrent BC. Moreover, an important prognostic value was demonstrated both for PFS and for OS, both considering general PET results and when applying threshold to semiquantitative parameters (i.e. SUVmax > 6 and TLG > 8.5). Not less important, a change in treatment management was reported in about 40 % of cases. While larger prospective trials are warranted, our work supports a broader application of FDG PET/CT in the restaging process, able to provide valuable information in the management of BC and in planning adequate effective therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Financial support The authors disclosure of any personal or financial support for this multicenter study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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