European Journal of Nuclear Medicine and Molecular Imaging (2023) 50:2477–2485
https://doi.org/10.1007/s00259-023-06173-9

ORIGINAL ARTICLE

Diagnostic effectiveness of [^{18}F]Fluoroestradiol PET/CT in oestrogen receptor-positive breast cancer: the key role of histopathology. Evidence from an international multicentre prospective study

Gianluca Bottoni[1] · Francesco Fiz[1] · Matteo Puntoni[2] · Federica Matteucci[3] · Manuela Monti[4] · Andrea DeCensi[5] · Oriana Nanni[6] · Etienne Brain[7] · Jean Louis Alberini[8] · Bassam Dib[9] · Gianmauro Sacchetti[9] · Pierpaolo Trimboli[10,11] · Giorgio Treglia[11,12,13] · Nadia Harbeck[14] · Simona Sola[15] · Alessandra Gennari[16] · Arnoldo Piccardo[1]

Received: 5 October 2022 / Accepted: 24 February 2023 / Published online: 7 March 2023

Abstract

Introduction [^{18}F]Fluoroestradiol ([^{18}F]FES) PET/CT has been proposed as a tool for detecting the oestrogen receptor density in patients with metastatic breast cancer (BC) non-invasively across all disease localizations. However, its diagnostic potential in terms of the detection rate (DR) of metastases is unclear. In this study, we pitted this method against [^{18}F]FDG PET/CT and tried to identify predictors of the diagnostic superiority of the [^{18}F] FES-based method.

Materials and methods From a multicentre database, we enrolled all patients with metastatic BC who had undergone both [^{18}F]FES PET/CT and [^{18}F]FDG PET/CT. Two readers assessed both images independently and used a patient-based (PBA) and lesion-based analysis (LBA) to calculate the DR. Pathology-related and clinical factors were tested as predictors of [^{18}F] FES PET/CT superiority using a multivariate model.

Results 92 patients, bearing a total of 2678 metastases, were enrolled. On PBA, the DR of [^{18}F]FDG and [^{18}F]FES PET/CT was 97% and 86%, respectively ($p = 0.018$). On LBA, the [^{18}F]FES method proved more sensitive than [^{18}F]FDG PET/CT in lymph nodes, bone, lung and soft tissue ($p < 0.01$). This greater sensitivity was associated with lobular histology, both on PBA (Odds Ratio (OR) 3.4, 95%CI 1.0–12.3) and on LBA (OR 4.4, 95%CI 1.2–16.1 for lymph node metastases and OR 3.29, 95%CI 1.1–10.2 for bone localizations).

Conclusions The overall DR of [^{18}F]FES PET/CT appears to be lower than that of [^{18}F]FDG PET/CT on PBA. However, the [^{18}F]FES method, if positive, can identify more lesions than [^{18}F]FDG at most sites. The higher sensitivity of [^{18}F]FES PET/CT was associated with lobular histology.

Keywords Breast cancer · Estrogen receptor · Lobular histology · FES · FDG · PET · Nuclear medicine

Introduction

^{18}F-fluoroestradiol ([^{18}F]FES) has recently been recognized by European and American pharmaceutical regulatory agencies as an effective positron emission tomography (PET) tracer in the evaluation of the oestrogen receptor (ER) expression of breast cancer (BC) metastases [1]. In patients with a history of ER+primary BC, this radiopharmaceutical is the only non-invasive alternative to biopsy in cases of new metastatic sites with unknown ER status [2]. Indeed, high concordance between [^{18}F]FES PET/computed tomography(CT) imaging and histopathology has recently been proved, and, notably, a very high positive predictive value (PPV) in predicting ER status (i.e., 93%) has been reported [3]. Given this background, [^{18}F]FES PET/CT imaging should be able to predict response to endocrine treatment. However, although some encouraging data are available, conflicting results have been reported and the real predictive value of this imaging procedure in terms of patient outcome has never been proved by large prospective studies [4].

Alessandra Gennari and Arnoldo Piccardo share senior co-authorship.

This article is part of the Topical Collection on Oncology - General

✉ Francesco Fiz
francesco.fiz@galliera.it

Extended author information available on the last page of the article

Beyond any ability to analyse metastatic ER status, the pure diagnostic role of [^{18}F]FES PET/CT and its ability to evaluate the metastatic burden have still not been recognized as the principal indication for this PET tracer. Indeed, only a limited number of small, retrospective studies have analysed the sensitivity of [^{18}F]FES PET/CT in disclosing disease relapse [5–12] and it has not yet been conclusively ascertained whether this diagnostic tool can be considered the first-line imaging procedure in this context.

The aim of our study was to evaluate the sensitivity of [^{18}F]FES PET/CT in a large population of ER+BC patients prospectively enrolled in an international multicentre clinical trial at the time of diagnosis of metastases. We also compared these results with those of [^{18}F]Fluorodeoxyglucose (FDG) PET/CT in the same setting. In addition, a multivariate logistic analysis was carried out in order to assess the association between [^{18}F]FES PET/CT results and the principal clinical and histopathological parameters.

Materials and methods

Patients' population

Patients were prospectively enrolled in an international, multicentre, phase II, randomized clinical study (ET-FES JTC 2011 TRANSCAN project, EUDRACT number 2013-000287-29), the goals of which were to predict the effectiveness of first-line endocrine-based therapy in patients with ER+, HER2- metastatic BC, and to validate the indication for [^{18}F]FES PET/CT. The patients were enrolled from January 2015 up to June 2020. This study was approved by the local ethics committees and the public medical agencies of all the centres involved in this clinical trial. Written informed consent was obtained from all patients. For our diagnostic purpose, we retrospectively analysed only patients who had undergone both [^{18}F]FDG PET/CT and [^{18}F]FES PET/CT at the time of diagnosis of distant metastases.

In all patients, the two PET scans were performed within 10 days of each other; no endocrine therapy or other salvage treatments were administered before and between the imaging procedures. Moreover, none of the patients was under active endocrine treatment at the time of [18F]FES PET/CT, with the exception of those who progressed under hormone treatment and were considered for a treatment change, as proposed by Peterson et al. [13]. Images were acquired in four centres, as previously reported, and in accordance with the available procedural guidelines [9, 14, 15].

PET/CT acquisition

As per the study design, [^{18}F]FES PET/CT had been acquired according to a standardized protocol, which was applied by all participating centres. Briefly, image acquisition started fifty minutes after the [^{18}F]FES administration (200 MBq) [16]. The scan protocol included a low-dose unenhanced CT (120 kV and 80 mA), a 3D PET acquisition covering the field of view from the head to the mid-thighs (3' per bed position). [^{18}F]FDG PET/CT was acquired 60' after the tracer injection, with the same parameters. The devices used for the study were: Discovery ST/ Discovery LS (GE Medical Systems, Chicago IL, USA), Philips Ingenuity 64 (Philips Medical Systems International B.V., Best, the Netherlands), and Biograph mCT Flow (Siemens Medical Solutions, Erlangen, Germany). The acquisition procedures were harmonized across all participating centres, in accordance with the EANM guidelines [17], additionally, a reference phantom was acquired in two of the institutions.

Image interpretation and analysis

Two experienced nuclear medicine physicians (G.B and A.P.) assessed [^{18}F]FDG PET/CT and [^{18}F]FES PET/CT separately independently from each other. Both readers were aware of the patient's clinical history, while they were blind to the morphological imaging (i.e., magnetic resonance imaging (MRI)/CT) and to the [^{18}F]FDG PET/CT or [^{18}F]FES PET/CT results respectively. Any doubtful or unclear interpretation was then resolved via a consensus review.

On [^{18}F]FDG PET/CT or [^{18}F]FES PET/CT, any region of focal, non-physiologic uptake higher than the surrounding background and corresponding to any morphological lesion or well-defined anatomical structure was considered positive [5]. Moreover, the tumour-to-background ratio was calculated for each lesion on both examinations as the ratio of the SUV_{max} of any given lesion and the SUV_{mean} of healthy background tissue, which was identified in the normal contralateral site whenever available or in the normal surrounding tissue [18]. TBR was quantified on all patients by two expert readers (GB and AP). In each district, the leading lesion (i.e., the one with the highest uptake) was identified and segmented semi-automatically using a commercial software application (AW Server, General Electric, Waukesha, WI, USA). The segmentation was carried out by placing a volume of interest encompassing the whole lesion, which was then segmented by adjusting the uptake threshold and performing manual correction if need be.

The two readers analysed the whole-body images by focusing on primary tumours, lymph nodes, lungs, liver, bone, and soft tissue metastases. Both examinations were assessed by means of a patient-by-patient (patient-based analysis) and a lesion-by-lesion (lesion-based analysis) approach. On patient-based analysis (PBA), the detection rate (DR) was defined as the ability of the method to identify at least one disease-related finding in each patient or tumour region in each patient. On lesion-based analysis (LBA), the

DR was defined as the ability to detect lesions in relation to the total number of lesions detected by the reference standard.

On LBA, we defined [^{18}F]FES PET/CT as superior to [^{18}F]FDG PET/CT when, in any given patient, it could detect at least one additional metastasis.

Standard of reference

Even though only DRs were estimated for each imaging procedure, we devised a specific standard of reference. Histopathology results were used as the standard of reference for the primary tumour. The standard of reference for distant localizations was multidisciplinary, i.e., based on pathology results, whenever available, or on diagnostic follow-up, including contrast-enhanced CT or MRI findings every 3 months after the PET/CT examinations (available for all patients). During the follow-up, all lesions visible on the morphological imaging were evaluated by the reporting radiologist using the RECIST criteria [19]. All histological confirmations were obtained by using imaging-guided core needle biopsies or open resection, as needed. Cytological tests were not allowed. Histology, as well as ER and PR receptor density, were tested in all cases. Follow-up procedures were carried out for at least two years after the [^{18}F]FES PET/CT.

Statistical analysis

Descriptive statistics, including mean, standard deviation, median and interquartile range (IQR) were calculated for continuous data; in the case of categorical factors, absolute and relative frequencies were utilized. In the diagnostic analyses, DRs, i.e., the percentage of positive subjects (in PBA) or lesions (in LBA), were computed in each modality and for each disease localization. We utilized the McNemar exact test to compare DRs between diagnostic modalities; we used an unpaired Student's T-Test to compare DR between patient subgroups within the same modality. Multivariate logistic modelling was used to estimate the association between [^{18}F]FES PET/CT and the principal clinical and histopathological parameters (i.e. age, staging at the time of diagnosis (pTNM), histopathology, grading, ER and progesterone receptor (PR) tumour expression, and time elapsed from diagnosis). Factors to be included in the multivariate analyses were primarily selected on the basis of a significant association with outcomes in univariate analyses; final logistic models were chosen by adopting a backward stepwise approach, considering as cut-off for inclusion a likelihood ratio test p-value ≤ 0.2.

All analyses were carried out by means of Stata software (version 17; StataCorp.). Two-tailed probabilities are reported, and a P value of 0.05 was used to define nominal statistical significance.

Results

Of the 147 patients prospectively enrolled in the ET-FES JTC 2011 TRANSCAN project [20], we had to exclude 55 patients due to the absence of [^{18}F]FDG PET/CT data; the resulting population included 92 subjects. Most of these patients ($N=65$, 71%) were affected by disease recurrence and all of them had ascertained loco-regional or distant BC metastases. Overall, 2678 sites of metastases were confirmed on our multidisciplinary follow-up examination (Supplemental Table 1). The principal characteristics of these patients are summarized in Table 1.

At the time of BC assessment, [^{18}F]FDG PET/CT proved positive in 89 of the 92 patients (97%), whereas [^{18}F]FES PET/CT was positive in 79 (86%) ($p<0.05$) (Fig. 1; Table 2).

On PBA, no significant differences between [^{18}F]FDG PET/CT and [^{18}F]FES PET/CT were observed in terms of DR in primary tumours or in lymph nodes, bone, lung and soft-tissue metastases (Table 2). By contrast, [^{18}F]FDG PET/CT proved significantly more sensitive than [^{18}F]FES PET/CT in detecting liver metastases. Indeed, [^{18}F]FDG PET/CT identified all 9 patients with liver metastases, whereas [^{18}F]FES PET/CT disclosed liver metastases in only 2 patients ($p<0.01$). On LBA, [^{18}F]FES PET/CT proved positive in 2357 of 2678 metastases (88%), whereas [^{18}F]FDG PET/CT was positive in 1499 of 2678 metastases (56%) ($p<0.0001$). Among the patients that were [^{18}F]FDG-positive and [^{18}F]FES-negative on PBA ($N=10$), the most represented metastatic sites were the bones and the lymph nodes (in five cases), followed by local recurrences (in two cases), liver lesions (two cases), and lung/soft tissue localizations (one case each).

No significant deviations from these results were obtained by considering patients without liver metastases only ($N=83$): [^{18}F]FDG PET/CT still performed better at PBA, while [^{18}F]FES PET/CT had a higher DR at LBA in nearly all disease localizations. See Supplemental Table 2 for details.

Out of the 2678 lesions, 1256 (47%) were positive on both examinations; conversely, 282 (11%) and 1140 metastases (42%) were positive on [^{18}F]FDG and [^{18}F]FES PET only, respectively.

When we evaluated the different locations of metastatic disease, the DR of [^{18}F]FES PET/CT in lymph-node, bone, lung and soft-tissue metastases was 87%, 90%, 85% and 91%, respectively—significantly higher ($p<0.0001$) than that of [^{18}F]FDG PET/CT, which was 59%, 54%, 65% and 67%, respectively (Fig. 1; Table 2). By contrast, [^{18}F]FDG

Table 1 Main clinical and histopathological features of the patients

Age, years, mean (SD)	61.3 (12.8)
Sex, female, n (%)	92 (100)
Histology, n (%)	
Ductal	74 (80%)
Lobular	18 (20%)
Clinical setting	27 (29%)
Staging	
Re-Staging	65 (71%)
Time to progression or recurrence in months median (IQR)	90 (25–184)
T, n (%)	
T1	28 (30.4)
T2	36 (39.1)
T3	14 (15.22)
T4	2 (2.17)
Tx	18 (19.6)
N, n (%)	
N0	27 (29.3)
N1	30 (32.7)
N2	14 (15.2)
N3	7 (7.6)
Nx	14 (15.2)
G, n (%)	
G1	3 (3.2)
G2	53 (57.6)
G3	36 (39.1
ER (%)	
median (IQR)	90 (80–95)
PR (%)	
median (IQR)	57.5 (15–90)
Ki-67 (%)	
median (IQR)	22 (15–30)
Lesion per patient: median (IQR)	
[^{18}F]FDG	9 (3–19)
[^{18}F]FES	7 (2–26)

Abbreviations: SD = standard deviation; IQR = interquartile range, T = tumour; N = Lymph-node; G = Grade; ER = oestrogen receptors; PG = progesterone receptors

PET/CT identified 33 out of 40 liver metastases (83%), while [^{18}F]FES PET/CT disclosed only 9 out of 40 (23%) ($p < 0.0001$).

There were some differences in the detection rate between the ductal and lobular histology. In fact, in patients with ductal carcinoma and showing a matching regional distribution of [^{18}F]FDG- and [^{18}F]FES-positive lesions ($N = 31$, 42%), the glucose-based tracer showed a higher DR in the liver, while the oestrogen-based one showed a higher number of lesions in the lymph node and bone compartments. However, in those where [^{18}F]FES detected more affected regions than [^{18}F]FDG ($N = 33$, 45%), the ER tracer had a higher DR across the board, including the liver and with the exception of local recurrences. In the [^{18}F]FES-negative ductal carcinoma patients ($N = 10$, 13%), [^{18}F]FDG showed a perfect DR at all localization except in the lungs, where it missed nearly 80% of all lesions. See Supplemental Fig. 1 for an outline of these results. In patients with lobular breast carcinoma [^{18}F]FES PET/CT showed a clear capability in detecting a higher number of lesions, independently of the anatomical region and of the number of affected regions (Table 3, Supplemental Fig. 1). Conversely, the clinical scenario (staging or re-staging), as well as the time elapsed between diagnosis and restaging were not associated with the detection rate of either method. Indeed, the lesion-based DR of [^{18}F]FES at the time of staging and restaging was 75% ± 33% and 90% ± 25%, respectively ($p = 0{,}15$). For [^{18}F]FDG, the corresponding DR value was 72% ± 36% and 84% ± 34% for staging and re-staging, respectively ($p = 0{,}32$).

When we conducted a multivariate logistic analysis to test the association between clinical and histopathological parameters and the superiority of [^{18}F]FES PET/CT over [^{18}F]FDG PET/CT in detecting metastases, we found a clear trend towards a significant association between predominant [^{18}F]FES PET/CT positive findings and lobular histology (OR 3.4, 95% CI 1.0–12.3 and $p = 0.06$) across all patients. Moreover, the superiority of [^{18}F]FES over [^{18}F]FDG in patients with lobular BC was particularly evident when the nodal (OR 4.4, 95% CI 1.2–16.1 and $p = 0.027$) or the skeletal (OR 3.29, 95% CI 1.1–10.2 and $p = 0.038$) localizations were concerned (Table 4). Moreover, none of the lobular BC patients had liver metastases. No differences in DR between the two tracers in patients with lobular BC were noted in the other organs. In patients affected by lobular BC, both methods were effective at the patient level, since they were both positive in 17 patients (95%). However, on LBA, [^{18}F]FES PET/CT revealed more metastatic sites than [^{18}F]FDG PET/CT in 15 patients (83%). On the other hand, in 74 BC patients with ductal histology, [^{18}F]FES PET/CT detected more metastatic sites than [^{18}F]FDG PET/CT in 33 patients (44.5%). On PBA, all 10 patients with negative [^{18}F]FES PET/CT and positive [^{18}F]FDG PET/CT had ductal histology, and 2 of them showed FES-negative liver metastases.

When evaluating the uptake intensity of the tracers, we found that the mean tumour-to-background ratio of all lesions was 14 and 18,7 for [^{18}F]FDG and [^{18}F]FES, respectively.

Discussion

To our knowledge, this was the first study to evaluate the sensitivity of [^{18}F]FES PET/CT in ER+BC in a large number of patients prospectively enrolled in an international

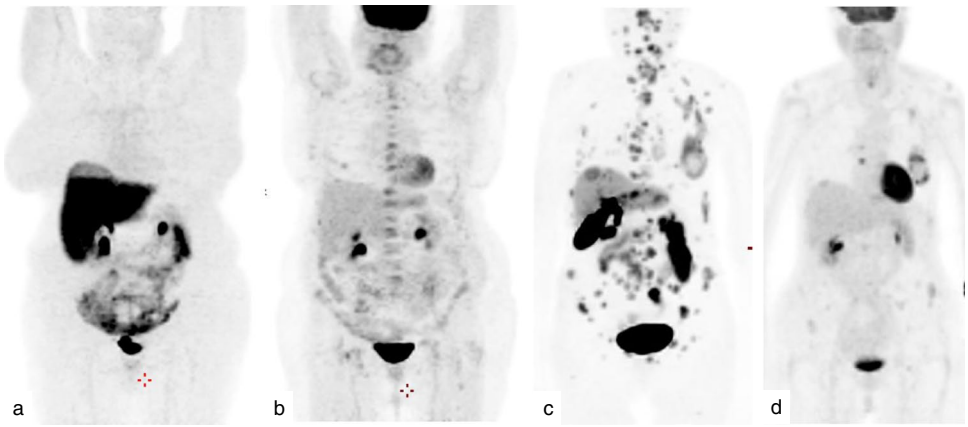

Fig. 1 70-year-old woman affected by ER+BC bone metastases. [18F]FES PET/CT was negative (**a**) and [18F]FDG PET/CT correctly identified multiple bone lesions (**b**). 67-year-old woman affected by ER+lobular BC with evidence of local relapse and bone metastases. [18F]FES PET/CT (**c**) detected more bone metastases than [18F]FDG PET/CT (**d**)

Table 2 Patient-based analysis (PBA) and Lesion-based Analysis (LBA). Detection rates (%) were calculated for each single diagnostic modality at each site of disease

	[^{18}F]FDG PET/CT	[^{18}F]FES PET/CT	p**
Patient-Based Analysis	89/92 (97%)	79/92 (86%)	0.013
Primary Tumour	28/33 (85%)	30/36 (83%)	1
Lymph-node metastases	56/66 (85%)	57/66 (86%)	1
Bone metastases	59/65 (91%)	57/65 (88%)	0.791
Liver metastases	9/9 (100%)	2/9 (22%)	0.016
Lung metastases	22/29 (76%)	24/29 (83%)	0.774
Soft Tissue metastases	18/25 (72%)	19/25 (76%)	1
Lesion-Based Analysis	1499/2678	2357/2678	<0.001
Primary Tumour	37/49 (76%)	44/49 (90%)	0.144
Lymph-node metastases	227/387 (59%)	338/387 (87%)	<0.001
Bone metastases	1066/1985 (54%)	1784/1985 (90%)	<0.001
Liver Metastases	33/40 (83%)	9/40 (23%)	<0.001
Lung Metastases	74/114 (65%)	97/114 (85%)	0.004
Soft Tissue Metastases	62/93 (67%)	85/93 (91%)	<0.001

** NOTE: = McNemar exact test p-value

Table 3 Lesion-based Analysis (LBA) for patients with lobular histology. Detection rates (%) were calculated for each single diagnostic modality at each site of disease

	[^{18}F]FDG PET/CT	[^{18}F]FES PET/CT	p**
Lesion-Based Analysis	184/339	286/339	<0.001
Primary Tumour	7/13 (54%)	12/13 (93%)	0.125
Lymph-node metastases	47/85 (55%)	84/85 (99%)	<0.001
Bone metastases	120/210 (57%)	160/210 (76%)	<0.001
Lung Metastases	8/24 (33%)	24/24 (100%)	<0.001
Soft Tissue Metastases	2/7 (29%)	6/7 (86%)	0.219

** NOTE: = McNemar exact test p-value

multicentre clinical trial. This was done by comparing [^{18}F]FES PET/CT results with those of [^{18}F]FDG PET/CT.

The present data do not indicate a real diagnostic advantage of [^{18}F]FES over [^{18}F]FDG for identifying the presence of ER+metastatic disease at the patient level, while it appears to play a relevant role in the accurate evaluation of the disease burden. This finding reinforces the impression conveyed by a recent meta-analysis, which reported a slight difference in favour of [^{18}F]FDG PET/CT when a PBA was conducted at the time of disease restaging [12]. Indeed, metastases may appear many years after the first BC diagnosis, and, in this case, disease localizations with varying degrees of differentiation might appear. Such a pattern was not observed in our population. Indeed, even patients with decades-long disease duration displayed oestrogen receptor density that was non-inferior to that of patients studied at

Table 4 Multivariate predictors of the superiority of [^{18}F]FES over [^{18}F]FDG at the logistic regression analysis

Dependent variable	Clinical or histological parameter	Hazard ratio	95%CI	*p*-value
Superiority of [^{18}F]FES PET/CT over [^{18}F]FDG PET/CT in detecting metastases	*Histology*			
	Ductal	1.0		
	Lobular	3.42	0.95–12.25	0.060
	pT			
	pN0/x	1.0		
	pN1-3	0.39	0.15–1.04	0.059
	Progesterone			
	≤80%	1.0		
	>80%	2.23	0.75–6.61	0.147
Superiority of [^{18}F]FES PET/CT over [^{18}F]FDG PET/CT in detecting lymph node metastases	*Histology*			
	Ductal	1.0		
	Lobular	3.36	1.14–9.91	0.028
	Age	1.03	0.99–1.07	0.083
Superiority of [^{18}F]FES PET/CT over [^{18}F]FDG PET/CT in detecting bone metastases	*Histology*			
	Ductal	1.0		
	Lobular	3.30	1.07–10.14	0.038
	ER	1.02	1.00–1.05	0.047

Abbreviations: 95%CI, 95% confidence interval; *ER*, Oestrogen Receptor

the time of disease onset. Moreover, patients with lobular BC presented a tracer distribution pattern favouring [^{18}F]FES in nearly all disease localizations, independently of the time elapsed from the diagnosis.

In the case of a positive [^{18}F]FES PET/CT result, this imaging procedure can often disclose more metastatic lesions than [^{18}F]FDG PET/CT, providing adequate information on the ER+metastatic burden. Indeed, in our LBA, we found that [^{18}F]FES PET/CT was significantly more sensitive than [^{18}F]FDG PET/CT in detecting lymph node, bone, lung and soft tissue metastases ($p < 0.001$). In the liver, by contrast, given the characteristic intense [^{18}F]FES uptake of this organ, we confirmed the low sensitivity of this imaging procedure in identifying metastases. However, there is growing evidence that ER+BC has a higher tendency toward bone involvement than other subtypes, which are more likely to spread to the liver [21, 22]. The histological type is also relevant to the spread pattern: lobular carcinoma has a tendency to diffuse to the lymph nodes and the bone, while ductal carcinoma mostly targets the bone and the liver.

These data suggest that [^{18}F]FES PET/CT may constitute the most valuable molecular procedure in the evaluation of tumour load. In addition, to better understand which patients could benefit from [^{18}F]FES PET/CT assessment, we conducted a logistic multivariate analysis to evaluate the association between [^{18}F]FES PET/CT LBA results and the principal clinical and histopathological findings. We found that the only parameter associated with the diagnostic superiority of [^{18}F]FES PET/CT over [^{18}F]FDG PET/CT was lobular histology. This confirmed what had been reported by a previous small study that included only 7 metastatic BC patients with lobular histology [11], and suggested that, in this particular subgroup of patients, in whom [^{18}F]FDG PET/CT could easily underestimate the extension of disease [23], [^{18}F]FES PET/CT may be the most valuable diagnostic option to identify metastatic lesions. This finding is particularly relevant given the emerging notion that lobular carcinoma has a worse prognosis than ductal one [24].

The difference in sensitivity is probably due to the lower glucose transporter expression of lobular BC than of ductal BC [25].

Interestingly, we did not find any association between [^{18}F]FES PET/CT and the percentage of ER expression. Indeed, the homogenous characteristics of the selected ER+BC patients, i.e., all HER2-negative patients with markedly elevated ER expression (IQR 80–90%), may have reduced the impact of ER expression on the [^{18}F]FES PET/CT results.

The evaluation of ER patterns across the disease localizations bears, other than diagnostic potential, prognostic relevance as well. Patients whose tumour load consists prominently of [^{18}F]FES-negative metastatic lesions are not only less likely to respond to the endocrine treatment, but can also face a direr long-term prognosis [9].

Although our results are encouraging, some limitations should be considered. First, the trial from which

the present data were extracted was initially aimed at evaluating the efficacy of endocrine therapy in ER+, HER2- metastatic BC. Thus, the present findings need to be confirmed in a larger study conceived to evaluate the diagnostic performance of [^{18}F]FDG PET/CT and [^{18}F]FES PET/CT specifically. However, it must be considered that the present one represents the largest [^{18}F]FES cohort analysed since all previous diagnostic studies have included retrospective series and enrolled small samples (i.e. less than 40) [5–8, 10–12]. The recruited population was rather heterogeneous in terms of previous treatments (i.e., hormone treatment).

Second, [^{18}F]FDG PET/CT was performed for clinical purposes and was not considered among the inclusion criteria of the ET-FES JTC 2011 TRANSCAN project. Thus, although all patients were prospectively enrolled in a clinical trial that only included ER+, HER 2-negative metastatic BC patients, their PET data were retrospectively analysed. In addition, a selection bias, due to the limited availability of [^{18}F]FDG PET/CT results (i.e. in 92 of 147 patients enrolled), could have affected our results.

Third, PET data were acquired by four different PET/CT scanners in four Nuclear Medicine Departments. Thus, the photon sensitivity of one PET/CT scanner might not be comparable to that of another. However, the acquisition protocol was harmonized across all the centres involved, in accordance with current EANM guidelines [26]; phantom images were additionally executed in two of the participating institutions. The physicians managing the patients during the follow-up were blinded to the results of the [^{18}F]FES PET/CT, but not to those of the glucose tracer examination since the latter was performed as a part of the normal workup of the patients. However, this knowledge is unlikely to have represented a bias, given that [^{18}F]FES was generally able to detect a higher number of lesions than [^{18}F]FDG.

Finally, we were able to evaluate only the sensitivity (i.e., DRs) of the diagnostic techniques examined, assuming *"a priori"* that all patients were true positives, in that they presented an ascertained clinical and radiological metastatic disease. Indeed, a biopsy confirmation was available in a small subset of patients only. To confirm this information, we introduced a multidisciplinary standard of reference based on histopathology results or on diagnostic follow-up, including contrast-enhanced CT or MRI findings every 3 months. However, given the lack of a completely independent third evaluation of all metastases (i.e., histopathology), we cannot exclude that our interpretation was excessively "imaging-based". Moreover, we cannot exclude the existence of false positive findings based on imaging reference standards during the follow-up.

Conclusion

[^{18}F]FES PET/CT should not be used in ductal ER+BC as the first-line imaging technique to identify patients affected by ER+BC metastases, as it proved less sensitive than [^{18}F]FDG PET/CT on PBA. However, [^{18}F]FES PET/CT, in the case of positivity, can disclose significantly more lesions than [^{18}F]FDG PET/CT, thereby providing important information on the real metastatic burden. This ability is particularly evident in patients with lobular BC, who are those who can benefit most from [^{18}F]FES PET/CT performed on restaging.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-023-06173-9.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Gianluca Bottoni, Francesco Fiz and Arnoldo Piccardo. The first draft of the manuscript was written by Arnoldo Piccardo and Andrea DeCensi; all authors commented on previous versions of the manuscript.

All authors read and approved the final manuscript.

Funding This research received grants from "Associazione Italiana per la Ricerca sul Cancro" (AIRC 2013) and ERA-Net TRANSCAN JTC 2011 Italian Ministry of Health.

Data availability The datasets analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was approved by the local ethics committees and the public medical agencies of all the centres involved in this clinical trial.

Informed consent Written informed consent was obtained from all patients.

References

1. Pabst KM, Decker T, Kersting D, Bartel T, Sraieb M, Herrmann K, et al. The future role of PET imaging in metastatic breast cancer. Oncol Res Treat. 2022; 45:18–25.
2. Chae SY, Ahn SH, Kim SB, Han S, Lee SH, Oh SJ, et al. Diagnostic accuracy and safety of 16α-[18 F]fluoro-17β-oestradiol PET-CT for the assessment of oestrogen receptor status in recurrent or metastatic lesions in patients with breast cancer: a prospective cohort study. Lancet Oncol. 2019;20:546–55.
3. van Geel JJL, Boers J, Elias SG, Glaudemans AWJM, de Vries EFJ, Hospers GAP, et al. Clinical validity of 16α-[18 F]Fluoro-17β-Estradiol positron emission tomography/computed tomography to assess estrogen receptor status in newly diagnosed metastatic breast cancer. J Clin Oncol. 2022;40:3642–52.

4. Evangelista L, Vittoria Dieci M, Guarneri V, Franco Conte P. 18F-Fluoroestradiol positron emission tomography in breast cancer patients: systematic review of the literature & meta-analysis. Curr Radiopharm. 2016;9:244–57
5. Gupta M, Datta A, Choudhury P, Dsouza M, Batra U, Mishra A. Can 18 F-Fluoroestradiol positron emission tomography become a new imaging standard in the estrogen receptor-positive breast cancer patient: a prospective comparative study with 18 F-Fluorodeoxyglucose positron emission tomography?. World J Nucl Med. 2017;16:133–9
6. Chae SY, Son HJ, Lee DY, Shin E, Oh JS, Seo SY, et al. Comparison of diagnostic sensitivity of [18F]fluoroestradiol and [18F] fluorodeoxyglucose positron emission tomography/computed tomography for breast cancer recurrence in patients with a history of estrogen receptor-positive primary breast cancer. EJNMMI Res. 2020;10:54.
7. Liu C, Gong C, Liu S, Zhang Y, Zhang Y, Xu X, et al. 18F-FES PET/CT influences the staging and management of patients with newly diagnosed estrogen receptor-positive breast cancer: a retrospective comparative study with 18F-FDG PET/CT. Oncologist. 2019;24: e1277–e1285.
8. Liu C, Xu X, Yuan H, Zhang Y, Zhang Y, Song S, et al. Dual Tracers of 16α-[18F]fluoro-17β-Estradiol and [18F]fluorodeoxyglucose for prediction of progression-free survival after fulvestrant therapy in patients with hr+/her2- metastatic breast cancer. Front Oncol. 2020;10:580277.
9. Bottoni G, Piccardo A, Fiz F, Siri G, Matteucci F, Rocca A, et al. Heterogeneity of bone metastases as an important prognostic factor in patients affected by oestrogen receptor-positive breast cancer. The role of combined [18F]Fluoroestradiol PET/CT and [18F] Fluorodeoxyglucose PET/CT. Eur J Radiol. 2021;141:109821.
10. Yang Z, Sun Y, Xue J, Yao Z, Xu J, Cheng J, et al. Can positron emission tomography/computed tomography with the dual tracers fluorine-18 fluoroestradiol and fluorodeoxyglucose predict neoadjuvant chemotherapy response of breast cancer? ----A Pilot Study. PLoS ONE. 2013;8.:e78192.
11. Ulaner GA, Jhaveri K, Chandarlapaty S, Hatzoglou V, Riedl CC, Lewis JS, et al. Head-to-Head evaluation of 18F-FES and 18F-FDG PET/CT in metastatic invasive lobular breast cancer. J Nucl Med. 2021;62:326–31.
12. Piccardo A, Fiz F, Treglia G, Bottoni G, Trimboli P. Head-to-Head comparison between18 F-FES PET/CT and18 F-FDG PET/CT in oestrogen receptor-positive breast cancer: a systematic review and meta-analysis. J Clin Med. 2022;11:1919.
13. Peterson LM, Kurland BF, Schubert EK, Link JM, Gadi VK, Specht JM, et al. A Phase 2 study of 16α-[18F]-fluoro-17β-estradiol positron emission tomography (FES-PET) as a marker of hormone sensitivity in metastatic breast cancer (MBC). Mol Imaging Biol. 2014;16:431–40.
14. Kurland BF, Peterson LM, Lee JH, Schubert EK, Currin ER, Link JM, et al. Estrogen receptor binding (18F-FES PET) and glycolytic activity (18F-FDG PET) predict progression-free survival on endocrine therapy in patients with ER+ breast cancer. Clin Cancer Res. 2017;23:407–15.
15. Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42:328–54
16. van Kruchten M, Glaudemans AWJM, de Vries EFJ, Schröder CP, de Vries EGE, Hospers GAP. Positron emission tomography of tumour [18F]fluoroestradiol uptake in patients with acquired hormone-resistant metastatic breast cancer prior to oestradiol therapy. Eur J Nucl Med Mol Imaging. 2015;42:1674–81.
17. Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42:328–54.
18. Mammatas LH, Venema CM, Schröder CP, de Vet HCW, van Kruchten M, Glaudemans AWJM, et al. Visual and quantitative evaluation of [18F]FES and [18F]FDHT PET in patients with metastatic breast cancer: an interobserver variability study. EJNMMI Res. 2020;10:40.
19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
20. Monti M, Degenhardt T, Brain E, Wuerstlein R, Argusti A, Puntoni M, et al. ERANET JTC 2011: submission and activation of an international academic translational project in advanced breast cancer. Experience From the ET-FES Study. Front Med (Lausanne). 2022;8:817678.
21. Lee SJ, Park S, Ahn HK, Yi JH, Cho EY, Sun JM, et al. Implications of bone-only metastases in breast cancer: Favorable preference with excellent outcomes of hormone receptor positive breast cancer. Cancer Res Treat. 2011;43:89–95.
22. Ji L, Cheng L, Zhu X, Gao Y, Fan L, Wang Z. Risk and prognostic factors of breast cancer with liver metastases. BMC Cancer. 2021;21:238.
23. Hogan MP, Goldman DA, Dashevsky B, Riedl CC, Gönen M, Osborne JR, et al. Comparison of 18F-FDG PET/CT for systemic staging of newly diagnosed invasive lobular carcinoma versus invasive ductal carcinoma. J Nucl Med. 2015;56:1674–80.
24. Mouabbi JA, Hassan A, Lim B, Hortobagyi GN, Tripathy D, Layman RM. Invasive lobular carcinoma: an understudied emergent subtype of breast cancer. Breast Cancer Res Treat. 2022;193:253–64.
25. Okcu O, Sen B, Ozturk C, Findik Guvendi G, Bedir R. GLUT-1 expression in breast cancer. Turk Patoloji Derg. 2022;38:114–21.
26. Aide N, Lasnon C, Veit-Haibach P, Sera T, Sattler B, Boellaard R. EANM/EARL harmonization strategies in PET quantification: from daily practice to multicentre oncological studies. Eur J Nucl Med Mol Imaging. 2017;44:17–31

Authors and Affiliations

Gianluca Bottoni[1] · Francesco Fiz[1] · Matteo Puntoni[2] · Federica Matteucci[3] · Manuela Monti[4] · Andrea DeCensi[5] · Oriana Nanni[6] · Etienne Brain[7] · Jean Louis Alberini[8] · Bassam Dib[9] · Gianmauro Sacchetti[9] · Pierpaolo Trimboli[10,11] · Giorgio Treglia[11,12,13] · Nadia Harbeck[14] · Simona Sola[15] · Alessandra Gennari[16] · Arnoldo Piccardo[1]

1 Department of Nuclear Medicine, E.O. "Ospedali Galliera", Mura delle Cappuccine 14, 16128, Italy

2 Clinical and Epidemiological Research Unit, University Hospital of Parma, Parma, Italy

3 Nuclear Medicine Unit, IRCCS Istituto Romagnolo per lo studio dei tumori (IRST)- Dino Amadori, Meldola, Italy

4 Biostatistics and Clinical Trials Unit, IRCCS Istituto Romagnolo per lo studio dei tumori (IRST)- Dino Amadori_, Meldola, Italy

5 Department of Medicine and Oncology, E.O. "Ospedali Galliera", Genoa, Italy

6 Biostatistics and Clinical Trials Unit, Istituto Scientifico Romagnolo per lo studio e la cura dei tumori, IRST, Meldola, Italy

7 Department of Clinical Research & Medical Oncology, Institut Curie (Hôpital René Huguenin), St Cloud, France

8 Nuclear Medicine Department Centre Georges-Francois Leclerc, 1 rue du Pr Marion, 21079 Dijon Cedex, France

9 Nuclear Medicine Unit, AOU Maggiore della Carità, Novara, Italy

10 Clinic of Endocrinology and Diabetology, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

11 Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI), Lugano, Switzerland

12 Clinic of Nuclear Medicine, Imaging Institute of Southern Switzerland, Ente Ospedaliero Cantonale, 6500 Bellinzona, Switzerland

13 Department of Nuclear Medicine and Molecular Imaging, Lausanne University Hospital and University of Lausanne, 1015 Lausanne, Switzerland

14 Breast Centre, Department of Obstetrics and Gynaecology, LMU University Hospital, Munich, Germany

15 Pathology Unit, E.O. "Ospedali Galliera", Genoa, Italy

16 Department of Translational Oncology, University of Eastern Piedmont, Novara, Italy