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Breast Cancer

^{18}F-FES PET/CT Influences the Staging and Management of Patients with Newly Diagnosed Estrogen Receptor-Positive Breast Cancer: A Retrospective Comparative Study with ^{18}F-FDG PET/CT

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Newly diagnosed breast cancer • ^{18}F-FES • ^{18}F-FDG • Management changes

Abstract

Purpose. We compared the clinical value of 16a-18F-fluoro-17b-estradiol (^{18}F-FES) positron emission tomography (PET)/computed tomography (CT) and ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET/CT and investigated whether and how ^{18}F-FES PET/CT affects the implemented management of newly diagnosed estrogen receptor positive breast cancer patients.

Materials and Methods. We retrospectively analyzed 19 female patients newly diagnosed with immunohistochemistry-confirmed estrogen receptor (ER)-positive breast cancer who underwent ^{18}F-FES and ^{18}F-FDG PET/CT within 1 week in our center. The sensitivity of ^{18}F-FES and ^{18}F-FDG in diagnosed lesions were compared. To investigate the definite clinical impact of ^{18}F-FES on managing patients with newly diagnosed ER positive breast cancer, we designed two kinds of questionnaires. Referring physicians completed the first questionnaire based on the ^{18}F-FDG report to propose the treatment regime, and the second was completed immediately after reviewing the imaging report of ^{18}F-FES to indicate intended management changes.

Results. In total, 238 lesions were analyzed in 19 patients with newly diagnosed ER-positive breast cancer. Lesion detection was achieved in 216 sites with ^{18}F-FES PET and in 197 sites with ^{18}F-FDG PET/CT. These results corresponded to sensitivities of 90.8% for ^{18}F-FES versus 82.8% for ^{18}F-FDG PET/CT in diagnosed lesions. Thirty-five physicians were given the questionnaires referring to the treatment strategy, with 27 of them completing both questionnaires. The application of ^{18}F-FES in addition to ^{18}F-FDG PET/CT changed the management in 26.3% of the 19 patients with newly diagnosed ER-positive breast cancer.

Conclusion. Performing ^{18}F-FES PET/CT in newly diagnosed ER-positive breast cancer patients increases the value of diagnosis equivocal lesions and treatment management compared with ^{18}F-FDG PET/CT. ***The Oncologist*** 2019;24:e1277–e1285

Implications for Practice: This study investigated whether 16a-18F-fluoro-17b-estradiol (^{18}F-FES) positron emission tomography (PET)/computed tomography (CT) affects the clinical management of patients with newly diagnosed estrogen receptor (ER)-positive breast cancer. Physicians completing two questionnaires comparing the clinical impact of 18F-FES and 18F-FDG on individual management plans in patients with newly diagnosed ER-positive breast cancer confirmed that 18F-FES scans led to change in management in 26.3% of the 19 patients with newly diagnosed ER positive breast cancer. This retrospective study indicates the potential impact of 18F-FES PET/CT on intended management of patients with newly diagnosed estrogen receptor positive breast cancer in comparison to 18F-fluoro-2-deoxy-D-glucose PET/CT.

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Introduction

Annual estimates suggest that 1.68 million new cases of breast cancer are diagnosed worldwide and result in approximately 400,000 deaths, making breast cancer the major cause of cancer-related mortality in women [1]. According to cancer statistics from China, breast cancer was estimated to account for 15% of newly diagnosed cancers in 2015 [2]. The diagnosis and staging of breast cancer are predominantly based on physical examination, pathological examination, and imaging [3]. Cancer imaging has evolved from morphological imaging to molecular imaging. Increasing evidence in the literature suggests that positron emission tomography (PET)/computed tomography (CT) has a higher sensitivity and specificity in the staging of many cancers compared with other imaging methods [4]. ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is the most commonly used PET tracer in routine clinical practice for diagnosis and monitoring responses to therapy in oncology [5–7]. In breast cancer, ^{18}F-FDG PET-CT is commonly required for metastatic examination, management response, and suspected recurrence of locally advanced cancer [8–10]; however, ^{18}F-FDG is not a cancer-specific tracer, and benign diseases related to infection or inflammation can also show false-positive intense ^{18}F-FDG uptake, which causes difficulty in distinguishing benign disorders from malignant diseases [11, 12].

Approximately 70%–80% of breast cancers are hormone receptor (HR)-positive (estrogen and/or progesterone receptor positive), which makes endocrine therapy an important therapeutic option [13]. Estrogen receptor (ER) plays a key role in the treatment regimen and prognosis [14]. 16a-18F-fluoro-17b-estradiol (^{18}F-FES) has been demonstrated to be a noninvasive, molecular imaging technique to observe and quantify in vivo ER expression [15, 16]. Previous studies have shown that the uptake of ^{18}F-FES could detect the ER-positive lesions and also highly corresponded to the degree of immunohistochemical (IHC) staining for ER on tumor biopsies [17–19]. In current clinical studies, however, ^{18}F-FES PET-CT is used either to reveal the existence of heterogeneity in the tumors or as a predictor of response to endocrine therapy in patients with advanced or metastatic ER-positive breast cancer [19–22].

Although the value of ^{18}F-FES and ^{18}F-FDG PET has been extensively studied in metastatic breast cancer [20, 21], the study of ^{18}F-FES application in cases of newly diagnosed breast cancer is extremely limited. The aims of this study were to evaluate and compare the clinical impact of ^{18}F-FES and ^{18}F-FDG on the sensitivity of lesion detection, correct staging, and individual management plans in patients with newly diagnosed ER-positive breast cancer.

Materials and Methods

Patients and Procedures

Patients with newly diagnosed breast cancer who underwent both ^{18}F-FES PET/CT and ^{18}F-FDG PET/CT in Fudan University Shanghai Cancer Center within 1 week, from August 2010 and June 2018, were retrospectively identified from an electronic database. Nineteen treatment-naive patients with newly diagnosed immunohistochemical confirmed ER-positive breast cancer were included in our study. All the patients were enrolled from these purposes: predicting response to fulvestrant 500 mg treatment, a phase II study (NCT03507088, n = 14), evaluating ambiguous lesions in routine workup (such as CT, magnetic resonance imaging [MRI], ^{18}F-FDG; n = 5). The study has been approved by the Fudan University Shanghai Cancer Center Ethic Committee and institutional review boards for clinical investigation. Informed written consent was obtained from all of these enrolled patients.

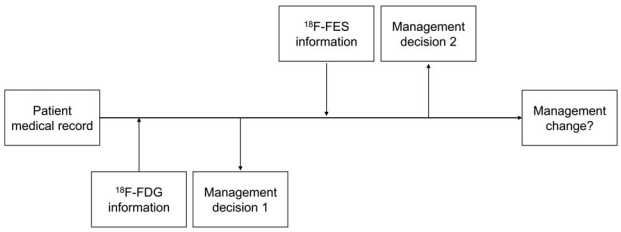

Figure 1. The questionnaire process.
Abbreviations: ^{18}F-FDG, ^{18}F-fluoro-2-deoxy-D-glucose; ^{18}F-FES, 16a-18F-fluoro-17b-estradiol.

The questionnaire design is depicted in Figure 1. Referring physicians completed the first questionnaire, including the full medical history and ^{18}F-FDG scan reports to indicate the treatment plan without ^{18}F-FES PET/CT information, and the second questionnaire, with the addition of an ^{18}F-FES scan to denote intended management changes.

To minimize individual differences, a definitive change in management was considered when over two-thirds of physicians chose to change the treatment strategy after the FES scan. A change in management was defined as a difference between the pre-^{18}F-FES treatment strategy and post-^{18}F-FES treatment strategy. Three categories of change in management were defined: (a) change in treatment objective (e.g., from curative to palliative and vice versa); (b) change in surgical management (e.g., surgery carried out or cancelled); and (c) change in systemic treatment (e.g., from endocrine therapy to chemotherapy).

Synthesis of ^{18}F-FES, ^{18}F-FDG, and Quality Control

The MMSE precursor and the authentic ^{19}F-FES were purchased from Jiangsu Huayi Chemical Co, Ltd. (Suzhou, Jiangsu, China). ^{18}F-FES was prepared according to published methods [23] and modified as reported in our previous study [19]. The total preparation time was approximately 100 min, and the corrected radiochemical yield was approximately 40% at the end of synthesis. ^{18}F-FDG was produced routinely and automatically by cyclotron (RDS Eclipse ST; Siemens, Knoxville, TN) using an Explora FDG4 module in our center. The ^{18}F-FES and ^{18}F-FDG radiochemical purity was greater than 99% and 95%, respectively.

PET/CT Imaging

For the ^{18}F-FDG PET/CT imaging, all patients were instructed to fast for at least 6 hours. At the time of the tracer injection, the patients presented blood glucose levels less than

Table 1. Changes in TNM stage by ^{18}F-FES versus ^{18}F-FDG based on the study population (no. 19)

Serial number	Age	Total number of lesions			Number of lesions of exclusive seen on		Number of ^{18}F-FDG+ lesions ^{18}F-FES help in characterization	TNM changing
		FDG+	FES+	Total	FDG	FES		
1	72	14	14	15	1 (CLN)	1 (ISLN)		IV
2	53	20	14	20	6 (5 MLNs, 1 CLN)	0	5 MLNs FES-	IV
3	61	40	49	49	0	9 (4 ALNs, 4 CLNs, 1 Abdo LN)	20 (4 CLNs, 4 MLNs, 2 Abdo LNs, 10 lung nodules) FES+	IV
4	46	12	8	12	4 (1 breast lesion, 3 bones)	0		IV
5	58	10	10	11	1 (ALN)	1 (bone)		IV
6	71	2	1	2	1 (bone)	0	1 bone FES-	IV → I
7	61	15	6	15	9 (3 liver, 6 bones)	0		IV
8	54	1	3	3	0	2 (ALNs)		IIA → IIB
9	56	3	3	3	0	0		IIA
10	68	12	16	17	1 (MLN)	5 (pleural nodules)	6 (1 MLN FES-, 5 Pleural nodule FES+)	IV
11	51	5	16	16	0	11 (6 ALNs, 2 IMLNs, 2 CHW, 1 ISLN)		IIIa→IV
12	49	2	1	2	1 (ALNs)	0	1 ALNs FES-	IIB → IIA
13	65	4	5	5	0	1 IMLN		IIIA→IIIB
14	63	21	31	31	0	10 (3 ALNs, 7 CLNs)	2 CLNs FES+	IV
15	64	9	8	9	1 (MLNs)	0	1 MLNs FES-	IV
16	44	9	9	9	0	0		IV
17	65	11	7	11	4 (2 CLNs, 2 ALNs)	0		IV
18	55	9	9	9	0	0		IIIA
19	70	5	6	6	0	1 (ALNs)	3 lung nodules FES+	IV
Total		204	216	245	29	41	39 (30 FES+, 9 FES-)	

Abbreviations: ALN, axillary lymph node; CWN, chest wall nodule; FDG+, ^{18}F-FDG positive; FES-,^{18}F-FES negative; FES+, ^{18}F-FES positive; IMLN, internal mammary lymph node; ISLN, ipsilateral supraclavicular lymph node; LN, lymph node; MLN, mediastinal lymph node.

10 mmol/L. Patients with medical comorbidities, such as diabetes, a chronic infection, or chronic inflammatory conditions, were not enrolled to prevent the sensitivity and specificity of ^{18}F-FDG PET/CT imaging. Before and after injecting 7.4 MBq/kg body weight of ^{18}F-FDG intravenously, the patients were kept lying comfortably in a quiet, dimly lit room and were administered 1 L of plain water orally before the PET/CT scanning. The scanning consisted of a whole-body PET/CT examination (2–3 minutes per table position) initiated 1 hour after administration of the tracer using a Siemens Biograph 16 HR PET/CT scanner.

Because all the patients were newly diagnosed and treatment naive, a washout period of the ER antagonist was not required [24]. Approximately 222 MBq (6 mCi) of ^{18}F-FES was injected intravenously over 1 to 2 minutes. The scanning was initiated 1 hour after administration of the tracer on the same PET/CT scanner as the ^{18}F-FDG.

Image Interpretation

Lesions identified via ^{18}F-FDG or ^{18}F-FES PET were corroborated by CT and/or other imaging. PET images were processed as for a typical clinical scan, corrected for radioactive decay of the tracer, and normalized to the injected dose (ID) and body weight (BW). This processing results in regional standardized uptake values (SUV): SUV = A / (ID / BW), where A is the tissue tracer uptake in microcuries per gram for the hottest pixel in the tumor (SUVmax), ID is the injected dose in millicuries, and BW is the body weight in kilograms. ^{18}F-FES SUVmax was used to quantify the ER expression. The cutoff value of ^{18}F-FES positivity and negativity was set at 1.8 based on our previous study [19]. In terms of the ^{18}F-FDG PET/CT scan, the lesions showing significant uptake (visually higher compared with the surrounding tissues) were defined as positive by two board-certified nuclear medicine physicians with over 5 years of experience. In patients with uncountable and widespread bone metastases, an arbitration count of up to 10 lesions of the largest ^{18}F-FES PET or ^{18}F-FDG PET intensity lesions were taken for the calculation.

Statistical Analysis

The number of lesions either ^{18}F-FES or ^{18}F-FDG positive was calculated as the total number and excluded if both were negative. The differences in tracer uptake between different sensitivities were calculated and compared. Because of this high physiological uptake of ^{18}F-FES in liver

tissues, liver lesions were excluded from the analyses. Statistical analyses were conducted using IBM SPSS Statistics 20 (IBM Corporation, Armonk, NY). For intended management, changes were analyzed using the ratio statistics and expressed as 95% confidence interval (CI).

Results

Patient Population

We analyzed the data of 19 patients with newly diagnosed ER positive breast cancer who underwent both ^{18}F-FES PET/CT and ^{18}F-FDG PET/CT within 1 week in our center. At the initial diagnosis, the patients were aged between 44 and 72 years (median, 61). The patient data are summarized in Table 1.

^{18}F-FES and ^{18}F-FDG PET/CT Data Analysis

In total, 245 lesions were identified in 19 patients with newly diagnosed ER-positive breast cancer. These lesions were identified as ^{18}F-FDG positive, ^{18}F-FES positive, or both. In 245 lesions, seven mediastinal lymph nodes (MLNs) were ^{18}F-FDG positive but ^{18}F-FES negative. During treatment follow-up, all the other lesions were responsive in subsequent ^{18}F-FDG PET/CT and/or other imaging, but the seven MLNs did not change following treatment based on the character of the CT image. Therefore, we defined this MLN lesion as false positive of ^{18}F-FDG (2.9%). We will discuss these remaining 238 lesions in the following sections [25].

Out of a total of 238 lesions, 197 lesions showed ^{18}F-FDG uptake and 216 lesions were avid in ^{18}F-FES PET. Therefore, the sensitivity of ^{18}F-FDG and ^{18}F-FES in the diagnosis of ER-positive lesions in newly diagnosed breast cancer was 82.8% and 90.8%, respectively. Because of the commonly known limitation of FES (high background uptake in the liver), we calculated the sensitivity of ^{18}F-FES and ^{18}F-FDG without liver lesions as well. Of the 238 lesions, we excluded 3 liver lesions. Out of 235 lesions without liver metastases, 194 lesions were ^{18}F-FDG positive, whereas 216 lesions remained avid in ^{18}F-FES PET, showing a sensitivity of 82.5% and 91.9%.

Of the 245 lesions, we also observed 41 lesions (16.7%) that were exclusively detected by ^{18}F-FES PET scan yet absent in ^{18}F-FDG PET scanning, seen at the following sites: lymph nodes (including supraclavicular, neck, axillary, internal mammary, mediastinal, and abdominal), bone, pleural, and chest wall nodule. These lesions were defined as metastases and classified as false negative lesions of ^{18}F-FDG. Additionally, 39 lesions of ^{18}F-FDG positive (15.9%) were either uncommon sites of metastatic lesions (n = 15) or common sites of inflammatory changes (n = 24, 13 lung lesions and 11 MLNs). Of these ambiguous lesions, 30 lesions (76.9%) were ^{18}F-FES positive, confirming the presence of ER-positive metastases. Hence, ^{18}F-FES added the value of diagnosis in 71 of 80 equivocal lesions (88.8%) in 19 patients with newly diagnosed ER-positive breast cancer.

Staging Changed After ^{18}F-FES PET Scan

Detailed changes in the TNM stage before and after ^{18}F-FES PET scanning is summarized in Tables 1 and 2. Of the 19 patients with newly diagnosed ER-positive breast cancer, 5 patients (26.3%) were staged differently by ^{18}F-FES PET and ^{18}F-FDG PET. M staging was adjusted in two patients, N stage in four patients, and N as well as M staging in one patient. In terms of the TMN status of these patients, the physicians indicated that ^{18}F-FES PET imaging led not only

Table 2. Treatment management changes for five patients after ^{18}F-FES

Stage	FDG	FES	TNM changing	Type of change in treatment strategy by means of ^{18}F-FES PET
Patient 1				
T	T1	T1	IV → I (sternum)	Change in treatment objective (palliative→ curative)
N	N0	N0		
M	M1	M0		
Patient 2				
T	T1	T1	IIA → IIB (ALN)	Change in surgical management (SLNB→ ALND)
N	N0	N1		
M	M0	M0		
Patient 3				
T	T2	T2	IIB → IIA (ALN)	Change in surgical management (ALND→SLNB)
N	N1	N0		
M	M0	M0		
Patient 4				
T	T2	T2	IIB → IIIB (IMLN)	Change in surgical management or radiotherapy (ALND→ALND +IMLND/IMLNI)
N	N1	N3		
M	M0	M0		
Patient 5				
T	T2	T2	IIB → IV (IMLN, ISLN, CWN)	Change in treatment objective (curative→ palliative)
N	N1	N3		
M	M0	M1		

Abbreviations: ALN, axillary lymph node; ALND, axillary lymph node dissection; CWN, chest wall nodule; IMLN, internal mammary lymph node; IMLND, internal mammary lymph node dissection; IMLNI, internal mammary lymph node irradiation; ISLN, ipsilateral supraclavicular lymph node; SLNB, sentinel lymph node biopsy.

Table 3. The proportion of changes in management after ^{18}F-FES PET

Changes	n = 19	Proportion (95% CI)
Change in management?		
Yes	5	0.263 (0.045–0.481)
No	14	
Change in surgical management?		
Yes	3	0.158 (−0.023–0.338)
No	16	
Change in treatment objective?		
Yes	2	0.105 (−0.047–0.257)
No	17	

Abbreviation: CI, confidence interval.

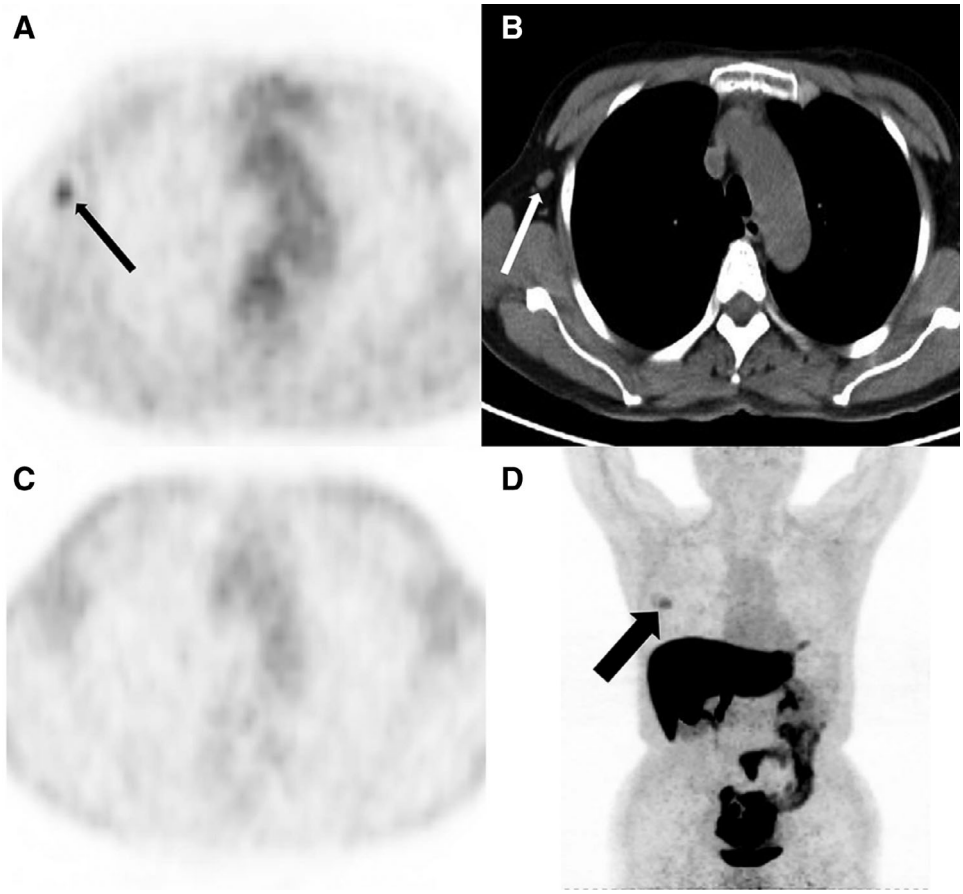

Figure 2. A 49-year-old woman with newly diagnosed estrogen receptor-positive breast cancer. **(A):** Axial ^{18}F-FDG positron emission tomography (PET) shows right axillary focal uptake (black thin arrow). **(B):** Axial computed tomography (CT) shows the right axillary lymph node on one level (white thin arrow). **(C):** At the same level, there is no focal uptake in the ^{18}F-FES PET. **(D):** ^{18}F-FES PET MIP showed breast mass uptake (black thick arrow) but no focal uptake in right axillary lymph node. The right axillary lymph node was not a metastasis as proven by pathology after operation.

to upstaging in three cases due to evidence of suspected metastases but also to downstaging in two cases.

Referring Physicians and Questionnaires

Subsequent treatment of these patients was taken from the medical history as follows: (a) five patients received radical surgery, radiotherapy, adjuvant chemotherapy, and endocrine therapy; (b) two patients received surgery, adjuvant chemotherapy, and endocrine therapy; (c) two patients received palliative chemotherapy and endocrine therapy; and 4) nine patients received palliative endocrine therapy only. The management of one patient was not determined because of loss of follow-up. Of the patients, 36.8% received radical surgery, 26.3% received adjuvant radiotherapy, 36.8% received adjuvant chemotherapy and adjuvant endocrine therapy, and 57.9% received palliative treatment (chemotherapy and/or endocrine therapy).

Thirty-five different physicians were given the questionnaires referring to the treatment strategy of 19 patients with newly diagnosed ER-positive breast cancer. Twenty-seven of the physicians (including 12 surgeons and 15 oncologists) completed both questionnaires. Table 2 summarizes the impact of ^{18}F-FES PET/CT on intended management. Based on predefined standards, the intended management was changed in five patients (0.263; 95% CI, 0.045–0.481). Most physicians chose to change the therapeutic goal after ^{18}F-FES PET/CT in two cases (0.158; 95% CI, −0.023 to 0.338) and change surgical management in three cases (0.105; 95% CI, −0.047 to 0.257), as depicted in Table 3.

As shown before, the implementation of ^{18}F-FES PET/CT changed the treatment strategy in five cases. The results of the ^{18}F-FES scans were further confirmed by postoperative pathology in three cases (Figs. 2,3).

Among the 27 physicians, 15 (55.6%) found that the implementation of ^{18}F-FES PET/CT in addition to ^{18}F-FDG PET/CT added value to the decision making of the treatment strategy in patients with newly diagnosed ER positive breast cancer.

Discussion

To our knowledge, this is the first explorative study conducted to systematically evaluate the clinical value of ^{18}F-FES PET/CT and ^{18}F-FDG PET/CT and investigate whether and how ^{18}F-FES affects the implemented management of patients with newly diagnosed estrogen receptor-positive breast cancer. Previous studies have successfully demonstrated that ^{18}F-FES PET/CT is a sensitive method to

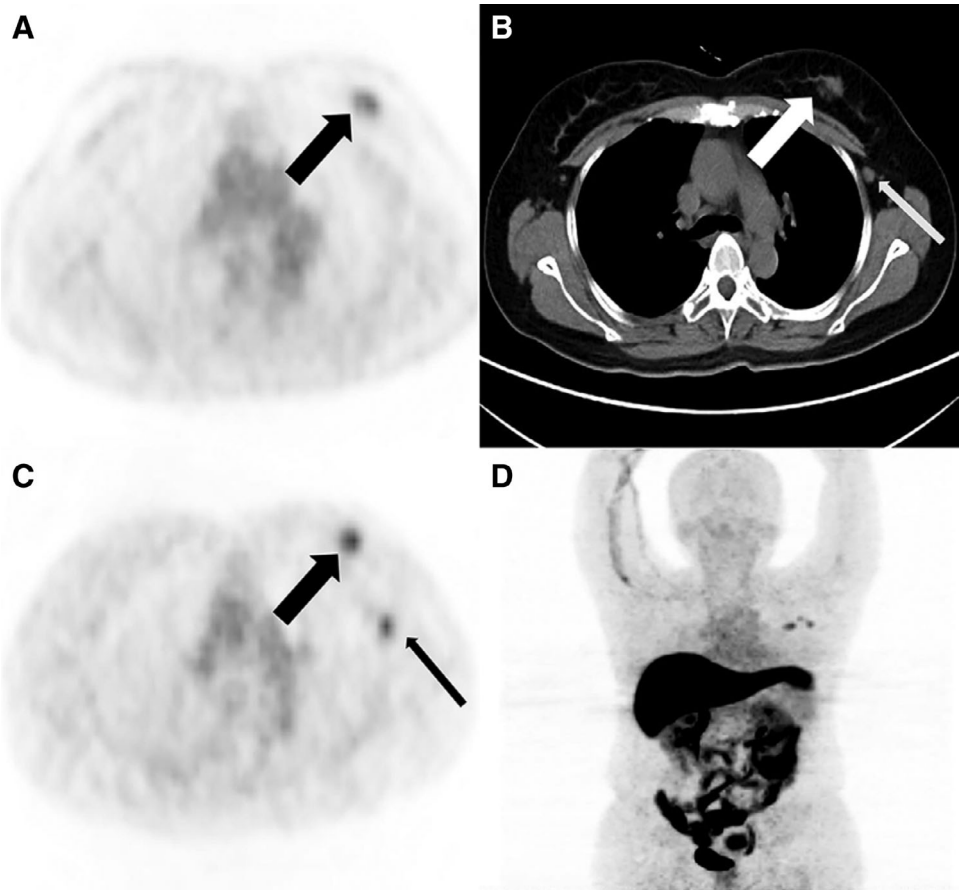

Figure 3. A 54-year-old woman with newly diagnosed ER-positive breast cancer. **(A):** Axial ^{18}F-FDG positron emission tomography (PET) show left breast mass uptake (black thick arrow). **(B):** Axial computed tomography (CT) shows a mass at the site of ^{18}F-FDG PET uptake, which is primary breast cancer (white thick arrow) and axillary lymph node (black thin arrow). **(C):** At the same level, ^{18}F-FES PET shows the mass (black thick arrow) and axillary lymph node (black thin arrow), considered to be estrogen receptor-positive lesions. **(D):** ^{18}F-FES PET MIP demonstrates ^{18}F-FES avid focus in left breast mass and axillary lymph node. The left axillary lymph node contained metastases as proven by pathology after operation.

monitor regional estrogen binding in advanced and metastatic ER-positive breast cancer [26] and validated that ^{18}F-FES uptake quantitation correlates well with ER expression measured by IHC [16, 18, 27]. Our previous study has confirmed this favorable statement as well [19].

Our retrospective review of 19 patients with newly diagnosed ER-positive breast cancer demonstrates that ^{18}F-FES PET and ^{18}F-FDG PET scanning both showed high sensitivity in the detection of suspected lesions. ^{18}F-FES PET showed a higher sensitivity in the diagnosis of metastatic lesions than ^{18}F-FDG PET (90.8% vs. 82.8%, respectively). The most critical shortcoming of ^{18}F-FES PET/CT is that it cannot be reliably measured in liver metastases because of high background ^{18}F-FES uptake [21]. Considering this, we recalculated the sensitivity of both tracers without liver metastatic sites. ^{18}F-FES was slightly higher in the sensitivity of lesion diagnosis (90.8% to 91.9%). In the study by Gupta et al., different results were observed in 10 treatment-naive patients with ER-positive breast cancer, where higher sensitivities in ^{18}F-FDG PET compared with ^{18}F-FES PET were reported (92.21% vs. 75.32%, respectively) [25]. Notably, some lesions of ER-positive characteristics were converted to ER-negative phenotypes after treatment, and the heterogeneity of ^{18}F-FES uptake was higher in patients with recurrent or metastatic breast cancer than untreated patients [19, 28]. Because of the transformation of some lesions from ER positive to ER negative, ^{18}F-FES PET sensitivity was lower than ^{18}F-FDG PET in lesions diagnosis.

Distinguishing inflammatory lesions from malignant disease is notoriously difficult via ^{18}F-FDG PET/CT [29] because the lungs and MLNs are one of the main sites of inflammatory lesions and can give rise to ^{18}F-FDG false positive results. ^{18}F-FES PET/CT, with higher specificity for the recognition of ER positive lesions, can play a significant role in the identification of ^{18}F-FDG equivocal lesions [21]. In this study, seven lesions (MLNs) were found to be ^{18}F-FDG positive but ^{18}F-FES negative. Under the outcome of subsequent treatment and the character of CT image, we can conclude that these seven MLN lesions were ^{18}F-FDG false positive for disease. Confirming the presence of ER-positive lesions, 71 out of 80 equivocal metastatic lesions on ^{18}F-FDG scans were shown to uptake ^{18}F-FES. Hence, ^{18}F-FES PET/CT showed a significant potential as a reference in some equivocal lesions detected via ^{18}F-FDG PET/CT.

Our results showed for the first time that ^{18}F-FES PET/CT could impact the management of newly diagnosed breast cancer. In the current study, the addition of ^{18}F-FES

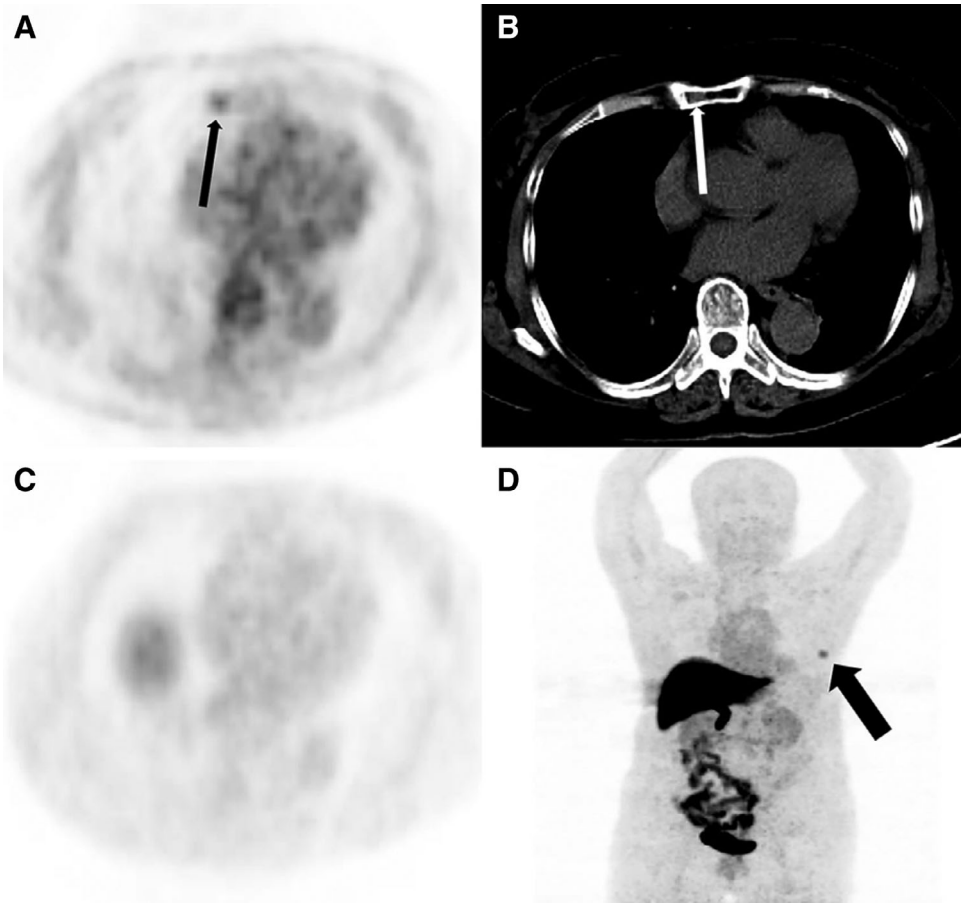

Figure 4. A 71-year-old woman with newly diagnosed estrogen receptor-positive breast cancer. **(A):** Axial ^{18}F-FDG positron emission tomography (PET) shows right manubrium focal uptake (black thin arrow). **(B):** Axial computed tomography (CT) show an inhomogeneous density of partial manubrium on one level (white thin arrow). **(C** and **D):** ^{18}F-FES PET has no uptake in the manubrium (black thick arrow shows breast mass uptake). The manubrium lesion was a considered to be a hemangioma during a recent follow-up.

PET/CT changed the treatment strategy in 23.6% of the patients. A series of studies have demonstrated that ^{18}F-FDG PET/CT can correct the initial clinical stage of breast cancer [30, 31]. Ulaner et al. conducted a retrospective review of 238 patients with ER-positive/HER2-negative breast cancer and found that correct staging with ^{18}F-FDG PET/CT led to the detection of 32 patients (13.4%) with unforeseen distant metastases, mainly in initial clinical stage IIB and stage III patients [32]. Notably, our study was based on the results of ^{18}F-FDG PET/CT imaging to further analyze the potential role of ^{18}F-FES PET/CT in correct staging and management of patients with newly diagnosed breast cancer. In the current study, ^{18}F-FES PET/CT led to intended treatment management changes in 5 of 19 patients (0.263, 95% CI 0.045–0.481), which is a considerable probability of changing treatment decisions. We believe that the role of ^{18}F-FES PET/CT in changing staging and treatment management will be more prominent compared with other traditional imaging methods in newly diagnosed ER-positive breast cancer. Further studies are needed to validate this point of view.

^{18}F-FES PET/CT that changed the course of operation was seen in almost half of the cases in operated patients. In one case, ^{18}F-FDG PET/CT showed one extra lesion not seen on ^{18}F-FES PET/CT (one solitary bone lesion in the sternum). Thus, ^{18}F-FES PET/CT downstaging a patient from stage IV to stage I lead to a management change from operation contraindications to operation indications and palliative to curative (Fig. 4). This change in therapeutic strategy was crucial to the patient's prognosis; however, this case has not been confirmed by pathology and is simply considered to be a hemangioma in accordance with the recent follow-up imaging techniques including MRI and CT.

The value of FES is recognized by more than half of referring physicians based on the questionnaire of the present study (55.6%). The study has several limitations. First, the sample size was relatively modest because the population we studied had newly diagnosed breast cancer, whereas other studies of ^{18}F-FES mainly focused on recurrent or metastatic breast cancer. In addition, because of the resolution limitations of PET, small lesions may not show ^{18}F-FDG or ^{18}F-FES uptake, which could lead to an underestimation of the total number of lesions. Furthermore, the major drawback of ^{18}F-FES is its high liver physiological uptake, which makes it unable to detect and diagnose liver lesions. Finally, we did not have access to serial tumor

biopsies, which could have contributed to a comprehensive comparison with PET/CT imaging.

Conclusion

^{18}F-FES PET/CT scanning can be helpful in the diagnosis and treatment management of newly diagnosed ER-positive breast cancer, especially in patients with equivocal lesions on ^{18}F-FDG PET/CT scanning. The proper application of ^{18}F-FES PET/CT could optimize the individual treatment strategy by avoiding ineffective and excessive management.

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Disclosures

The authors indicated no financial relationships.

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