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Original Research

ER status conversion and subsequent treatment: an assessment of negative ER expression detected by 18F-FES PET in metastatic breast cancer patients with ER-positive primary tumors

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Abstract

Background: The 18F-fluoroestradiol positron emission tomography/computed tomography (18F-FES PET/CT) technique provides a convenient method to evaluate the overall estrogen receptor (ER) expression in metastatic breast cancer (MBC) patients. There are long debates on the characteristics and treatment strategy of patients with positive primary ER lesions but negative ER expression in metastatic disease. 18F-FES PET offers an opportunity to answer this question.

Objectives: This study aimed to characterize the primary ER-positive patients with advanced-stage FES negativity and investigate the real-world treatment decisions made by physicians subsequently, and compare the efficacy between different regimens.

Design: This observational cohort study was conducted at Fudan University Shanghai Cancer Center, enrolling breast cancer patients with ER-positive primary tumors who showed advanced-stage FES negativity.

Methods: Descriptive statistics were used in clinicopathologic characteristics and compared with a chi-square test or *t*-test. In addition, progression-free survival (PFS) was estimated by the Kaplan-Meier method and compared by log-rank test.

Results: 16.6% (52/314) of patients with an ER-positive primary tumor had negative ER expression assessed by 18F-FES for MBC prior to receiving first-line systemic therapy, among whom adjuvant endocrine therapy was prevalently utilized (86.5%, 45/52). The rate of FES negativity in the advanced stage was negatively correlated with levels of ER expression of primary tumors. Chemotherapy (83.3%, 40/48) was the most common treatment strategy afterward, among which capecitabine monotherapy (62.5%, 25/40) was a dominant alternative. PFS was significantly prolonged with capecitabine alone *versus* other chemotherapy (median PFS: 13.14 *versus* 6.21 months, $p = 0.029$).

Conclusion: Negative conversion of ER in MBC detected by 18F-FES occurred frequently. Patients with lower ER expression in the primary lesion were more likely to have negative ER expression in the metastasis. In real-world clinical practice, most physicians primarily opted for chemotherapy, with capecitabine monotherapy being a commonly selected regimen.

Trial registration: ClinicalTrials.gov identifier: NCT05797987.

Keywords: 18F-fluoroestradiol positron emission tomography/computed tomography, breast cancer, diagnosis, ER heterogeneity, treatment pattern

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Introduction

Breast cancer (BC) is a prevalent form of invasive cancer affecting women worldwide, and it remains one of the leading causes of cancer-related death among women.[1] Among the various subtypes of BC, estrogen receptor (ER)-positive BC is the most common, accounting for about 75% of all cases.[2] Previous research has indicated a substantial conversion of ER status from positive to negative in a considerable proportion of individuals between primary lesions and metastases,[3] exhibiting changes in ER expression ranging from 16% to 40% between the primary tumor and metastatic sites.[4,5] Furthermore, we are interested in the potential influence of baseline clinicopathological characteristics such as primary tumor ER expression on this ER status conversion, as prior research suggests the level of initial ER expression could impact the receptor's status in advanced disease.[6,7] This understanding is crucial given that hormone receptor loss in BC may affect treatment response and overall prognosis.[8] Consequently, understanding this subtype is critical in developing effective treatment strategies for a significant number of BC patients.

Therefore, regular examination of the ER status is essential for the optimal diagnosis and treatment strategy. Immunohistochemistry is the current gold standard for determining ER expression in BC,[9] but there are limitations to this gold standard. Metastatic biopsies may result in sampling errors or may be impossible due to the invasive nature of the procedure or the location of the lesion.

Recent advancements in the 18F-fluoroestradiol positron emission tomography/computed tomography (18F-FES PET/CT) technique provide a promising method for evaluating overall ER expression in metastatic breast cancer (MBC) patients.[10,11] Notably, two large prospective studies underscore the utility of 18F-FES PET in patients with MBC before the first-line treatment,[12,13] suggesting it as a noninvasive, valid alternative when ER retesting of biopsy is unfeasible. Moreover, 18F-FES PET is also utilized to identify and determine the prognostic implications of ER heterogeneity.[3,10,14] 18F-FES PET can detect the ER expression of all tumor lesions and estimate the heterogeneity of ER expression in metastatic lesions throughout the body and, therefore, can be used for individualized therapy decision-making.[15,16] Hence, the 18F-FES PET scan has extra value in patients with BC who present a clinical dilemma to the physician.

Although 18F-FES PET imaging holds great promise for revealing disease heterogeneity in MBC,[17,18] there has been little research focusing on patients who display ER-positive primary lesions but negative ER expression as assessed by 18F-FES PET in metastatic disease. It is worth noting that 18F-FES PET images ER that can actively bind to estrogen, thus not all ER identified on immunohistochemistry (IHC) may reflect ligand binding, and not all ER identified on IHC will be positive on 18F-FES PET. The implications of this distinction are significant as it can influence treatment decisions.

Therefore, this study aimed to delineate the clinical and pathological characteristics of MBC patients who originally presented with ER-positive primary tumors by IHC but later converted to FES negative in the advanced stage, with a specific focus on the level of ER expression in the primary tumors. Furthermore, we sought to critically assess the treatment strategies employed post-conversion in clinical practice and to evaluate their efficacy among this specific group of patients.

Methods

Patients

We screened all BC patients with ER-positive primary tumors who underwent 18F-FES PET/CT at the Fudan University Shanghai Cancer Center between June 2010 and August 2022. Our study enrolled 52 patients diagnosed with primary ER-positive tumors and who later exhibited FES negativity in the advanced stage (Figure 1). Patients who had received systemic therapy in the advanced stage prior to the 18F-FES PET/CT test, those with incomplete medical records, and those diagnosed with secondary primary tumors were excluded from the study. The ER status of the primary tumor in our study was determined *via* IHC analysis of the primary tumor mass. ER positivity was defined as an ER expression of $>1\%$. ER binding status in the advanced stage assessed by FES PET/CT is also indicative of ER expression. MBC was characterized as BC that was unresectable, recurring, or metastatic, with the exclusion of locally recurrent instances due to their potential for curative surgical interventions.

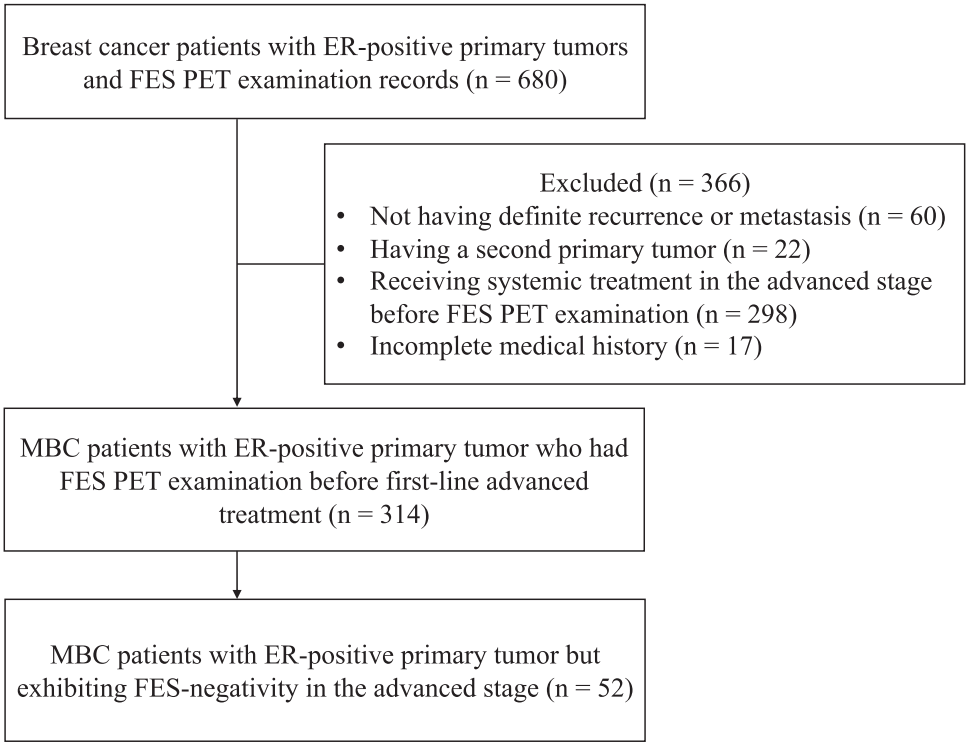

Figure 1. Flow diagram of patient selection.

The diagnostic decision of MBC was corroborated by a combination of available pathological biopsy, computed tomography (CT), magnetic resonance imaging (MRI), 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), bone scintigraphy, and clinical follow-up. In this study, treatment strategies were determined by a holistic evaluation of numerous factors, including 18F-FES PET results, surgical pathology, IHC results, and when available, pathological results from metastatic sites, with the patient's overall health status, preferences, and the clinician's professional judgment further contributing to the decision-making process. We categorized the FES-negative MBC patients into different treatment groups based on their initial therapy in the advanced setting. The patients were divided into three groups: the capecitabine monotherapy group, the other chemotherapy group, and the other therapy group.

The medical records, treatment data, and PET/CT data were retrospectively collected from the electronic medical database system. The Fudan University Shanghai Cancer Center Institutional Review Board (SCCIRB) granted a waiver for ethical review and approval (waived by SCCIRB, 1812195-6). This clinical investigation was authorized by the Ethics Committee and Institutional Review Board of Fudan University Shanghai Cancer Center, and all techniques and procedures were carried out in conformity with the Declaration of Helsinki and other relevant regulations.

Imaging

In terms of 18F-FES PET/CT imaging, all compounds were procured from commercial sources and utilized without further purification. The precursor (3-methoxymethyl 16β, 17β-epiestriol-O-cyclic sulfone, MMSE) and authentic 18F-FES were obtained from Jiangsu Huayi Chemical Co., Ltd. (Suzhou, Jiangsu, China), and 18F-FES was synthesized according to established procedures.[19] To ensure accurate 18F-FES results, ER antagonists were discontinued at least 5 weeks prior to the study while aromatase inhibitors were allowed.[20]

Each patient received an injection of approximately 222 MBq (6 mCi) of 18F-FES over a period of 2 min. Regarding 18F-FDG PET/CT imaging, according to the guidelines of the European

Association of Nuclear Medicine (EANM), patients should fast for at least 4 h prior to the injection of 18F-FDG (3.7 MBq/kg) and the blood glucose levels should be below 11 mmol/L. Image acquisition was performed 60 min after injection with a PET/CT scanner (Biograph 16 HR or mCT Flow, Siemens Medical Systems, Knoxville, TN, USA). The transaxial intrinsic spatial resolution in the center of the field of view was 4.1 mm (full width at half maximum). The PET/CT data acquisition protocol was as follows: A low-dose CT scan was first obtained from the proximal thighs to the skull base and then a separate head scan was performed (120 kV, 80–250 mA, pitch 3.6, rotation time 0.5 ms). Following the CT scan, a PET emission scan was performed covering the same transverse field of view. PET emission scans covering the corresponding areas of CT were obtained with FlowMotion in three-dimensional mode (2–3 min per station) at a speed of 2. Iterative reconstruction of the PET data was performed using ordered subset expectation maximization iterative reconstruction (OSEM) (iteration 2; subset 21; image size 200). And PET/CT scans were performed in 15–20 min. PET images were reconstructed using an iterative method with a Gaussian filter and co-registered images were displayed on a workstation.

Image interpretation

To conduct image review and manipulation, a multimodality computer platform called Syngo (Siemens, Knoxville, TN, USA) was utilized. Two experienced nuclear medicine physicians (>5 years of working experience) who are board-certified independently evaluated the images, and they agreed in case of discrepancies. Depending on the patients' condition, different imaging modalities can be used to identify the lesions on 18F-FES PET/CT scans, including 18F-FDG PET/CT and diagnostic CT, MRI, and bone scintigraphy. While it is generally recommended that patients undergoing 18F-FES PET/CT also receive 18F-FDG PET/CT, it is not a mandatory requirement. The decision to administer 18F-FDG PET/CT was made on an individual basis, taking into account each patient's clinical presentation, overall health status, and personal preferences. Lesions in 18F-FES PET/CTs were identified using paired 18F-FDG PET/CT images. In patients with a negative FES PET/CT, FDG can help delineate active disease areas and play a role in subsequent treatment planning. Moreover, it can act as a complement to FES in understanding the tumor's metabolic activity *versus* its hormone receptor status, providing a more holistic view of the disease. The 18F-FES uptake of a lesion was semi-quantitatively expressed as a standardized uptake value (SUV) adjusted to body weight. To determine the maximal SUV (SUVmax) for each metastatic lesion, a region of interest was manually placed around each tumor on all subsequent slices containing the lesion on co-registered and fused transaxial PET/CT images. Liver lesions were excluded, where it was metabolized. Results were classified as ER positive or negative based on a cutoff value of SUVmax 1.8.[18,21] To reduce partial volume effects and resolution limitations, quantitative 18F-FES uptake was performed in measurable lesions larger than 1.0 cm in diameter. Patients who did not present with any ER-positive lesions detected by 18F-FES PET/CT were characterized as having negative ER expression or FES negativity.

Outcome measurements

In this study, the primary outcome was progression-free survival (PFS), with the secondary outcome being treatment safety. PFS was defined as the duration between the first dose of treatment and either disease progression or death from any cause. The treatment response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,[22] with complete response, partial response (PR), stable disease, and progressive disease being assessed.

Statistical analysis

The study presented numeric data as medians (ranges) or patient counts, and categorical data as counts (percentages). Descriptive statistics were employed for clinicopathologic characteristics, and the chi-square test was used to compare groups. Secondary outcomes were also analyzed with descriptive statistics. Survival analyses were performed using the Kaplan–Meier method, and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were determined using the Cox proportional hazard model. Univariate and multivariate Cox regression models were used to evaluate prognostic factors with a 95% CI. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using either SPSS (IBM) version 25.0 or GraphPad Prism version 8.0.0 for Windows.

Results

Patient characteristics

Among 608 ER-positive primary BC patients who underwent 18F-FES PET/CT at the Fudan University Shanghai Cancer Center between June 2010 and August 2022, 52 who exhibited FES negativity prior to advanced systemic therapy were enrolled in this study (Figure 1). These patients were subsequently classified into different treatment groups according to their initial therapy in the advanced setting (treatment details for four patients in the advanced stage were not available): 25 patients received capecitabine monotherapy, 15 patients were administered other chemotherapy, and 8 patients underwent other therapies (including endocrine therapy and a combination of chemotherapy with endocrine therapy).

In our study, the majority of the patients were over the age of 50 in each treatment group (Table 1). The median disease-free interval was 3 years across all groups. A small fraction of patients (10%) was diagnosed as de novo stage IV. All the patients, except one, exhibited an Eastern Cooperative Oncology Group performance status of 0–1. In terms of primary ER expression, 8% of patients registered levels between 1% and 9%, 27% between 10% and 49%, 62% between 50% and 95%, and a minor 4% exceeded 95%. Turning to primary PR status, the majority of patients were PR positive. Focusing on HER2 status, positivity was limited to the Capecitabine group, whereas the other groups reported no HER2-positive cases. The prevalent tumor grade among patients was grade II. The number of metastatic sites was either one or two in 84.6% (44/52) of the patients. Analysis of the metastatic sites revealed that the bone was the most common site (44.2%, 23/52), followed by the lungs (32.7%, 17/52).

In terms of previous treatments in the early stage, our data showed that a significant proportion of patients across all groups (86.5%, 45/52) had received adjuvant/neoadjuvant chemotherapy, with the majority being treated with taxanes and/or anthracyclines. Similarly, adjuvant endocrine therapy was also prevalently utilized (86.5%, 45/52), with tamoxifen and exemestane being the most commonly employed agents (Table 1).

FES negative conversion probability in MBC

In this study, 680 BC patients with ER-positive primary tumors who received 18F-FES PET/CT were screened, and 314 patients received 18F-FES PET/CT before first-line systemic treatment for advanced BC. Prior to receiving first-line systemic therapy for MBC, 16.6% (52/314) of MBC patients with an ER-positive primary tumor had negative ER expression assessed by 18F-FES PET/CT (Figure 2).

The distribution of ER status tested by 18F-FES by ER expression is shown in Figure 3. The rate of FES negativity was negatively correlated with levels of ER expression by IHC in the early stage, with ER-positive to FES-negative conversion in 2 of 3 (66.7%) ER-low (i.e. ER 1–9%) tumors, 7 of 10 (70.0%) ER-moderate (i.e. ER 10–49%) tumors, 16 of 114 (14.0%) ER-high (i.e. ER 50–95%) tumors, and 1 of 8 (12.5%) ER-very high (i.e. ER $>$ 95%) tumors ($p < 0.001$) (Figure 3). The average SUVmax value for metastatic lesions in the ER-low and ER-moderate groups was 1.19, while this value was 1.35 for the ER-high and ER-very high groups ($p = 0.290$).

Treatment pattern and efficacy

Regarding the first-line systemic therapy during the advanced stage, we examined 52 patients with ER-positive primary tumors by IHC who transitioned to FES negativity in the advanced stage of MBC. Of these, four were lost to follow-up. Among the remaining 48 patients, chemotherapy was opted as the first-line treatment by a majority (83.3%, 40/48), three (6.3%, 3/48) were offered chemotherapy combined with endocrine therapy, and five (10.4%, 5/48) chose endocrine therapy alone [Figure 4(a)]. Of the 40 patients who selected chemotherapy, the majority were treated with single-agent chemotherapy (70.0%, 28/40), with capecitabine monotherapy being the most commonly used regimen [62.5%, 25/40; Figure 4(b)]. The other three patients were administered monotherapy with albumin paclitaxel. For those on combination chemotherapy, the regimens included capecitabine with either vinorelbine or docetaxel for six patients, and various combination therapies for another six patients (docetaxel + trastuzumab + pertuzumab, albumin paclitaxel + carboplatin, albumin paclitaxel + gemcitabine, doxorubicin + cyclophosphamide + sequential albumin paclitaxel, gemcitabine + cisplatin, albumin paclitaxel + cisplatin + camrelizumab).

Notably, capecitabine monotherapy was found to be significantly more effective than other chemotherapy regimens in terms of median

Table 1. Baseline characteristics of the enrolled patients.

Characteristics	Capecitabine monotherapy *N* = 25 *n* (%)	Other chemotherapy *N* = 15 *n* (%)	Other therapy[a] *N* = 8 *n* (%)	All[b] *N* = 52 *n* (%)
Median age (years)	57	52	51	52
(range)	(32–83)	(38–69)	(38–61)	(32–83)
Age > 50	15 (60)	9 (60)	5 (63)	30 (58)
Median disease-free interval (years)	3	3	5	3
(range)	(0–18)	(0–15)	(2–8)	(0–18)
De novo stage IV	1 (4)	2 (13)	1 (13)	5 (10)
ECOG score				
0–1	25 (100)	15 (100)	8 (100)	51 (98)
⩾2	0 (0)	0 (0)	0 (0)	1 (2)
Primary ER expression				
1–9%	2 (13)	0 (0)	0 (0)	2 (8)
10–49%	5 (33)	1 (13)	1 (50)	7 (27)
50–95%	7 (47)	7 (88)	1 (50)	16 (62)
>95%	1 (7)	0 (0)	0 (0)	1 (4)
Unknown	10	7	6	27
Primary PR status				
Positive	13 (54)	11 (73)	5 (63)	32 (63)
Negative	11 (46)	4 (27)	3 (37)	19 (37)
Unknown	1	0	0	1
Primary HER2 status				
Positive	4 (17)	0 (0)	0 (0)	6 (12)
Negative	20 (83)	15 (100)	8 (100)	44 (88)
Unknown	1	0	0	2
Primary tumor grade				
II	11 (58)	12 (100)	4 (67)	29 (55)
II–III	2 (11)	0 (0)	1 (17)	3 (6)
III	6 (32)	0 (0)	1 (17)	8 (15)
Unknown	6	3	2	12
Number of metastatic sites				
1–2	23 (92)	12 (80)	5 (63)	44 (85)
⩾3	2 (8)	3 (20)	3 (37)	8 (15)

(Continued)

Table 1. (Continued)

Characteristics	Capecitabine monotherapy *N* = 25 *n* (%)	Other chemotherapy *N* = 15 *n* (%)	Other therapy[a] *N* = 8 *n* (%)	All[b] *N* = 52 *n* (%)
Metastatic sites				
Visceral[c]	6 (24)	7 (47)	6 (75)	21 (40)
Liver	0 (0)	1 (7)	1 (13)	2 (4)
Lung	6 (24)	6 (40)	5 (63)	17 (33)
Bone	11 (44)	8 (53)	2 (25)	23 (44)
Adjuvant/neoadjuvant chemotherapy	23 (92)	13 (87)	7 (88)	45 (87)
Taxanes	16 (64)	7 (47)	4 (50)	30 (58)
Anthracyclines	14 (56)	9 (60)	5 (63)	29 (56)
Adjuvant endocrine therapy	23 (92)	12 (80)	7 (88)	45 (87)
Tamoxifen	6 (24)	0 (0)	4 (50)	11 (21)
Exemestane	7 (28)	4 (27)	0 (0)	11 (21)
Anastrozole	5 (20)	2 (13)	1 (13)	9 (17)
Letrozole	4 (16)	2 (13)	2 (25)	8 (15)
Toremifene	1 (4)	1 (7)	0 (0)	3 (6)

[a]Other therapies included both endocrine therapy and a combination of chemotherapy with endocrine therapy.
[b]Treatment information was unavailable for 5 out of the 52 patients included in the study.
[c]Visceral metastases were defined by the following locations: liver, lung, ascites, pleural effusion, and metastases in the central nervous system.
ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, partial response.

progression-free survival (mPFS: 13.14 *versus* 6.21 months, $p = 0.029$; Figure 5).

Discussion

This study aimed to investigate the prevalence of ER-positive primary tumor patients with ER-negative metastasis using the 18F-FES PET/CT method and to evaluate the characteristics of the target patients as well as treatment patterns and efficacy. Importantly, this was the first study to evaluate the value of 18F-FES PET in the group with conversion from ER positivity in primary BC to FES negativity in the advanced stage, yielding valuable insights into the management of such patients. The results indicate that 18F-FES PET/CT imaging may have clinical utility in guiding treatment decisions in patients with ER-positive primary tumors.

Building upon two large prospective trials that underscored the clinical validity of 18F-FES PET/CT in MBC as an alternative to biopsy for ER status determination,[12,13] our investigation has further explored its utility in assessing shifts in ER status. In terms of ER-negative conversion, a meta-analysis[23] of 39 studies indicated that for Erα, the random effects pooled positive to negative conversion percentages were 22.5% (95% CI = 16.4–30.0%) from primary breast tumors to paired distant BC metastases. In our study, we observed a slightly lower rate of conversion, with 16.6% of patients transitioning from ER positive to completely FES negative. This may be attributed to the use of 18F-FES PET/CT imaging for detecting lesions in late-stage metastasis, which enables the detection of lesions throughout the body, compared to pathological biopsy which can only detect one of the metastatic sites.

Prior research[14,16,18] consistently reveals the heterogeneous nature of ER expression in MBC and the utility of 18F-FES PET imaging to noninvasively track this heterogeneity over time. However,

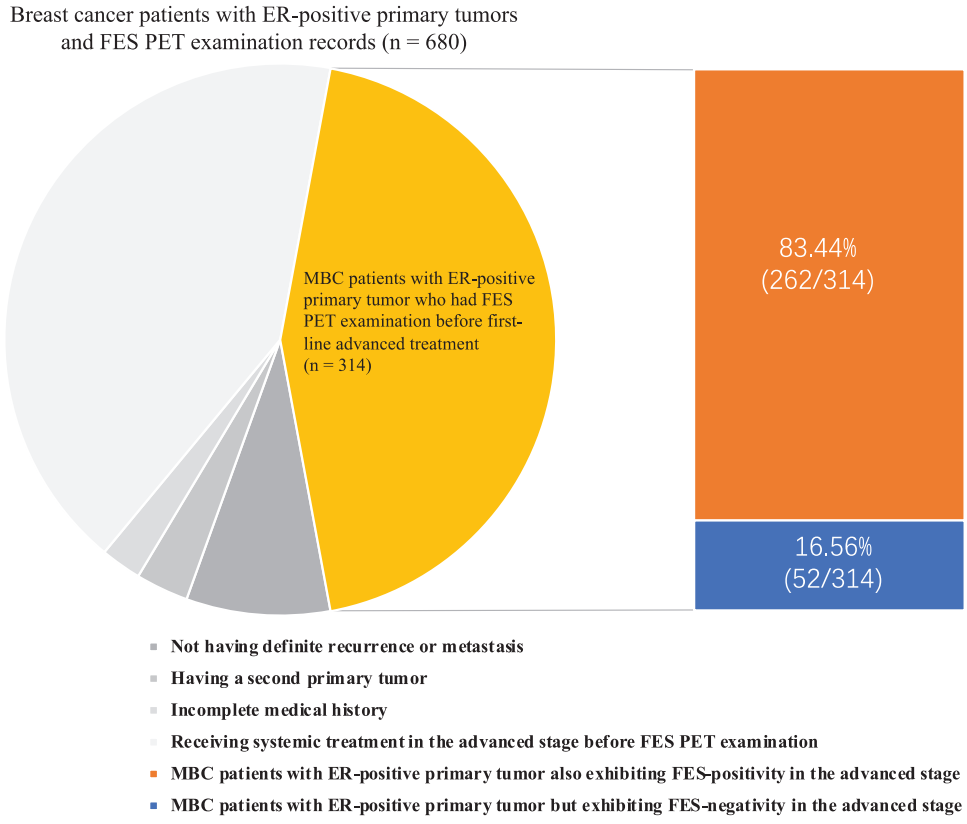

Figure 2. Distribution of breast cancer patients with ER-positive primary tumors who underwent FES PET examination and their ER expression status in the metastatic setting before first-line advanced treatment. 'FES negativity' means that all sites of metastases in the advanced stage were negative for FES uptake.
ER, estrogen receptor; FES PET, fluoroestradiol positron emission tomography.

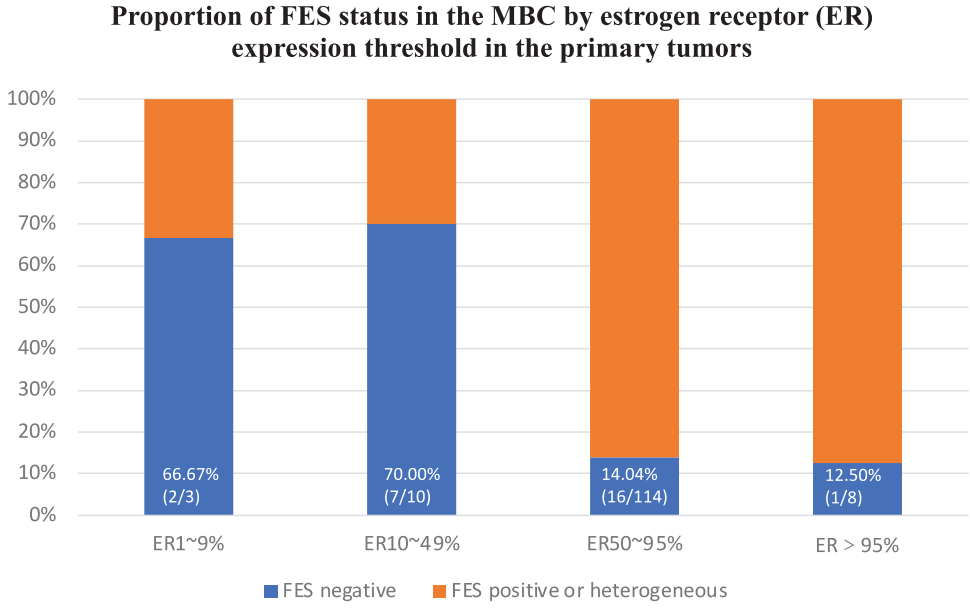

Figure 3. Proportion of FES status in the MBC by ER expression threshold in the primary tumors. ER threshold was determined by IHC.
ER, estrogen receptor; FES, fluoroestradiol; IHC, immunohistochemistry; MBC, metastatic breast cancer.

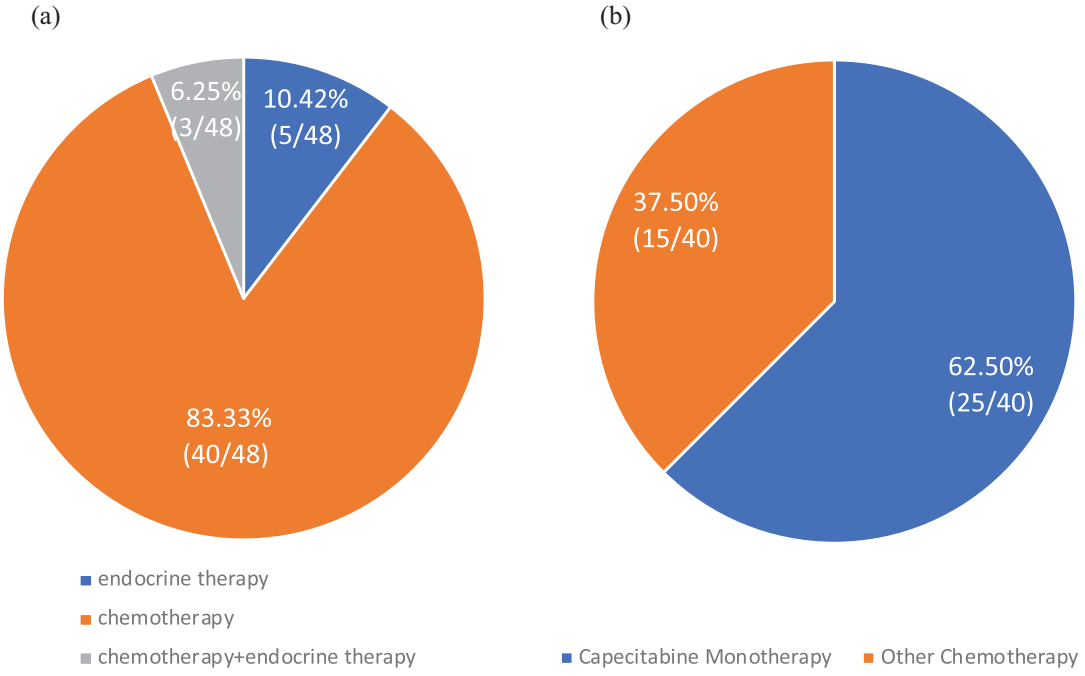

Figure 4. Treatment patterns of MBC patients with FES negative conversion. (a) First-line systemic treatment options and (b) chemotherapy regimen in the first-line systemic treatment.
FES, fluoroestradiol; MBC, metastatic breast cancer.

in this study, we excluded patients who had received advanced systemic treatment, thus eliminating the potential confounding effect of such treatment on the evolution of ER expression. Furthermore, our investigation focused on patients with entirely negative ER expression in the advanced stage, which is a departure from previous research. In addition, the results of our study indicate a negative correlation between the rate of ER negativity tested by 18F-FES in the advanced setting and the levels of ER expression in early-stage BC. The finding that the rate of negative conversion is higher in ER-moderate and ER-low tumors suggests that this population of patients may require more frequent monitoring for changes in ER expression and 18F-FES PET/CT can be a promising tool. While previous research suggests that ER-moderate and ER-low tumors are generally associated with lower FES uptake,[12] our research uniquely concentrates on tracking the conversion from an initial ER-positive status, as verified by IHC during primary tumor surgery, to an ER-negative status identified through FES during the advanced stages of the disease. This focus underscores the clinical utility of FES in detecting such conversions in real-world settings. Moreover, we explored the treatment patterns and assessed their effectiveness in the real-world setting for patients with MBC who underwent conversion from ER-positive primary tumor to FES-negative status in the advanced stage, using 18F-FES PET as a measure. To our knowledge, this study is the first of its kind and makes a pioneering contribution to the field.

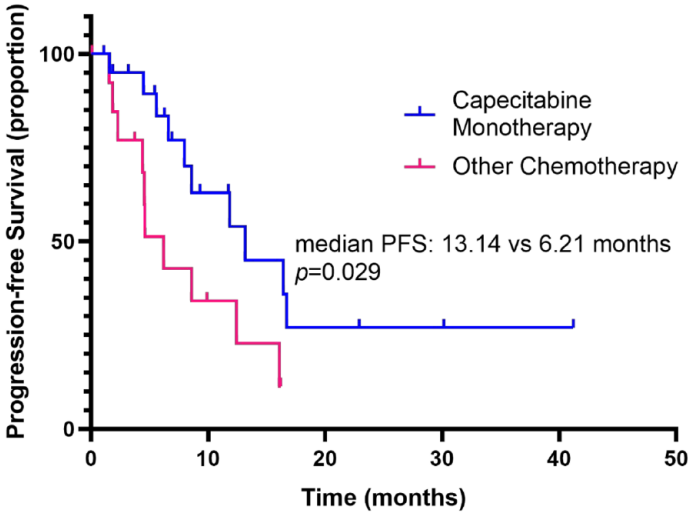

Figure 5. Kaplan–Meier curves for progression-free survival by treatment arm (capecitabine monotherapy *versus* other chemotherapy).

Prior studies have shown that patients with ER-positive disease, as identified by IHC, yet demonstrating FES-negativity typically failed to respond to endocrine therapy and experienced poorer outcomes, underscoring the utility of 18F-FES PET in guiding treatment decisions.[24,25] However, temporal heterogeneity of ER expression may impact treatment efficacy. Modification of therapeutic plan based on biopsy of the metastasis has been reported in 62% of converted patients for Erα.[26] Based on previous studies, it has been observed that approximately 15–20% of patients with tumors tend to experience a loss of ER expression in their metastatic lesions, which can contribute to the development of endocrine resistance.[27] This trend reflects the complexities and challenges associated with treating this subset of patients, who typically exhibit a more aggressive disease progression and have limited effective treatment options.[28] Our study has shown that in clinical practice, chemotherapy was the primary treatment choice for most physicians when treating patients who exhibited an ER status conversion from ER positive to FES negative in advanced stages. This aligns with existing literature, which suggests that chemotherapy may indeed be a viable treatment approach for ER-negative BC, particularly given its typically aggressive nature and the often-limited effectiveness of hormone-based therapies in this context.[29] Specifically, our results also identified capecitabine monotherapy as demonstrating good efficacy, which substantiates the utility of this treatment modality for such patients. Several studies[30,31] have demonstrated that capecitabine monotherapy is effective and safe in the first-line treatment of advanced disease, which is consistent with our findings. In addition, the oral administration of capecitabine enables convenient, patient-oriented therapy, making it an attractive treatment option. Therefore, even though the primary tumor showed ER positivity, entirely ER-negative results as assessed by 18F-FES PET in the advanced setting suggest that chemotherapy, rather than endocrine therapy, is commonly opted in clinical practice. Specifically, capecitabine monotherapy is often more effective than other chemotherapy for the first-line systemic treatment.

There are also some limitations to this research article that should be considered. First, the study is retrospective in nature, which may introduce bias and confounding factors that cannot be controlled for. Second, the study was conducted at a single institution, which may limit the generalizability of the findings to other populations and settings. Another major limitation is that not all cases of metastatic disease were not biopsy confirmed. Specifically, only 7 of the 52 patients underwent biopsy of metastatic lesions. We acknowledge that the lack of biopsy confirmation in all patients could introduce some degree of diagnostic uncertainty. However, the approach used in our study reflects real-world clinical practice where biopsy is not always feasible or practical.

In conclusion, this study revealed that 16.6% of 314 MBC patients with ER-positive primary tumors can exhibit negative ER conversion, as visualized through 18F-FES PET. Patients with ER-moderate and ER-low primary tumors are more likely to be FES negative in metastatic sites. In clinical practice, most physicians primarily opt for chemotherapy, especially capecitabine monotherapy.

Declarations

Ethics approval and consent to participate

This study was carried out in adherence to the guidelines of the Declaration of Helsinki. As it is a retrospective investigation, the Institutional Review Board of Fudan University Cancer Hospital (SCCIRB) granted a waiver for ethical review and approval (waived by SCCIRB, 1812195-6).

Consent for publication

Given the retrospective nature of this study, the requirement for explicit patient consent for publication was waived. Nevertheless, all patient data were de-identified to maintain confidentiality and comply with privacy regulations.

Author contributions

Shuhui You: Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Yizhao Xie: Conceptualization; Formal analysis; Investigation; Writing – review & editing.

Mengjing Ji: Investigation; Methodology; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to hospital policy but are available from the corresponding author upon reasonable request.

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