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Editorial

^{18}F-FES PET/CT in invasive lobular breast cancer: assessment of axillary lymph node metastasis

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Abstract: Estrogen receptor (ER) is highly expressed in approximately 95% of invasive lobular breast cancer (ILC) and represents a key target for endocrine therapy. ^{18}F-fluoroestradiol (^{18}F-FES), a radiolabeled estrogen analog, specifically binds to ER and enables real-time, non-invasive, and whole-body evaluation of ER functional status, providing intuitive visualization of the spatial and temporal heterogeneity of ER expression. ^{18}F-FES PET/CT sensitively detect primary tumor and distant metastases and accurately identifies axillary lymph node involvement in ILC. Therefore, ^{18}F-FES PET/CT can serve as a valuable diagnostic tool that can guide the selection of appropriate therapeutic strategies for patients with ILC.

Keywords: Invasive lobular carcinoma, axillary lymph node, estrogen receptor, ^{18}F-fluoroestradiol, positron emission tomography

Introduction

Invasive lobular carcinoma (ILC) is a common subtype of breast cancer, ranking second in incidence after invasive ductal cancer (IDC) and accounting for approximately 10-15% of all invasive breast cancer [1]. ILC is characterized by a deficiency of E-cadherin, resulting in its hallmark single-file infiltration and non-adhesive growth pattern. In contrast to IDC, which typically presents as spiculated masses, ILC often manifests as subtle structural distortions or tissue asymmetry, leading to underestimation of tumor volume and higher re-excision rates. This morphological feature contributes to a distinct metastatic pattern [2]; besides commonly involving bones, lymph nodes, and liver metastasis, ILC is also frequently metastasizes to the peritoneum, retroperitoneum, gastrointestinal tract, and pia matter [3-5]. Moreover, its unique biological characteristics make it difficult to detect early stage ILC in dense breast tissue using conventional and metabolic imaging modalities, including mammography, ultrasound, CT, MRI, and ^{18}F-FDG PET/CT.

Estrogen receptor (ER) is an important target of endocrine therapy for breast cancer, and ER overexpression is found in approximately 70-80% of breast cancer [6]. The majority of ILCs (95%) are ER/progesterone receptor (PR) positive while exhibiting low expression of human epidermal growth factor receptor 2 (HER2), classifying them as the luminal A intrinsic subtype. An ER-targeted radiopharmaceutical ^{18}F-fluoroestradiol (^{18}F-FES) has increasingly attracted research attention and ^{18}F-FES PET/CT has demonstrated considerable potential for assessing ER distribution in primary or metastatic breast cancer [7]. Currently, ^{18}F-FES has been approved by the U.S. Food and Drug Administration as a diagnostic agent on May 2020, for assessing ER status, the systematic staging or restaging, selecting appropriate patients for hormonal therapy, and assisting in the development of novel ER-targeted therapeutic drugs in breast cancer [8, 9]. Previous studies regarding ^{18}F-FES PET/CT in ILC have mainly focused on metastatic or locally advanced disease, highlighting its diagnostic advantage over ^{18}F-FDG PET/CT [10-12]. However, few studies have investigated the diagnostic value of ^{18}F-FES PET/CT for detecting axillary lymph node (ALN) metastasis in early stage ILC.

In the recent issue of *Journal of Nuclear Medicine*, Ryu and Han et al. investigated the diagnostic performance of ER-targeted PET/CT using ^{18}F-FES as a radiotracer in detecting ALN metastasis in ILC (**Figure 1**) [13]. In this phase 2 open-label nonrandomized single-center prospective study (NCT05960201) performed between August 2023 and August 2024, eligible participants were enrolled in this study with newly diagnosed ER-positive ILC, who had suspected or confirmed axillary lymph node (ALN) metastasis based on ultrasound imaging or physical examination. All subjects were scheduled to receive sentinel lymph node (SLN) biopsy or ALN dissection with median time interval of 13 days (interquartile range, 5-22 days) between ^{18}F-FES PET/CT and surgery. The exclusion criteria were (a) patients with staging of cN2/N3 or distant metastases, (b) patients with history of ipsilateral ALN resection or SLN biopsy before ^{18}F-FES PET/CT, (c) patients received ILC-related anti-tumor therapy. All subjects were advised to drink plenty of water and empty their bladder before ^{18}F-FES PET/CT scan, without any other special requirement. ^{18}F-FES PET/CT was performed approximately 90 minutes after i.v. administration of

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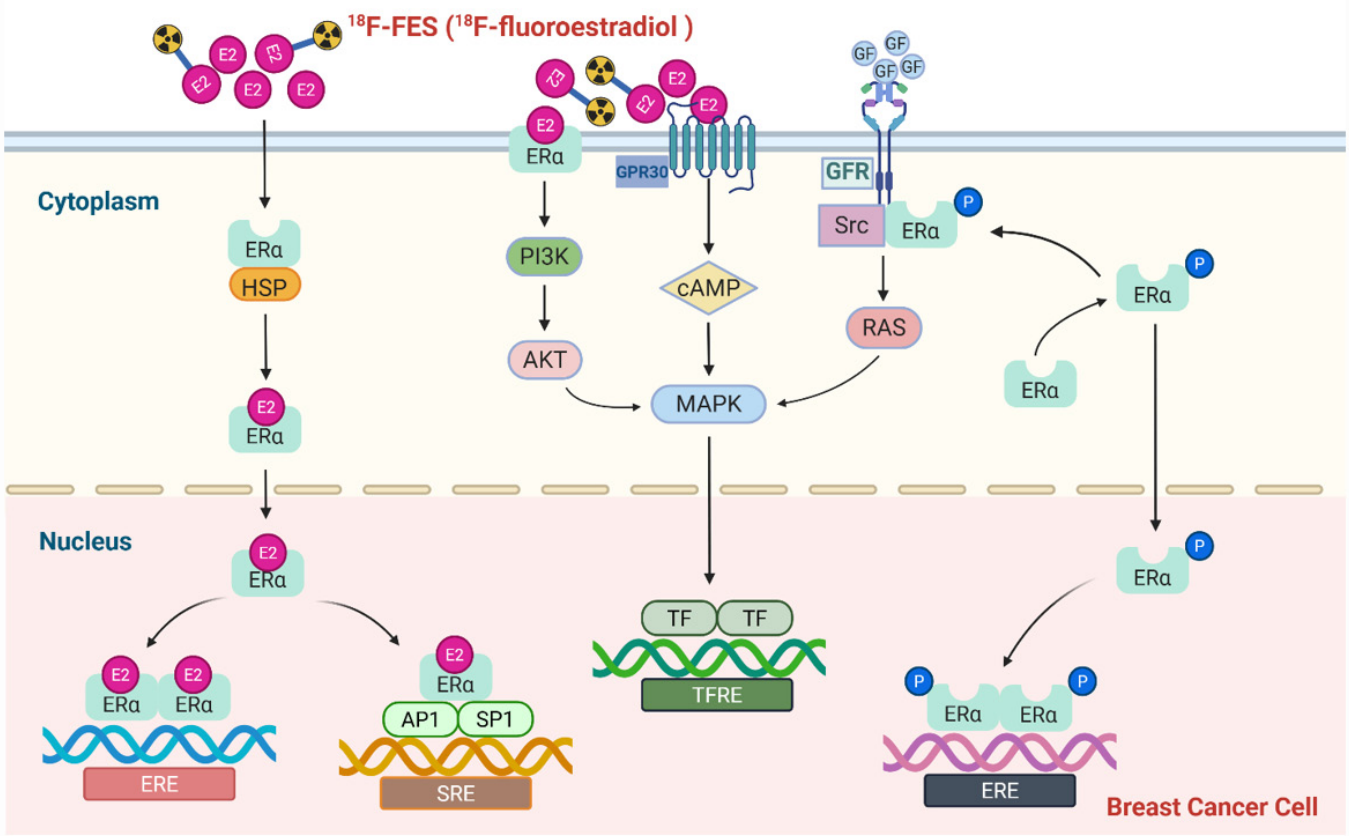

Figure 1. Schematic diagram of ^{18}F-fluoroestradiol (^{18}F-FES) imaging of estrogen receptor (ER) positive breast cancer. E2, estrogen; HSP, heat shock protein; ERE, estrogen responsive element; SRE, serum responsive element; AP1, activating protein 1; SP1, specificity protein 1; MAPK, mitogen-activated protein kinase; GPR30, G protein-coupled receptor 30; GF, growth factor; GFR, growth factor receptor; P, phosphate; PI3K, phosphoinositide 3-kinase; TF, transcription factor.

^{18}F-FES (range, 111-222 MBq). Two nuclear medicine physicians independently reviewed all PET/CT images with no access to clinical and pathological information. They conducted both visual analysis and semi-quantitative evaluation for ipsilateral axillary (level I-III), internal mammary, and supraclavicular lymph nodes. Histological examination of surgery or biopsy specimens from each participant was performed, and the expression of hormone receptors including ER, PR, and HER2 were evaluated by Allred score.

A total of 20 female participants with median age of 52 years (range, 44-76 years) met inclusion criteria and were analyzed. Of these 20 participants, two cases underwent local mass resection surgery before ^{18}F-FES PET scan. Nineteen of 20 participants' primary tumor exhibited intense ER-positive with an Allred score of 8, and the remaining participant had an Allred score of 6. In terms of the detection of primary tumor, 1 of 18 primary tumors exhibited false-negative finding on ^{18}F-FES PET/CT but with an intense ER-expression confirmed by immunohistochemistry. The median maximum standardized uptake value (SUV_{max}) of primary tumor was 3.7 (interquartile range, 3.0-6.9).

Sentinel lymph node biopsy was performed in all 20 subjects, while axillary lymph node dissection was performed in 7 of 20 cases. Among these 20 participants, 8 had no evidence of metastasis to ALN, whereas 12 showed ALN metastases including 9 pN1 and 3 pN2 or higher disease, with median diameter of metastatic lymph nodes of 8 mm (range, 1-21 mm). ^{18}F-FES PET/CT correctly identified 8 of 12 participants (5 with pN1 and 3 with pN2 or higher disease) who had ALN metastasis with maximum size of metastatic lymph node from 6 to 21 mm and all 8 subjects who showed no ALN metastasis, with diagnostic sensitivity of 67%, specificity of 100%, positive predictive value of 100%, negative predictive value of 67%, respectively. On semi-quantitative evaluation, the median SUV_{max} of metastatic ALN with histological evidence was 3.4 (interquartile range, 1.2-9.5), with an excellent detection performance (area under of curve = 0.89); when the optimal SUV_{max} cutoff was 1.2, the corresponding sensitivity, specificity, positive predictive value, negative predictive value was 75%, 100%, 100%, and 73%, respectively. Overall, in terms of the detection of ALN metastasis, the diagnostic performance was the same or similar whether visual or semiquantitative assessment was used. For treatment management, a participant changed surgical regimen because a positive non-SLN lymph node was identified on ^{18}F-FES PET/CT. Another participant with pN2 modified the radiotherapy area because an ipsilateral internal mammary lymph node was successfully detect-

ed on ^{18}F-FES PET/CT. In addition, the authors also demonstrated the sensitivity of ultrasound-guided fine-needle aspiration (FNA) of ALN was similar to ^{18}F-FES PET/CT, suggesting that the latter may replace the FNA, allowing patients to avoid invasive examinations.

The false-negative findings on ^{18}F-FES PET/CT were found in 4 participants with pN1 disease, who had only single SLN metastasis with maximum diameter range from 1 to 6 mm. Partial volume effect is the primary cause of false-negative results in small lymph nodes on ^{18}F-FES PET/CT. Due to the routine need for SLN biopsy in patients with no axillary lymph node metastasis on imaging or physical examination in clinical practice, false-negative results in micro-metastatic lymph node will not affect the final clinical outcome. The research results from the IBCSG 23-01 trial (NCT00072293) demonstrated that breast cancer patients with SLN micrometastasis did not need to receive further axillary dissection because there was no difference in 5-year disease-free survival between no axillary dissection and axillary dissection group [14]. Additionally, there may be ER-negative conversion in the metastatic lymph nodes. Aitken et al reported that approximately 31.8% (35/110) ER-positive primary breast tumor occurred ER-conversion in paired nodal metastasis [15]. In Ryu and Han et al.'s study, a false-negative patient on ^{18}F-FES PET/CT showed a conversion to weakly ER-positive expression in metastatic ALN.

It is noteworthy that ^{18}F-FES PET/CT imaging has its own limitations. For instance, a general limitation is that the liver and gastrointestinal tract have high physiological background uptake, making it difficult to accurately detect liver, gastrointestinal, and peritoneal metastasis, which are common sites of distant metastasis in ILC. Therefore, when performing ^{18}F-FES PET/CT examination, it may be necessary to combine abdominal and pelvic contrast-enhanced CT/MRI to improve the diagnostic accuracy of systematic evaluation. In actual clinical practice, we also need to recognize that after systematic treatment of breast cancer patients, ER-positive lesions have the potential to transition into ER-negative metastatic lesions [11]. Therefore, when using PET/CT with ^{18}F-FES to detect ILC, we need to consider the possible changes in ER expression status caused by the patient's treatment. In this situation using ^{18}F-FES and ^{18}F-FDG dual imaging agents to detect ILC will be more advantageous.

Conclusion

The expression and distribution of ER is related to the formulation of treatment plan for breast cancer patients. The ER status of breast cancer lesions is currently determined by immunohistochemistry of tumor tissues. However, tissue biopsy is an invasive examination and in some cases tumor sample may not be obtained. Whole-body PET imaging with ^{18}F-FES makes it possible to non-invasively assess ER status in breast cancer patients, which may assist in treatment decision-making. The general axillary management principles for ILC are the same as those for IDC. The lymph node involvement of ILC is often underestimated due to its unique biological behavior characteristics. A previous study demonstrated a higher axillary metastatic nodal burden in ILC, with at least four positive metastatic nodes in 31% of ILC cases [16]. In summary, Ryu and Han et al. first evaluated the potential utility of ^{18}F-FES PET/CT for N-staging in early-stage ILC patients. They demonstrated that ^{18}F-FES PET/CT could provide an accurate assessment of metastatic burden in ALN, helping surgeons determine the extent and scope of ALN dissection or preoperative adjuvant therapy in advance. ^{18}F-FES PET/CT can serve as a valuable preoperative staging tool in ILC patients, which may help identify the best indications, update practice guidelines, and manage patients.

Disclosure of conflict of interest

None.

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