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Molecular Imaging for Estrogen Receptor-Positive Breast Cancer:

Clinical Applications of Whole Body and Dedicated Breast Positron Emission Tomography

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Keywords

Fluoroestradiol; Molecular imaging; Breast cancer; Lobular breast cancer; Staging; Positron emission tomography

INTRODUCTION

An estimated 3.5 million women in the United States are living with breast cancer, with nearly 290,000 new cases expected in 2022.[1] During the past several decades, there have been significant strides in breast cancer diagnosis and management. The appreciation for tumor subtypes defined by receptor status has fundamentally changed our understanding of breast cancer and is used to direct treatment strategies. For estrogen receptor-positive (ER+) tumors, treatment with endocrine therapy such as ER modulators or aromatase inhibitors dramatically improves outcomes.[2] For those with overexpression or amplification of the human epidermal growth factor receptor-2 (HER-2), targeted treatment with HER-2 antibody-based therapy is now standard.[3]

For many years, investigators have studied whether these receptors can also be used for imaging breast tumors.[4,5] Such targeted molecular imaging has the promise of improved tumor detection, potentially determination of response to therapy, and could guide treatment strategies and improve surgical approaches. The imaging agent ^{18}F-fluoroestradiol (^{18}F-FES) is a PET radiopharmaceutical used for noninvasive imaging of the ER in vivo. In this article, we discuss the history and development of ^{18}F-FES PET, its clinical applications, its

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DISCLOSURE

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potential utility in invasive lobular carcinoma (ILC), and its use with the novel imaging tool, dedicated breast PET (dbPET).

DISCUSSION

History and Development of ^{18}F-Fluoroestradiol

The development of ^{18}F-FES is largely credited to Dr John A. Katzenellenbogen, a chemist from the University of Illinois. His early study began by efforts to obtain gamma-emitting estrogens, specifically using radioiodinated steroidal estrogens with estradiol substituted at the 16α-position. Guided by the study of Dr Richard Hochberg, who found that 16α-[^{125}I]iodoestradiol had better ER-binding affinities in vivo, Katzenellenbogen began experimenting with other radioisotopes substituted at the 16α-position. Eventually, his team identified that 16α-[^{77}Br]bromoestradiol had improved binding over 16α-[^{125}I]iodoestradiol, but translation from rats to humans proved disappointing.[6] A change in isotope to fluorine-18 allowed the team to benefit from the timely progress in PET imaging technology. The team prepared a variety of [^{18}F]-labeled steroidal and nonsteroidal estrogens but focusing on the 16α-[^{18}F]-FES in particular, which they named ^{18}F-FES. In 1984, Katzenellenbogen and his team first reported favorable bio-distribution characteristics of ^{18}F-FES in rats, and the first images of ER + breast tumors in human subjects were published in 1988.[7] Subsequent years have seen studies evaluating the technical validity, clinical validity, and clinical utility of ^{18}F-FES in the diagnosis and management of breast cancer, with more studies ongoing.[8] Approval from the US Food and Drug Administration (FDA) for its use in recurrent or metastatic ER + breast cancers in conjunction with biopsy was received in May 2020.

Clinical Applications of ^{18}F-Fluoroestradiol in Breast Cancer

^{18}F-FES has binding affinity for the ER, ranging from 60% to 100% across reported studies.[9-11] As such, when paired with standard imaging procedures such as PET and computed tomography (CT), ^{18}F-FES can serve as a “noninvasive whole-body biopsy” to identify ER+ lesions.[9]

^{18}F-FES is administered intravenously over 1 to 2 minutes, with PET image acquisition occurring after a 30 to 100-minute uptake period, with imaging at 80 minutes recommended.[9,12-15] The agent is metabolized by the liver and excreted through the biliary tract into the small bowel, with additional excretion by the kidneys. Of note, physiologic uptake is more pronounced in liver and small bowel than kidney and bladder.[16] Ligand quantities are low enough to avoid physiological effects.[17] Because ^{18}F-FES binds to the ER, the use of ER antagonists or degraders results in decreased ^{18}F-FES PET signal.[18] The currently recommended washout period before imaging with ^{18}F-FES is 8 weeks for selective ER modulators (SERMs) and 28 weeks for selective ER downregulators/degraders (SERDs). As a result, repeat ^{18}F-FES PET imaging is generally only feasible in patients not on SERMs or SERDs.

Detection of estrogen receptor

There have been several studies suggesting a strong correlation between ^{18}F-FES uptake and ER positivity as measured by immunohistochemistry (IHC). Compared with IHC, ^{18}F-FES PET was found to have a pooled sensitivity of 82% and specificity of 95% for ER positivity in a meta-analysis of 9 prospective studies.[19] A more recent meta-analysis evaluating the ability of FES to determine ER status of breast and non-breast lesions in patients with metastatic breast cancer found an overall sensitivity of 81% and specificity of 85%.[20] Fig. 1 demonstrates a left breast cancer visible on dynamic contrast-enhanced MRI, with no uptake on ^{18}F-FES PET, consistent with biopsy-proven ER-negative status. One study found that ^{18}F-FES had a positive predictive value of 100% and a negative predictive value of 78%, which changed depending on the threshold of the maximum standardized uptake value (SUV_{max}),[12] with the caveat that patients with bone metastases were excluded. In this study, the authors suggest that tumors that are ER + on IHC but negative on ^{18}F-FES PET might reflect the lack of ER functionality as opposed to a false-negative imaging test; more investigation into this hypothesis is needed.

Although IHC analysis remains the gold standard for determining the presence of ER, there are benefits of ^{18}F-FES over biopsy alone. One potential advantage to ^{18}F-FES is the ability to noninvasively assay the whole tumor, providing a more comprehensive assessment of functional ER status than IHC of a limited tumor sample. Evaluation of ^{18}F-FES uptake within a tumor could reflect intratumoral heterogeneity not elucidated from biopsy alone. Moreover, receptor status may not be uniform across all tumors in a given patient with metastatic disease. Yang and colleagues showed that 37.5% of patients with metastatic breast cancer presented with both ER+ and ER-disease, which may or may not be identified based on biopsy alone, depending on the number of sites biopsied. ^{18}F-FES, however, can help identify metastatic lesions based on the uptake of the tracer in a single test, which has the potential to guide treatment, improve response to therapy, and perhaps even prolong survival.[9] Additionally, whole-body ^{18}F-FES PET can be used to evaluate multiple lesions in a noninvasive manner, including sites such as the brain that would be challenging to biopsy. In fact, imaging of brain metastases is of particular clinical interest because PET scanning using fluorodeoxyglucose (FDG-PET) can be limited due to the high FDG avidity of normal cerebral cortex and deep gray nuclei.[21] In one study by Ivanidze and colleagues[21], ^{18}F-FES brain PET/CT demonstrated increased avidity in a brain lesion suggesting metastatic disease, although also showing decreased avidity in a lesion that was thought to represent posttreatment change.

Systemic therapy selection

One of the proposed clinical applications for ^{18}F-FES is for therapy selection. Some of the initial studies assessing ^{18}F-FES and treatment response were in patients with advanced breast cancer treated with tamoxifen.[22-24] Mortimer and colleagues[23] postulated that ^{18}F-FES PET could be used to identify hormonally responsive cancers. In their pivotal 2011 study, the authors found that the functional status of ER can be determined using ^{18}F-FES PET and can predict response to tamoxifen. In another study of 51 patients with advanced ER + breast cancer, higher baseline ^{18}F-FES uptake was predictive of response to tamoxifen; additionally, a detectable “metabolic flare” on FDG-PET after estradiol challenge was observed in patients who were more responsive to tamoxifen.[25] Indeed, combining characteristics of tumors on both ^{18}F-FES and FDG-PET may allow for further patient stratification.[26]

In the metastatic setting, disease with low uptake of ^{18}F-FES has been associated with worse response to endocrine treatment, with a cohort study of 47 patients with pretreated metastatic breast cancer identifying a threshold SUV of less than 1.5 being predictive of lack of response.[24] Interestingly, van Kruchten and colleagues[27] found that although baseline ^{18}F-FES uptake was not associated with disease progression, the persistence of uptake on follow-up ^{18}F-FES PET after SERD initiation was associated with earlier progression, possibly indicating incomplete ER degradation.

^{18}F-FES has also been used to assess potential benefit of other therapeutic agents used in metastatic breast cancer, including cyclin-dependent kinase (CDK) inhibitors. Although adding CDK inhibitors to endocrine treatment has been shown to improve invasive disease-free survival in some patients with metastatic ER + breast cancer, better understanding of ER heterogeneity could potentially improve patient selection for treatment.[28] In a prospective analysis of 30 patients with metastatic ER + breast cancer, ER heterogeneity was determined by measuring what proportion of lesions visible on either FDG-PET or CT were avid on ^{18}F-FES PET.[29] Those with the highest proportion of ^{18}F-FES-positive disease at baseline had the longest time to progression on combination endocrine therapy with CDK4/6 inhibition. Additionally, those with better response to combination treatment, as measured by reduced lesion metabolic activity on FDG-PET, had higher ^{18}F-FES uptake. These findings suggest that combining ^{18}F-FES imaging with other imaging modalities can be used to differentiate among those with ER-positive disease and identify heterogeneous disease patterns that might benefit from differing treatment strategies.

A novel potential application of ^{18}F-FES imaging includes determining whether resistance to endocrine therapy has been overcome. In a recent study, histone deacetylase inhibition with vorinostat was used with the goal of restoring endocrine therapy sensitivity in 23 patients with metastatic ER + breast cancer.[30] Although subsequent ^{18}F-FES PET imaging did not show increased uptake compared with baseline to indicate restored ER ligand binding, higher baseline ^{18}F-FES uptake was again associated with improved progression free survival.[30] The authors note, however, that although ^{18}F-FES uptake indicates the ability of the ER to bind ligand, this is not necessarily indicative of endocrine therapy sensitivity, particularly given multiple pathways influencing such sensitivity, and challenges with the definition of sensitivity which may differ by disease site (eg, disease progression in visceral versus bone metastases). However, achieving complete blockade or suppression of ER as measured by lack of ^{18}F-FES uptake on known ER + lesions has been reported for purposes of finding optimal doses for ER-modulating agents.[31]

Resolving clinical dilemmas

^{18}F-FES PET may be useful in patients with ER + breast cancer who present with clinical dilemmas where conventional workup is inconclusive. For example, a Dutch study included patients with metastatic breast cancer whose staging imaging, including CT chest/abdomen/pelvis, abdominal ultrasound, and bone scan, yielded equivocal findings.[32] ^{18}F-FES PET was most sensitive for bone metastases and improved diagnostic understanding in 88% of patients, leading to a change in therapy in 48% of those patients. Similar results were presented by Sun and colleagues,[33] who found that ^{18}F-FES PET aided the diagnosis and changed treatment plans in approximately half of patients in their study. Fig. 2 demonstrates imaging findings from a patient with biopsy-proven ER + ILC of the left breast with imaging studies identifying an oropharyngeal lesion of unclear cause despite attempted biopsy; this case illustrates the potential additive role of ^{18}F-FES PET for clinical decision-making.

The Use of ^{18}F-Fluoroestradiol in Invasive Lobular Carcinoma of the Breast

Although ^{18}F-FES PET may have wide applicability in the diagnosis and management of breast cancer, there are certain subtypes of breast cancer that may benefit even more from this technology. One such subtype is ILC. ILC is the second most common type of breast cancer, accounting for 10% to 15% of all patients with breast cancer. Due to the infiltrative growth pattern of ILC compared with the more common invasive ductal carcinoma (IDC), it is often harder to detect with standard imaging modalities, including FDG-PET. Moreover, nearly 95% of all lobular cancers are ER positive. As such, ^{18}F-FES PET is promising for the evaluation of this breast cancer subtype.

One of the first studies to evaluate the use of ^{18}F-FES PET in ILC was a case series by Venema and colleagues in 2017.[34] The authors reported 3 lobular breast cancer cases, where confirmation of metastatic disease was imperative for subsequent treatment, and biopsy was not possible. In these 3 cases, standard imaging modalities such as CT, MRI, and FDG-PET returned equivocal results, whereas ^{18}F-FES PET provided definitive diagnosis of metastatic lesions. The authors concluded that ^{18}F-FES PET may have added value compared with conventional staging mechanisms.

Further studies have compared the use of ^{18}F-FES versus FDG-PET in the diagnosis of metastatic ILC. Ulaner and colleagues[35] evaluated results from 7 patients with ILC who underwent both ^{18}F-FES and FDG-PET imaging. The authors found that ^{18}F-FES detected more metastatic lesions in patients with ILC compared to FDG-PET, and no patients presented with only FDG-avid metastases. As such, ^{18}F-FES was considered to compare favorably to FDG for assessing metastases in ILC patients. Fig. 3 illustrates a case of de novo metastatic ER + ILC in which additional lesions were seen on ^{18}F-FES PET compared with FDG-PET.

Given the predilection of ILC for a diffuse growth pattern, further research is needed to assess the use of ^{18}F-FES PET in settings of poorly visualized disease, including peritoneal carcinomatosis, leptomeningeal disease, and pleural effusions.

Challenges in the Implementation of ^{18}F-FES Imaging Studies

One of the primary limitations of ^{18}F-FES PET is the evaluation of liver metastases. As described previously, there is a high level of normal physiologic uptake of ^{18}F-FES in the liver resulting from rapid metabolism of the agent. This issue led one research group to conclude that ^{18}F-FES PET should not be used to evaluate liver metastases.[34] However, a recent article by Boers and colleagues sought to evaluate whether ^{18}F-FES could be used to identify ER + liver metastases, confirmed by biopsy, comparing visual and quantitative measures, and evaluating the impact of modifying region of interest. Although quantitative analysis improved sensitivity of detection over visual analysis, specificity was reduced.[36] Currently, ^{18}F-FES PET may have limited clinical utility in the detection of liver metastases.

An additional concern about ^{18}F-FES PET is the cost when compared with biopsy alone, assuming that biopsy is feasible. There has been only one cost-effectiveness model that has been published to date about the use of ^{18}F-FES in metastatic breast cancer, which was based on hospitals within the Dutch health-care system.[37] Although more metastatic lesions were identified using ^{18}F-FES PET, the diagnostic costs to evaluate receptor status and treatment costs were higher compared with biopsy alone.

As with many PET radiotracers, ^{18}F-FES uptake quantitation can be influenced by body mass index, with higher body mass index being associated with increased uptake; this can be overcome by correcting quantitative measurements for lean body mass.[38] Additionally, many ER + lesions have a low tumor to background ratio; the low SUV_{max} threshold for positivity on ^{18}F-FES PET can pose a sensitivity challenge in FES PET image interpretation.

Dedicated Breast Positron Emission Tomography and ^{18}F-Fluoroestradiol

Although the literature contains many studies evaluating the use of ^{18}F-FES with whole-body PET imaging, dbPET is a promising new technology that may be a complementary tool. Imaging the breast only, dbPET provides higher resolution of breast lesions than whole-body PET, and it may be especially relevant for the evaluation of early stage disease and surgical planning.

Compared with whole-body PET, dbPET uses a lower dose of radiotracer (185 vs 370 MBq) and less radiation, potentially allowing more opportunities for serial imaging.[39] Moreover, the positioning of the patient prone rather than supine in dbPET prevents breast compression, thereby allowing full breast volume imaging akin to breast MRI. dbPET has demonstrated higher sensitivity in detecting subcentimeter lesions and may identify response to neoadjuvant chemotherapy earlier than MRI.[40] Importantly, however, this high sensitivity comes with the possibility of detecting benign lesions and higher false-positive rates.[41] Recently, there has been a push to standardize reporting and descriptors of uptake in dbPET given its increasing use.[41]

The literature evaluating the use of ^{18}F-FES in dbPET is extremely limited. One feasibility study by Jones and colleagues[40] outlined their initial experiences with dbPET using ^{18}F-FES in assessing ER + breast cancer in 6 patients, including 2 with ILC. The results suggest the potential of ^{18}F-FES PET imaging to provide early predictions of neoadjuvant treatment efficacy and thus aid in therapy selection. The authors also noted important limitations to the technology, including variations in ^{18}F-FES uptake in different ER-positive breast cancer subtypes and the exclusion of axillary lymph nodes.[40]

Future Directions

As of this writing, ^{18}F-FES PET is FDA-approved for imaging ER-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer. However, ^{18}F-FES

PET could be used as a beneficial adjunct to FDG-PET and other diagnostic imaging modalities to aid in initial staging.[42] In particular, ^{18}F-FES may be able to reduce false-positive FDG-PET results caused by inflammation or improve staging in difficult to detect tumors such as ILC, as described above.[42,43]

Currently, there is an open clinical trial evaluating the use of ^{18}F-FES for staging and detection of recurrent ER-positive breast cancer compared with standard of care with chest, abdominal, and pelvic CT and bone scan (NCT04883814).[44] Other ongoing trials evaluating the clinical utility of ^{18}F-FES include the ECOG-ACRIN EAI 142 trial (NCT02398773), a phase II study of patients with ER + metastatic breast cancer prospectively evaluating ^{18}F-FES PET as a predictor of clinical benefit and progression free survival to first-line endocrine therapy. Similarly, the ongoing ET-FES TRANSCAN trial (EUDRACT 2013–000–287–29) is testing tumoral heterogeneity on ^{18}F-FES PET as a predictor of endocrine therapy response.[45] The Imaging Patients for Cancer Drug Selection – Metastatic Breast Cancer study (NCT01957332) tests the clinical utility of ^{18}F-FES PET for reducing biopsies and improving treatment selection. Results from these results may solidify ^{18}F-FES's place in staging and detection of recurrent breast cancer, and treatment selection for metastatic disease.

With increased resolution compared with whole body PET, dbPET may prove useful in accurate assessment of breast tumor size, facilitating surgical planning, and potentially reducing the need for re-excisions. In addition, dbPET may be a useful adjunct to MRI for assessing response to neoadjuvant therapy.

SUMMARY

Recently FDA-approved, ^{18}F-FES is a well-studied radiopharmaceutical with the ability to provide molecular imaging of ER-positive breast cancer. In the setting of whole-body PET scanning, ^{18}F-FES uptake can confirm the presence of ER + metastases and provide insight into tumor heterogeneity. Uptake values may reflect sensitivity to therapy and guide treatment selection. In the setting of ILC, ^{18}F-FES may provide improved disease detection compared with standard FDG-PET. The novel dedicated breast PET technology may provide improved tumor resolution that can be used both for evaluating the response to neoadjuvant treatment and for providing more accurate staging for surgical planning.

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KEY POINTS

- ^{18}F-Fluoroestradiol (^{18}F-FES) is a radiopharmaceutical for molecular imaging of ER + breast cancers
- Baseline ^{18}F-FES uptake may be used to guide treatment strategies
- Molecular imaging may improve disease staging
- Dedicated breast positron emission tomography scanning with ^{18}F-FES may provide more accurate tumor assessments in early-stage disease, and noninvasive therapy response indicators
- Estrogen receptor (ER) modulators and degraders will block ^{18}F-FES binding, and should be held for a minimum of 6 to 8 weeks selective ER modulators or 28 weeks selective ER downregulators/degraders before imaging to avoid false negatives

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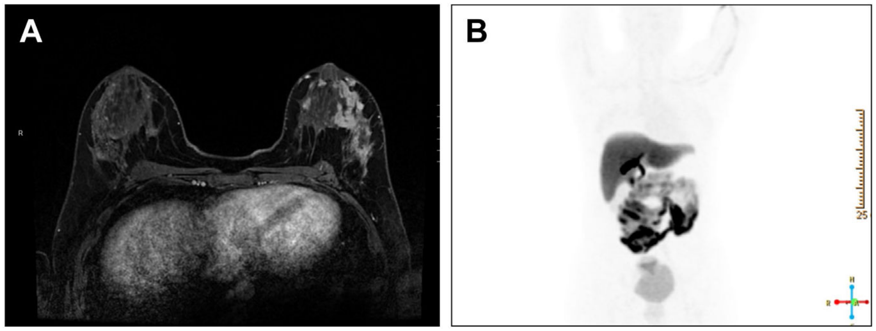

Fig. 1.

Patient with left breast multicentric left breast ER-negative, progesterone receptor-negative, HER 2-positive IDC. (*A*) shows dynamic contrast-enhanced MRI showing extensive mass and nonmass enhancement in outer left breast. In (*B*), ^{18}F-FES PET scan shows no uptake in left breast, consistent with ER negativity of known tumor, with expected uptake in liver and gastrointestinal tract.

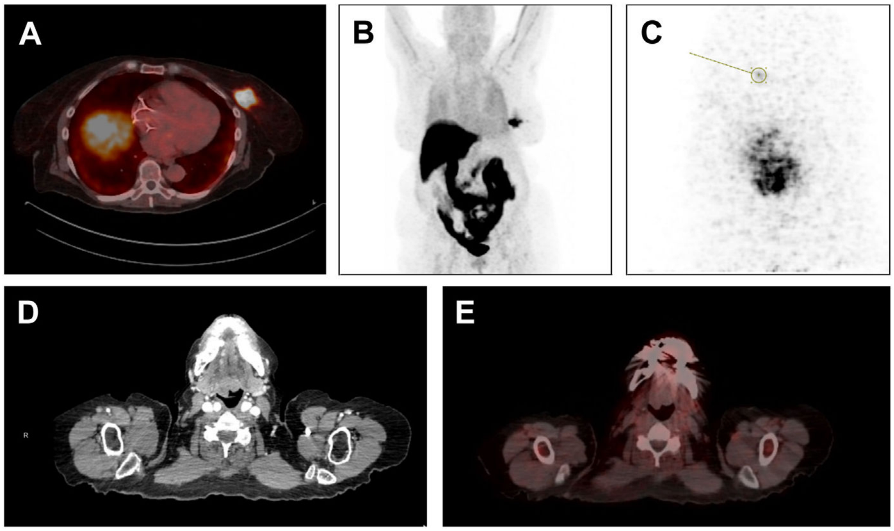

Fig. 2.

^{18}F-FES imaging in patient with left breast ER-positive HER2-negative ILC and oropharyngeal mass for which nondiagnostic biopsy had been performed. (*A*) Shows left breast mass with ^{18}F-FES uptake on fused PET-CT reflecting ER positivity. (*B*) Shows 18-F PET highlighting tumor in left breast, with expected uptake of ^{18}F-FES in liver and gastrointestinal tract. In (*C*), left breast is imaged with dedicated breast PET using 18-F FES, identifying a possible satellite lesion anterior to known tumor. Finally, (*D*) shows image from CT scan demonstrating irregular oropharyngeal mass, and fused image from 18-F FES PET-CT (*E*) shows no uptake in mass, suggesting that this mass was unrelated to primary ILC tumor.

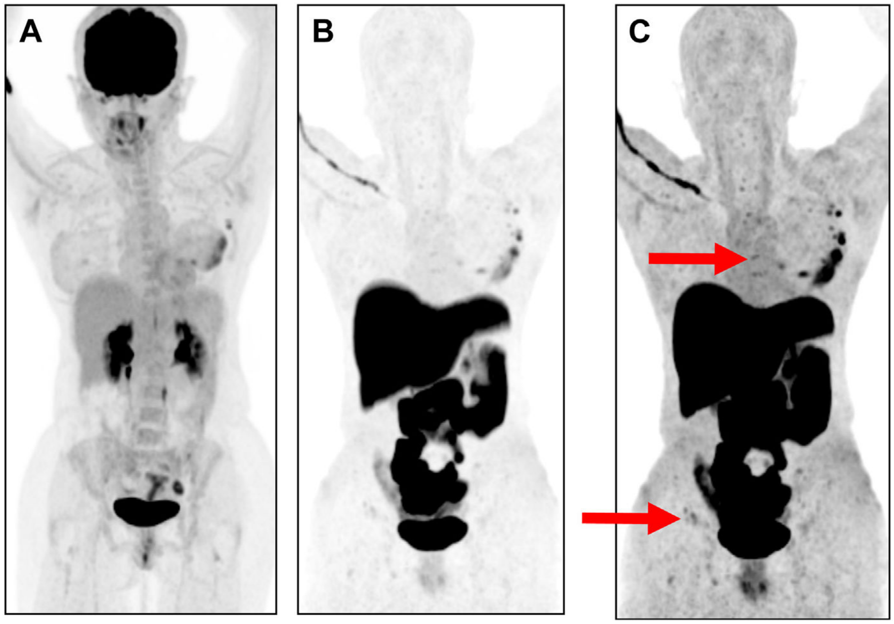

Fig. 3.

Patient with left breast palpable ER-positive HER2-negative ILC with de novo stage IV disease. Panel A shows FDG-PET with uptake at known left breast mass. (*B, C*) show 18-F FES PET demonstrating foci of low-level avidity on rewindowing images for higher sensitivity, consistent with bone metastases. Bone metastases in sternum and iliac crest denoted by red *arrows.*