

Utility of [18F]-fluoroestradiol (FES) PET/CT with dedicated brain acquisition in differentiating brain metastases from posttreatment change in estrogen receptor-positive breast cancer

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We present the application of dedicated brain positron emission tomography (PET)/computed tomography (CT) with 16α -[18F]-fluoro- 17β -estradiol (FES) in estrogen receptor (ER)-positive breast cancer. A 41-year-old woman with metastatic ER-positive breast cancer underwent resection of brain metastases with subsequent stereotactic radiosurgery (SRS) to bifrontal resection cavities, as well as SRS to a left cerebellar metastasis. Postoperative magnetic resonance imaging (MRI) demonstrated an enlarging, enhancing left cerebellar lesion, equivocal on fluorodeoxyglucose (FDG) PET/CT, and left frontal curvilinear enhancement which was photopenic on FDG PET/CT. Dedicated FES brain PET/CT demonstrated significantly increased avidity of the left cerebellar lesion, favoring viable ER-positive neoplasm. Lack of FES avidity in the non-FDG-avid left frontal lesion favored posttreatment change. FES brain PET findings thus helped guide management, supporting repeat SRS to the left cerebellar lesion.

Case Presentation

A 41-year-old woman presented with recurrent, metastatic, ER-positive invasive ductal carcinoma. The patient had initially presented 10 years prior with a palpable breast lesion. Pathology at the time of initial diagnosis was remarkable for a 7-cm invasive ductal carcinoma with lymphovascular invasion, as well as positive metastatic lymph nodes with evidence of extracapsular extension. Immunohistochemistry demonstrated the tumor to

be ER-positive (70%), progesterone receptor-negative, and HER2-positive.

Clinical Course

The patient was initially managed with mastectomy, adjuvant Adriamycin, and Cytoxan as she was pregnant at the time of her initial diagnosis. After giving birth, she was treated with Taxol and Herceptin, followed by Herceptin alone. Five years after initial diagnosis, the patient presented with low back pain, and [18F]fluorodeoxyglucose ([18F]FDG) PET/CT demonstrated widespread bone metastases and lymphadenopathy. The patient was treated with radiation therapy to multiple metastatic disease sites, including the chest wall, right hip, right leg, and multiple thoracic and lumbar vertebral bodies.

Systemic therapy was initiated with ado-trastuzumab emtansine (TDM1) and lupron. Three and a half years later she developed multifocal supra- and infratentorial brain metastases and underwent bilateral frontal craniotomy for resection of 3 frontal brain metastases. Pathology of the resected cerebral metastases was remarkable for more than 90% ER-positive staining, less than 1% progesterone receptor-positive staining, and 3+ HER2-positive staining. She subsequently was treated with fractionated SRS (27.5 Gray in 5 fractions) to the bilateral frontal resection cavities and to a left cerebellar lesion.

Contrast-enhanced MRI performed 18 months after craniotomies and SRS demonstrated increased curvilinear

enhancement deep to the left frontal resection cavity and new nodular enhancement at the site of the previously treated left cerebellar metastasis (Figure 1). [18F]FDG PET/CT was subsequently performed to help clarify the etiology of these new MRI findings.

The left frontal resection cavity as well as the area of curvilinear enhancement deep to the cavity demonstrated a lack of [18F]FDG avidity, favoring posttreatment change. The left cerebellar enlarging focus of nodular enhancement with surrounding edema demonstrated equivocal findings on [18F]FDG PET, with SUV of 10, however, without a definite increase in avidity relative to surrounding parenchyma (Figure 1). [18F]-FES PET/CT performed shortly thereafter demonstrated no significant FES avidity in the left frontal region of abnormal enhancement, supporting the diagnosis of posttreatment change suspected based on [18F]FDG PET appearance. However, the enlarging left cerebellar lesion demonstrated significant FES avidity, SUV 4.0, favoring viable ER-positive neoplasm (Figure 1).

The patient was subsequently managed with palliative repeat SRS (20 Gray in one fraction) to the enlarging left cerebellar lesion. Staging scans demonstrated stable extracranial disease and systemic therapy with TDM1 and lupron was continued. Follow-up MRI 2 months after repeat SRS demonstrated evidence of treatment response with a slight decrease in size of the left cerebellar lesion, and no evidence of new suspicious intracranial enhancement (Figure 1).

Discussion

$^{16}\alpha$ -[18F]-fluoro- $^{17}\beta$ -estradiol ([18F]FES) is a PET radiotracer that binds ER with high avidity. The specificity of FES PET/CT is greater than 90%,¹ while the sensitivity ranges from 70% to 90%.^{2,3} [18F]FES PET/CT has been utilized in various clinical scenarios, including as a problem-solving tool in patients with heterogeneous ER expression,⁴ to select patients suitable for neoadjuvant endocrine therapy and evaluate treatment response,^{5,6} to more accurately stage patients with ER-positive invasive lobular cancer which can be occult or underdiagnosed on FDG PET/CT, and extent of disease assessment and quantification of suspected metastatic disease burden.⁷ At present, there are limited data available regarding the detection of brain metastases using [18F]-FES PET/CT. [18F]FDG PET is commonly used to better characterize intracranial lesions on contrast-enhanced MRI in the postradiation setting, to differentiate enlarging viable neoplasm from radiation necrosis. An important limitation of [18F]FDG PET is the target-to-background ratio, given the high physiologic FDG avidity of normal cerebral cortex and deep gray nuclei. Furthermore, high FDG avidity is not specific to neoplastic cells and can be seen in the setting of inflammation or infection. In this patient, [18F]FDG PET/CT demonstrated photopenia of the bilateral resection cavities, as well as of the left frontal curvilinear enhancement, thus

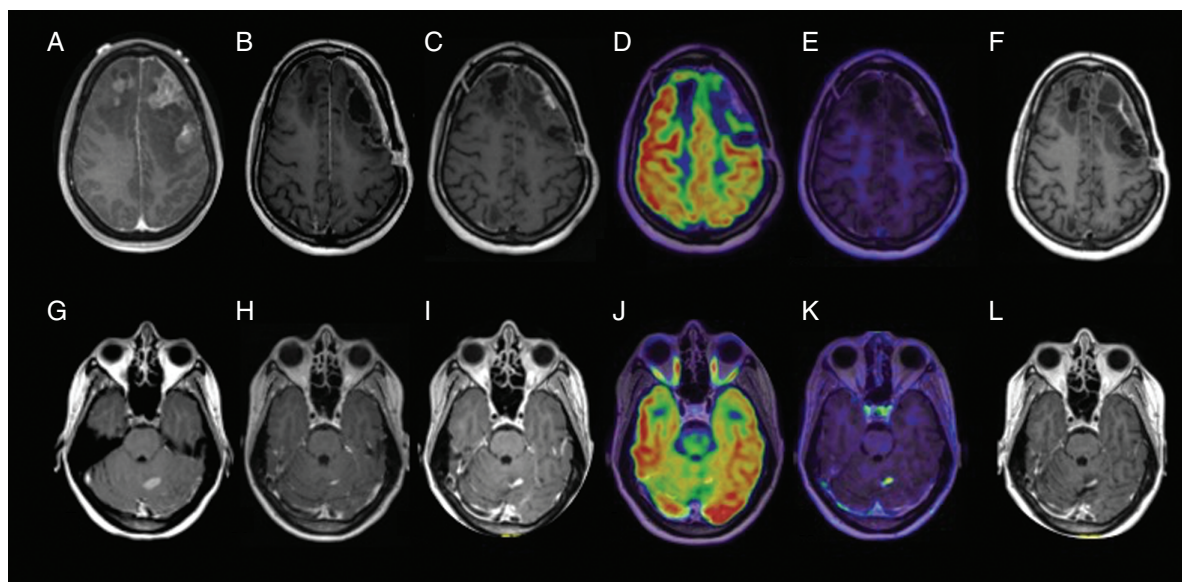


Figure 1. Preoperative axial postcontrast T1-weighted images (A and G); follow-up postcontrast T1-weighted images 6 months post-bilateral frontal craniotomies and 5 months post-SRS to the bilateral resection cavities and to the left cerebellar lesion (B and H). At 18 months postsurgery/SRS, there was slightly increased curvilinear enhancement deep to the left frontal resection cavity (C), and new nodular enhancement at the site of the previously treated left cerebellar metastasis (I). The left frontal resection cavity as well surrounding enhancement demonstrated a lack of [18F]FDG avidity, favoring posttreatment change (D). The left cerebellar enlarging focus of enhancement with surrounding edema demonstrated equivocal findings on FDG PET, with SUV of 10, however, without a definite increase in avidity relative to surrounding parenchyma (J). [18F]-FES PET/CT demonstrated no significant FES avidity in the left frontal enhancing lesion, supporting the diagnosis of posttreatment change (E). However, the enlarging left cerebellar lesion demonstrated significant FES avidity, SUV 4.0, favoring viable ER-positive neoplasm (K). Based on the combination of MRI, FDG PET, and FES PET findings, the decision was made to pursue palliative repeat SRS to the left cerebellar lesion. Follow-up MRI 2 months after repeat SRS demonstrated no new suspicious enhancement supratentorially (F) and a slight decrease in size of the left cerebellar lesion (L).

confirming the diagnosis of evolving posttreatment change suspected on MRI. The enlarging nodular enhancing left cerebellar lesion was suspicious for recurrent neoplasm on MRI and equivocal on [18F]FDG PET/CT due to high physiologic FDG avidity in the adjacent cerebellar cortex. Dedicated [18F]-FES PET/CT confirmed the suspected diagnosis, demonstrating a focus of increased avidity with a high target-to-background ratio due to lack of physiologic [18F]-FES avidity in normal brain parenchyma.

Dedicated [18F]-FES brain PET thus may present a promising approach in the workup of suspected brain metastases in ER-positive breast cancer.

While contrast-enhanced MRI has high sensitivity for the detection of parenchymal metastases, it can lack specificity, particularly in the postsurgical and postradiation settings.⁸ [18F]FDG PET has significant limitations given its lack of specificity and partial volume effects related to physiologically avid cerebral cortex. In this context, FES PET can help increase the specificity in patients with estrogen-positive disease⁹ and support management decisions,¹⁰ such as the decision to pursue SRS in this patient.

The added value of targeted PET/CT and PET/MR in brain metastases, as well as primary brain tumors, is an area of active research in recent years. Amino acid analog tracers such as [11C]-methyl-L-methionine (MET), 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (FDOPA), and *O*-(2-[18F]-fluoroethyl)-L-tyrosine (FET) represent a promising group of PET radiotracers in both primary and secondary brain neoplasms¹¹ due to their high target-to-background ratio resulting from overexpression of L-type amino acid transporters in neoplastic cells.¹² For brain metastases, FET PET with texture analysis has demonstrated utility in differentiating viable neoplasm from radiation injury.¹³

[18F]-FES PET/CT has several notable limitations. To be able to undergo FES PET/CT, patients have to be off-selective ER modulators for 8 weeks, and off-selective ER degraders for 28 weeks, which may make this imaging approach prohibitive for a subgroup of patients with ER-positive breast cancer. Furthermore, the lack of FES avidity in an enhancing lesion should be interpreted with caution, given that approximately 20%–30% of patients with ER-positive breast cancer eventually develop ER-negative disease.^{14,15} Because of this heterogeneity of ER expression in breast cancer metastases, FES PET should not be performed nor interpreted in isolation. In the patient presented here, who had pathology-proven high ER expression in her previously resected brain metastases, supratentorial findings of lack of FES avidity supported the diagnosis of posttreatment change in conjunction with MRI appearance and lack of [18F]FDG avidity.

In summary, dedicated FES brain PET/CT is a promising adjunct modality in the evaluation of patients with ER-positive metastatic breast cancer. The PET radiotracer FES has recently been FDA-approved and can be used in the clinical setting to facilitate treatment planning by increasing specificity and providing in vivo assessment of ER status of metastatic disease.¹⁶ Dedicated brain PET/CT and PET/MR imaging with FES can form the basis for future prospective clinical trials with the goal of optimizing radiosurgical treatment delivery to ER-positive metastatic breast cancer.

Keywords

brain metastases | breast cancer | estrogen receptor | PET/CT

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Data availability

All data generated and analyzed during this study are included in this published article.

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