Utility of $[18\text{F}]$-Fluoroestradiol (FES) PET/CT with dedicated brain acquisition in differentiating brain metastases from post treatment change in estrogen receptor-positive breast cancer.

Jana Ivanidze$^1$, Kritika Subramanian$^1$, Trisha Youn$^1$, Tessa Cigler$^2$, Joseph R. Osborne$^1$, Rajiv Magge$^3$, Onyinye Balogun$^4$, Jonathan Knisely$^4$, and Rohan Ramakrishna$^5$

$^1$Division of Molecular Imaging and Therapeutics, Department of Radiology, New York Presbyterian Hospital – Weill Cornell Campus, New York, NY

$^2$Department of Breast Oncology, New York Presbyterian Hospital – Weill Cornell Campus, New York, NY

$^3$Department of Neuro Oncology, New York Presbyterian Hospital – Weill Cornell Campus, New York, NY

$^4$Department of Radiation Oncology, New York Presbyterian Hospital – Weill Cornell Campus, New York, NY

$^5$Department of Neurosurgery, New York Presbyterian Hospital – Weill Cornell Campus, New York, NY

*Corresponding Author: Jana Ivanidze, MD/PhD, jai9018@med.cornell.edu
Corresponding author’s contact information

Jana Ivanidze, M.D., Ph.D.
jai9018@med.cornell.edu
Cell 347-514-1491
Office 212-746-6194
Fax 212-746-4590

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Introduction

We present the application of dedicated brain PET/CT with 16$\alpha$-[18F]-fluoro-17$\beta$-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 MRI demonstrated an enlarging, enhancing left cerebellar lesion, equivocal on 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 post-treatment 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 ten 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 estrogen receptor 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]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 >90% estrogen receptor positive staining, <1% progesterone receptor positive staining, and 3+ HER2 positive staining. She subsequently was treated with fractionated stereotactic radiosurgery (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 post 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]fluorodeoxyglucose ([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 lack of [18F]FDG avidity, favoring post treatment 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 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 estrogen receptor 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 two months after repeat SRS demonstrated evidence of treatment response with slight decrease in size of the left cerebellar lesion, and no evidence of new suspicious intracranial enhancement (Figure 1).

Discussion

16α-[18F]-fluoro-17β-estradiol ([18F]FES) is a positron emission tomography (PET) radiotracer which binds estrogen receptor (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 expression4, to select patients suitable for neoadjuvant endocrine therapy and evaluate treatment response5,6, 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 burden7. At present, there are limited data available regarding the detection of brain metastases using [18F]FES PET-CT. [18F]fluorodeoxyglucose ([18F]FDG) PET is commonly used to better characterize intracranial lesions on contrast-enhanced magnetic resonance imaging (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 confirming the diagnosis of evolving post treatment change suspected
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 adjacent cerebellar cortex. Dedicated [18F]FES PET/CT confirmed the suspected diagnosis, demonstrating a focus of increased avidity with 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 post-surgical and post-radiation setting. [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 disease, and support management decisions 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 neoplasms due to their high target-to-background ratio resulting from overexpression of L-type aminoacid transporters in neoplastic cells. For brain metastases, FET PET with texture analysis has demonstrated utility in differentiating viable neoplasm from radiation injury.

[18F]FES PET/CT has several notable limitations. To be able to undergo FES PET/CT, patients have to be off selective estrogen receptor modulators for 8 weeks, and off selective estrogen receptor 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 estrogen receptor-positive breast cancer eventually develop estrogen receptor-negative disease\textsuperscript{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 post-treatment change in conjunction with MRI appearance and lack of lack of [18F]FDG avidity.

In summary, dedicated FES brain PET/CT is a promising adjunct modality in the evaluation of patients with estrogen receptor-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 estrogen receptor status of metastatic disease\textsuperscript{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 estrogen receptor-positive metastatic breast cancer.
**Figures and Figure Legends:**

![Figures](image)

**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 post surgery/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 lack of [18F]-FDG avidity, favoring post treatment change (D). The left cerebellar enlarging focus of enhancement with surrounding edema demonstrated equivocal findings on FDG PET, with SUV of 10, however without 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 two months after repeat SRS demonstrated no new suspicious enhancement supratentorially (F) and slight decrease in size of the left cerebellar lesion (L).
References:


