Case report

^{18}F-FES PET CT Scan in Patients Of Histopathologically Proven Estrogen Positive Breast Carcinoma at aTertiary Care Facility

ABSTRACT

Aims: To ascertain successful labeling and image performance of ^{18}F-FES PET CT scan in patients who have histopathologically diagnosed estrogen positive breast carcinoma.

Study design: Histopathologically proven Estrogen Receptor positive (ER-pos) patients were enrolled for ^{18}F-FES PET CT scan.
Place and Duration of Study: Department of Nuclear Medicine, Department of Radiopharmacy and Department of Oncology, Institute of Nuclear Medicine and Oncology Lahore (Aug 2021)

Methodology: 18F-FES was produced by direct nucleophilic radio-fluorination of 3-O-methoxymethyl-16,17 O sulfuryl-16-epiestriol followed by acidic hydrolysis. Before injecting the patients all the quality control tests were done according to the US pharmacopeia.
Discovery STE PET-CT system (GE, healthcare, USA) with 16 slice CT scanner was used. After 60 minutes of injection, each patient was positioned supine. CT was acquired followed by PET acquisition from mid-thigh to vertex. Images were carried out for 2-3 minutes per bed position frame. The CT data for attenuation correction, and co-registered images were displayed on a workstation. Image interpretation and processing was performed.
Results: Study was performed on 2 patients. The first patient had ER-pos breast tumor on trucut biopsy and second the patient presented after excision biopsy. The second patient demonstrated skeletal, nodal and pulmonary metastases.^{18}F-FES uptake was observed in the primary tumor as well as in all metastatic sites.
Conclusion: ^{18}F-FES can successfully be labeled and ^{18}-FES-PET CT can be performed in ER-pos, Breast Cancer (BCa) patients to take appropriate treatment decisions.

Keywords:, FES PET CT, BCa, Estrogen receptors ,Endocrine therapies.

1. INTRODUCTION

BCa (BCa) is one of the most frequently diagnosed cancers and is the leading cause of cancer death in women. According to World Health Organization, 2.3 million women were diagnosed with BCa and 0.6 million BCa related deaths globally in 2020. Nearly 75% BCa expresses estrogen receptors (ER) at the time of initial diagnosis [1]. The hormone-binding receptor acts as a transcription factor and activates signaling pathways that induce proliferation and tumor growth. The estrogen and progesterone receptors are the most important hormone receptors involved in tumor progression in BCa [2]. Consequently, endocrine therapies are developed that aim to interfere with hormone receptor-mediated pathways by either reducing the level of the hormone or blocking of the hormone receptor. Despite the utility of endocrine therapy, nearly 20% of the cases show low treatment response rates, either due to ER discordance or inter-tumor

heterogeneity [3]. ER discordance, the difference between the receptor expressions of primary and metastatic or recurrent lesions, results in treatment failure. Tumor heterogeneity also contributes to low response to therapy because cancers that switch to low ER expression often have characteristics more similar to ER negative tumors. These types of tumors are unlikely to respond to hormone driven therapy. Moreover, preclinical and clinical evidences have suggested that ER-positive BCas are less responsive to chemotherapy than ER negative tumors, indicating that ER might interfere with factors determining the sensitivity to chemotherapy [4]. Knowledge of receptor status of metastatic or recurrent lesions hence becomes necessary prior to initiating the therapy to gain maximum benefit and cost effectiveness. Immuno-histochemistry (IHC), is still the gold standard for determining ER status in metastatic and recurrent (BCa) that requires tissue biopsies from the primary or a single metastatic tumor. Multiple metastases in metastatic (BCa) patients, occurring frequently in bones and lung pose a challenge in obtaining tissue by biopsy from these sites and it is not practically possible to biopsy all the sites. Additionally, IHC is not used consistently in metastatic bone cancer (MBC) patients, even if recommended by guidelines like those of the NCCN. As a result, treatment decisions are often based on incomplete and imperfect information.

Use of ^{18}F-FDG PET-CT in treatment naïve or recurrent BCa is limited to situations where standard staging studies are equivocal or suspicious [5,6].

The histological and biological characteristics of BCa have an important impact on tumor visualization with ^{18}F-FDG PET/CT. ^{18}F-FDG uptake correlates with histologic grade and tumor proliferation index, and ^{18}F-FDG uptake is higher in ER-negative tumors. Accordingly, the relatively lower ^{18}F-FDG uptake in ER-pos BCa may affect the diagnostic accuracy. To date, the accuracy of ^{18}F-FDG PET/CT for the diagnosis of recurrent BCa has not been separately reported in patients with ER-pos primary BCa [7]. In conclusion FDG PET CT does not give complete information regarding receptor status. To overcome this problem many radio-labeled steroids have been evaluated as PET tracers for imaging of the hormone receptors since 1980's, but most of these tracers failed in preclinical or early-clinical evaluation. So far, only 16 α- 17 β estradiol ^{18}F-FES seems to be an interesting PET tracer for estrogen receptor (ER) imaging in BCa patients.

BCa incidence in Pakistan is reportedly high and a large number of patients present annually at our hospital (approximately 1500/year). Stage II or III BCa and hormone receptor positive BCa are more frequent. Unfortunately, some patients develop metastasis despite treatment and few patients present with recurrence after a certain time period after the end of their treatment. Because majority of the patients at our facility belong to poor socioeconomic status therefore cost-effective treatment is much desired. For staging and restaging workup of BCa patients, in-house facility of Cyclotron and PET CT scanner besides 64 slice CT, 6 Tesla MRI, SPECT-CT scanner and Applio USG machine are available at the hospital. Foreseeing the potential benefits of ^{18}F –FES PET CT to our patients we planned to devise ^{18}F –FES PET CT scanning at our center. It is not being done in any of the public or private sector hospital in our country.

2. PRESENTATION OF CASES:

A 67 years old female patient, known case of biopsy proven carcinoma breast (IDC grade III, ER-pos, PR negative) presented on the day of scan. Her workup showed a speculated tumor in the lower inner quadrant of her left breast measuring 1.8cm. Both of her axillae and right breast were unremarkable on mammography. Another patient was a 70 years old lady with biopsy proven breast carcinoma (IDC grade III, ER-pos, PR negative) who presented after excision biopsy with known skeletal and nodal metastasis.

2.1 Planning the Procedure:

A meeting of Nuclear Medicine Consultants, technologists, heads of Nuclear Medicine and Radiopharmacy departments was held to decide upon the injection technique, imaging and acquisition protocols.

2.2 ^{18}F FES Kit preparation:

Fluorine-18 is one of the isotopes that are routinely being used in radio-labeling of bio-molecules for PET; because of its positron emitting property and favorable half-life of 109.8 min. 18F-FES was produced by direct nucleophilic radio fluorination of 3-*O*-methoxymethyl-16,17 O sulfuryl-16-epiestriol (MMSE) followed by acidic hydrolysis. Practical radiochemical yields were high (several GBq) consequently, doses for multiple patients were obtained from a single preparation. Before injecting the patients all the quality control tests were done according to the US pharmacopeia and results were in the accepted range.

2.3 Staffing:

As F18-FDG PET-CT is already being done so we did not require hiring / training of staff for this study.

2.4 Patient Preparation and Injection:

History and physical examination of both patients was done by Nuclear Medicine Consultant**.** Vital signs were recorded by Staff Nurse. I/V cannulation were done. The patients were asked to drink plenty of water to ensure adequate hydration prior to administration of 18F-FES and to void frequently during the first hours following administration to reduce radiation exposure. Recommended activity mentioned in clinical trials is 222 MBq (6 mCi), with a range of 111 MBq to 222 MBq (3 mCi to 6 mCi). 18F-FES was diluted with 0.9% Sodium Chloride Injection, USP and given as a single IV injection of 10 ml over 1 to 2 minutes.

Aseptic technique and radiation shielding was done during withdrawing and administering 18F-FES.

2.5 Image Acquisition Protocol:

^{18}F-FES was injected intravenously into the patients. The patients were asked to wait for a period of 60 min. Discovery STE PET-CT system (GE, healthcare, USA) with 16 slice CT scanner was used.

2.6 Patient Positioning and Procedure:

The patients were asked to empty their urinary bladder before the scan and to remove any metallic objects and jewelry and they were instructed to wear hospital gown.

After 60 minutes of injection, the patients were positioned supine with their arms above their heads. First low dose CT was acquired followed by PET acquisition from mid-thigh to vertex. Images were carried out for 2-3 minutes per bed position frame. The CT data for attenuation correction, and co-registered images were displayed on a workstation.

2.7 Image Interpretation and reporting:

Image interpretation and processing was performed by a team of three nuclear medicine doctors, with expertise in PET-CT image reading.

3. RESULTS AND DISCUSSION

With regard to the first patient a tumor was identified in the left lower inner quadrant with ^{18}F-FES uptake (SUV_{max} 1.4) as expected [Fig 1]. The rest of the imaged scan was unremarkable, therefore surgery was done followed by chemotherapy and hormonal therapy. With regard to the second patient who presented after excision of her primary tumor there were post surgical changes in the surgical bed while all already known metastatic (skeletal, nodal, and pulmonary) lesions showed increased tracer uptake e.g SUV_{max} values 2.2 [Fig 2 and 3], therefore hormonal therapy was started.

For therapy management, it is important to realize that the ER status of the primary tumor is not always predictive for the ER status of the metastasis. Two ^{18}F-FES PET studies showed that lesions with discordant ER status are present in 15–24% of the patients with multiple metastatic foci. Obviously, the discordant ER status could affect therapy outcome and therefore should be taken into account by the leading physician [2]. With regard to our patient who had known metastatic disease it was found that all known metastatic lesions were positive on ^{18}F-FES PET therefore the patient would likely respond to hormone driven therapy. In the clinic, ^{18}F-FES PET might also be useful in distinguishing an ER-pos tumor from a non-tumor related problem in patients with metastatic disease. Cancer patients often experience complaints caused by degenerative processes and treatment-induced complications, like edema, necrosis and fibrosis. Often, a major problem for clinicians is how to discriminate whether the problem is caused by tumor activity or not, especially for bone lesions. MRI and the bone scan are often inconclusive and the sensitivity of ^{18}F FDG PET for the detection of bone metastases is rather low (lesion-based sensitivity: 69%). In addition, ^{18}F FDG PET can give false positive results when an inflammatory response is involved or when recent treatment like radiotherapy was given. ^{18}F FES PET, on the other hand, could provide the required information and thus guide the patient's treatment [2].

[PLEASE REFER TO FIGURES 1, 2 and 3 IN THE TEXT TO ILLUSTRATE THE POSITION OF THE FIGURES IN RELATION TO WHAT YOU ARE SAYING IN YOUR ARTICLE]

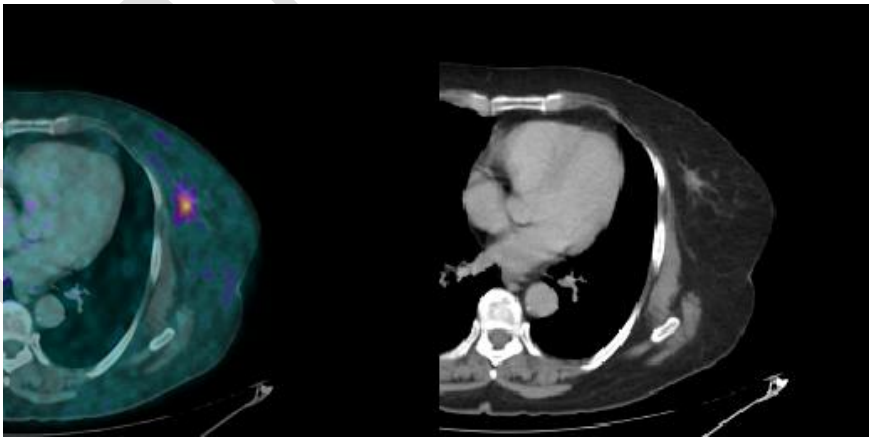

Figure 1: 18-F FES uptake in primary breast tumor

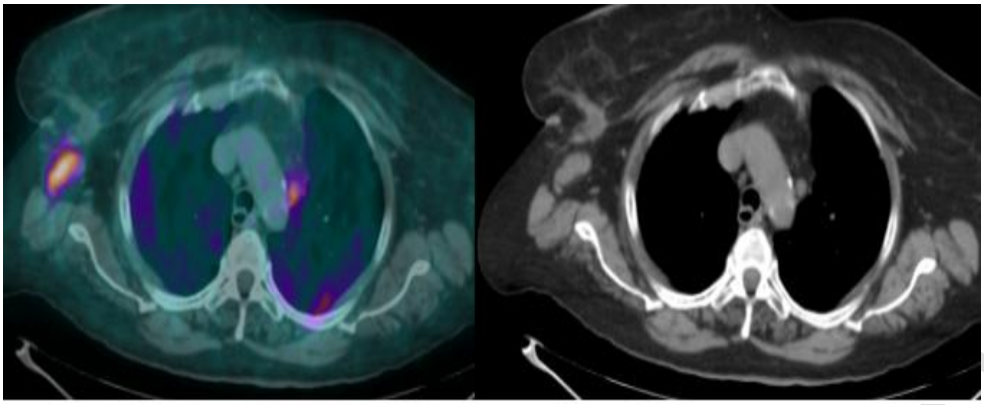

Figure 2: FES uptake in right axillary node and mediastinal node

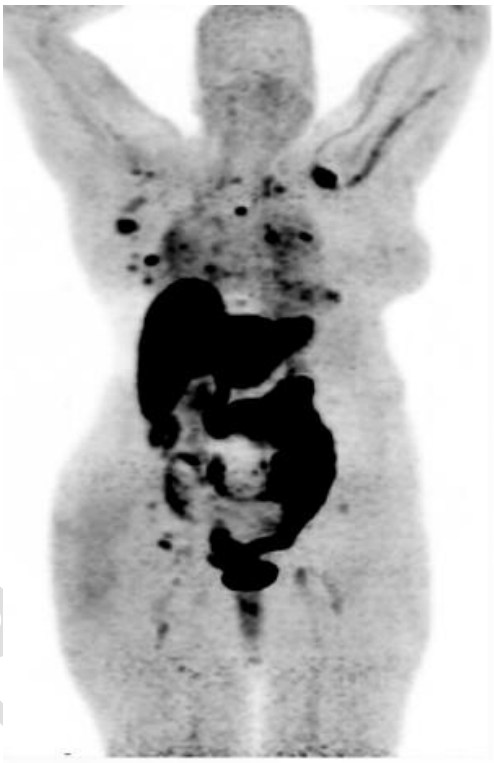

Figure 3: MIP image showing 18 F-FES uptake in metastatic sites and physiologic uptake in liver, gut and bladder

4. CONCLUSION

^{18}F-FES can successfully be labeled and ^{18}-FES-PET CT can be performed in ER-pos BCa patients to take appropriate treatment decisions.

CONSENT (WHERE EVER APPLICABLE)

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal."

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

For manuscripts involving human experiments, Authors may use the following wordings for this section: "All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

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