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^{18}F-FES PET-CT Scan in Patients of Histopathologically Proven Estrogen Receptor Positive Breast Carcinoma at a Tertiary Care Facility

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Authors' contributions

This work was carried out in collaboration among all authors. Author SA designed the study, performed the statistical analysis, wrote the protocol and author MNY and author TY did the literature survey, prepared the manuscript, supervised and interpreted the scans. Author IUK performed the preparation and quality control testing of FES and author AF designed the study acquisition protocol and author MM did the patient selection and helped in discussion writing. Author AS helped in obtaining ethical approval, analysis of results and literature searches. All authors read and approved the final manuscript.

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Case Report

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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 cancer.
Study Design: Histopathologically proven estrogen receptor positive 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- INMOL. Duration of the study including planning phase and performance of imaging was 6 weeks spanning between July till Aug 2021.
Methodology: ^{18}F-FES was produced by direct nucleophilic radio-fluorination of 3-O-

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methoxymethyl-16,17 O sulfuryl-16-epiestriol followed by acidic hydrolysis at INMOL. After quality control tests, 18F-FES was injected to the patients. At 60 minutes post injection, each patient underwent PET-CT imaging in supine position as per standard protocol given in the published literature. Image interpretation and processing was performed.

Results: Study was performed on 2 patients. The first patient had estrogen receptor positive breast tumour on trucut biopsy and the second patient presented after excision biopsy. The second patient demonstrated skeletal, nodal and pulmonary metastases. ^{18}F-FES uptake was observed in the primary tumour as well as in all metastatic sites.

Conclusion: ^{18}F-FES can successfully be labeled and ^{18}-FES PET-CT can be performed in estrogen receptor positive breast cancer patients to take appropriate treatment decisions.

Keywords: FES PET-CT; Breast Carcinoma; Estrogen receptors; Endocrine therapies.

1. INTRODUCTION

Breast Cancer (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 tumour growth.

The estrogen and progesterone receptors are the most important hormone receptors involved in tumour 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-tumour heterogeneity [3]. ER discordance, the difference between the receptor expressions of primary and metastatic or recurrent lesions, results in treatment failure. Tumour heterogeneity also contributes to low response to therapy because cancers that switch to low ER expression often have characteristics more similar to ER negative (ER-neg) tumours. These types of tumours are unlikely to respond to hormone driven therapy. Moreover, preclinical and clinical evidences have suggested that ER-positive (ER- pos) BCa are less responsive to chemotherapy than ER-neg tumours, indicating that ER might interfere with factors determining the sensitivity to chemotherapy [4]. Knowledge of the 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 tumour. 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 BCa patients, even if recommended by guidelines such as NCCN. As a result, treatment decisions are often based on incomplete and imperfect information.

Use of Fluorine-18 labeled Fluoro-deoxy-glucose positron emission tomography- computed tomography (^{18}FDG PET-CT) in treatment naïve or recurrent BCa is limited to the situations where standard staging studies are equivocal or suspicious [5,6].

The histological and biological characteristics of BCa have an important impact on tumour visualization with ^{18}F-FDG PET-CT scan. ^{18}F-FDG uptake correlates with histologic grade and tumour proliferation index, and ^{18}F-FDG uptake is higher in ER-negative tumours. 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 radiopharmaceutical is Fluorine-18 labeled 16 α-17 β estradiol (^{18}F-FES) that seems to be an interesting and promising PET tracer for 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) presented on the day of scan. Her workup showed a spiculated tumour 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, pulmonary and nodal metastasis.

2.1 Planning the Procedure

A consensus document was prepared in a meeting of nuclear medicine physicians, technologists, heads of Nuclear Medicine and Radiopharmacy departments to finalize protocols of the study including 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-CT imaging; because of its positron emitting property and favorable half-life of 109.8 min. ^{18}F-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 ^{18}F -FDG PET-CT is already being done at our center, hence hiring and general training of staff for this study was not required.

2.4 Patient Preparation and Injection

Clinical history and physical examination of both patients was done by Nuclear Medicine physician followed by intravenous cannulation of arm veins. The patients were asked to drink plenty of water to ensure adequate hydration prior to administration of ^{18}F-FES and were encouraged to void frequently during the first hours following administration to reduce radiation exposure. Each patient received a dose of 200 MBq of radiopharmaceutical intravenously. ^{18}F-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 techniques and radiation shielding were followed during withdrawing and administering ^{18}F-FES.

2.5 Image Acquisition Protocol:

The patients were asked to wait for a period of 60 min post injection. During the interval patient maintained adequate hydration and continued to void. 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 tumour was identified in the left lower inner quadrant with ^{18}F-FES uptake demonstrating standardized uptake value (SUV) of 2.4 as expected (see 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 tumour there were post-surgical changes in the surgical bed (see Fig. 2) while all already known metastatic sites including skeletal, nodal, and pulmonary regions showed increased tracer uptake e.g SUV 3.2 (see Figs. 2 and 3), therefore hormonal therapy was started.

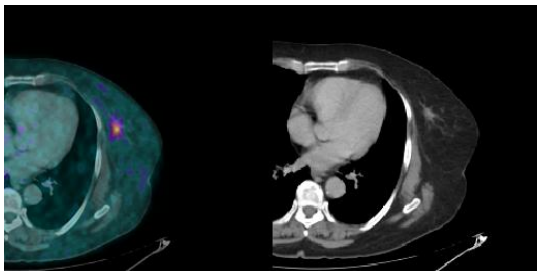

Fig. 1. ^{18}F-FES uptake in primary breast tumour

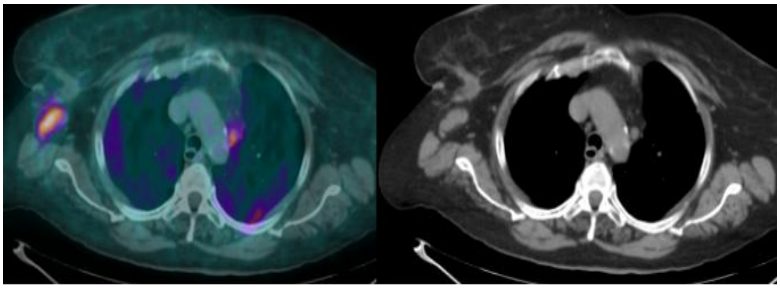

Fig. 2. ^{18}F-FES uptake in right axillary node and mediastinal node

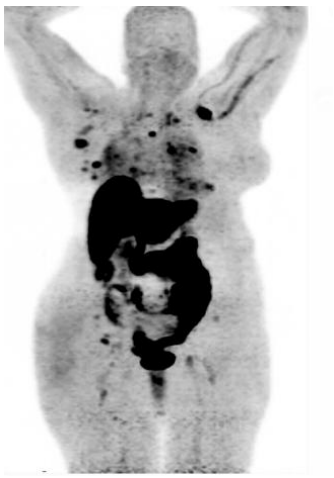

Fig. 3. MIP image showing ^{18}F-FES uptake in metastatic sites and physiologic uptake in liver, gut and bladder

For therapy management, it is important to realize that the ER status of the primary tumour is not always predictive for the ER status of the metastasis. As high as 18%–55% of the patients present with discordant ER expression between primary tumour and metastasis [8,9]. Obviously, the discordant ER status could affect therapy outcome and therefore should be taken into account by the leading physician.

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-CT therefore the patient would likely respond to hormone driven therapy. In the clinic, ^{18}F-FES PET-CT might also be useful in distinguishing an ER-pos tumour from a non-tumour related problem in patients with metastatic disease. Cancer patients often experience symptoms 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 tumour activity or not, especially for bone lesions. MRI and the bone scan are often inconclusive and the sensitivity of ^{18}F FDG PET-CT for the detection of bone metastases is rather low (lesion-based sensitivity: 69%). In addition, ^{18}F-FDG PET-CT can give false positive results when an inflammatory response is involved or when recent treatment like radiotherapy was given. ^{18}F-FES PET-CT, on the other hand, could provide the required information and thus guide the patient's treatment [2]. Further recent studies have shown the detection rate and degree of tracer uptake in ^{18}F-FES PET-CT imaging is not related to tumour sub-type, contrary to ^{18}F-FDG PET-CT imaging where the tracer uptake may be absent or very low in primary and metastatic tumour sites of invasive lobular type BCa [10]. In a recently published meta-analysis authors have analysed various studies that included more than 300 non-breast metastatic sites and were able to identify potential applications of ^{18}F-FES PET-CT in clinical practice [11]. Our limited data demonstrates that ^{18}F-FES PET-CT imaging can be performed successfully in a PET-CT and cyclotron facility using standard radio-pharmacy techniques for labeling and production of ^{18}F-FES followed by PET-CT imaging in appropriately selected patients. The technique may be considered in patients with ER-pos BCa for metastatic work-up, inconclusive ER status, identifications of unknown primary with ER-pos histology and solving clinical dilemma [12], particularly in the regions with high incidence of BCa.

4. CONCLUSION

^{18}F-FES can successfully be labeled using in-house radio-pharmacy facility and ^{18}-FES PET-CT imaging can be performed in appropriately selected BCa patients to identify primary as well as metastatic sites. Our limited data favors a regular use of this imaging technique for appropriate treatment decisions in patients of BCa. At the same time, successful accomplishment of the ^{18}F-FES PET-CT imaging may encourage other PET-CT centers of the country to establish this imaging service.

CONSENT

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

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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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