18F FES PET/CT in Oncology

AWJM Glaudemans, University Medical Centre Groningen
EFJ de Vries, University Medical Centre Groningen

1. Introduction

Around 70% of all patients with breast cancer have oestrogen receptor-positive tumours. These receptors are a target for endocrine therapy, which is an attractive treatment option in adjuvant and metastatic settings. The success rate of breast cancer treatment is heavily reliant upon the oestrogen receptor status, which is currently assessed by immunohistochemistry. This is well suited to test primary breast tumours, but accuracy is lower in metastases. Oestrogen receptor expression can change over time, and discordant expression between primary tumours and metastases is seen in up to 40% of patients. Biopsies are generally recommend for reassessment of oestrogen receptor status prior to the start of each new line of endocrine treatment. This is not always feasible. Moreover, heterogeneous oestrogen receptor expression within the tumour and between tumours can lead to sampling errors.

The most potent endogenous oestrogen receptor agonist is oestradiol. The development of PET tracers that target oestrogen receptors has focused on radio labelling of oestradiol and structural analogues. Around 20 ^{18}F-labelled oestrogen analogues have been described. Of these, ^{18}F-FES is the most extensively characterised and is most frequently used in clinical studies.

^{18}F-FES has a high binding affinity to oestrogen receptors (60-100% relative to oestrogen). Affinity to oestrogen receptor α is 6,3 times higher than that for oestrogen receptor β, but greater specificity has been shown in vivo in knockout mouse studies. In animal studies various oestrogen receptor tracers, including ^{18}F-FES, showed specific uptake in the uterus and ovaries. This was blocked by the addition of unlabelled oestradiol.

2. Methodology

This guideline is based on available scientific literature on the subject, international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

Breast cancer:

a. Diagnosis when conventional imaging techniques do not suffice and/or when biopsy is not possible
b. Prediction of treatment response
c. To provide a rationale for antihormonal therapy
d. Assessment of heterogeneous oestrogen receptor expression
e. To determine the oestrogen receptor binding (receptor saturation) during endocrine therapy, which can be used to adjust the drug dose to the individual patient.

Ovarian cancer:

a. Diagnosis when conventional imaging techniques do not suffice and/or when biopsy is not possible

b. To provide a rationale for antihormonal therapy

Diagnostic dilemma in all other oncological diseases with a high probability of oestrogen receptor expression, e.g.:
a. Leiomyoma of the uterus
b. Endometrial carcinoma or endometrial stromal sarcoma
c. Gastric cancer
d. Prostate cancer
e. Other

4. Relation to other diagnostic procedures
When applicable, ^{18}F-FES PET should be used in conjunction with other nuclear medicine techniques, such as ^{18}F-FDG PET and bone scintigraphy, or other radiological techniques, such as ultrasound, CT and MRI.

5. Medical information necessary for planning
a. Oestrogen receptor status of the primary tumour
b. Oestrogen receptor status of metastases (if available)
c. Results of other imaging techniques
d. Past and current treatments
e. Use of antihormonal drugs (see patient preparation)
f. Reason for performing the scan (diagnostic dilemma, current receptor status, therapy rationale)
g. Date and location of radiotherapy
h. Date and type of surgical interventions

6. Radiopharmaceutical

Tracer:	16α-^{18}F-fluoro-17β-oestradiol (^{18}F-FES)
Nuclide:	fluorine-18
Activity:	200 MBq (minimal dose 100 MBq)
Mass:	≤ 5 µg
Administration:	intravenous

7. Radiation safety
The radiation burden for patients is 0,023 mSv/MBq, resulting in 4,6 mSv per 200 MBq ^{18}F-FES injection (comparable to the radiation burden of ^{18}F-FDG). The organs exposed to the highest radiation doses are the liver (0,13 mGy/MBq), gallbladder (0,10 mGy/MBq), and urinary bladder (0,05 mGy/MBq). According to ICRP 106 there is no need to interrupt breastfeeding.

8. Patient preparation/essentials for procedure
a. Discontinue oestrogen receptor antagonists (fulvestrant, tamoxifen, faslodex, oestrogens) for at least 5 weeks. Aromatase-inhibitors may be used.
b. No other preparations are required. (When ^{18}F-FES-PET is accompanied by a diagnostic CT scan, the usual guidelines apply with regards to i.v. contrast).

9. Acquisition and processing

The level of binding of [18]F-FES to the oestrogen receptors remains stable between 20 and 120 min post injection. For logistical reasons, we have chosen to start the scanning procedure 60 min after injection.

For scan acquisition and processing, the same protocol is followed as for [18]F-FDG. The EARL reconstruction technique is used for SUV calculation.

Scanning time per bed position depends on the patient's weight (see table 1, based on mCT Biograph Siemens camera).

	Body weight		
Activity		**>150 MBq**	**<150 MBq**
	0-60 kg	1 min	2 min
	60-90 kg	2 min	4 min
	>90 kg	3 min	6 min

10. Interpretation

a. All radiolabelled oestrogens are rapidly metabolised in the liver and excreted via the gastrointestinal tract. The radiolabelled metabolites, glucuronides and sulphates, are reabsorbed into the circulation and excreted via the gallbladder and the bile ducs into the intestinal tract kidneys.

b. First use low intensity levels for the evaluation of the liver uptake: homogeneous, cold oestrogen receptor negative lesions or "hot" (uptake > physiological liver uptake) oestrogen receptor positive lesions. Then increase the intensity level to evaluaten all other tissues.

c. Based on both preclinical and clinical studies, a SUV > 1,5 is considered positive for increased oestrogen receptor expression.

d. In premenopausal women, oestrogen receptor-specific uptake can be seen in the uterus (with SUVs of roughly 2,5 in the myometrium and 4-6 in the endometrium, endometrial SUVs higher in the proliferative phase of the menstrual cycle than in the secretory phase), ovaries and breast tissue.

[18]F-FES is lipophilic. Patients with increased fat mass may have lower tumour [18]F-FES uptake than leaner patients, because of an increased pharmacological distribution volume.

f. Despite the rapid hepatic uptake and metabolism of [18]F-FES, liver function is unlikely to affect quantitative measurements of oestrogen receptor expression.

g. Since oestrogen receptor antagonists clearly affect tracer uptake, most studies require a drug-free period of 5-8 weeks before baseline quantitative measurements are taken. It is unknown whether this is sufficient time to completely eliminate competitive binding, particularly for fulvestrant, which has a half-life of 40 days and both blocks and degrades oestrogen receptors. A longer drug-free period might be needed.

h. Uptake in the injected blood vessel may be expected in a majority of patients, despite extensive flushing or longer administration time. This is probably due to the tracer sticking to the vessel wall/endothelial cells. However, the amount is negligible.

i. In a few patients, aspecific uptake can be seen in the irradiated part of the lungs after radiotherapy. It remains unclear whether the increased tracer accumulation is due to

enhanced extravasation due to radiation damage, or to tracer binding to infiltrating immune cells that also express oestrogen receptors.

11. Report

a. Describe areas of physiological uptake/metabolism/excretion.
b. Describe areas of increased (SUV > 1,5) ^{18}F-FES uptake (increased oestrogen receptor expression).
c. If there are findings on other conventional imaging techniques (CT, MRI), describe the ^{18}F-FES uptake (oestrogen receptor-positive or negative) at that site.
d. If the scan is performed because of a diagnostic dilemma, describe whether or not there is ^{18}F-FES uptake in the equivocal lesion(s), thereby reporting the oestrogen receptor expression of the lesion(s).
e. If the scan is performed to find out about heterogeneity within all known metastases, describe which metastases show increased oestrogen receptor expression and which do not.
f. If the scan was performed for therapy rationale, describe the overall oestrogen receptor status of the metastases.
g. If the patient has recently received radiotherapy, describe aspecific radiation-induced increase of tracer uptake.

12. Literature

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