



## 16 $\alpha$ -[<sup>18</sup>F]Fluoro-17 $\beta$ -estradiol [<sup>18</sup>F]FES

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<b>Chemical name:</b>	16 $\alpha$ -[ <sup>18</sup> F]Fluoro-17 $\beta$ -estradiol	
<b>Abbreviated name:</b>	[ <sup>18</sup> F]FES	
<b>Synonym:</b>	16-Fluoroestradiol, fluoroestradiol	
<b>Agent category:</b>	Compound	
<b>Target:</b>	Estrogen receptor	
<b>Target category:</b>	Receptor	
<b>Method of detection:</b>	PET	
<b>Source of signal:</b>	<sup>18</sup> F	
<b>Activation:</b>	No	
<b>Studies:</b>	<ul style="list-style-type: none"> <li><i>In vitro</i></li> <li>Rodents</li> <li>Humans</li> </ul>	

## Background

[PubMed]

Estrogens and progestins are endogenous hormones that produce many physiological effects. Estrogens act primarily by regulating gene expression. Estrogen receptors are found in the cell nucleus of the female reproductive tract, breast, pituitary, hypothalamus, bone, liver, and other tissues, and also in various tissues in men. Estrogens are lipophilic that they enter the cell passively by diffusion through the cellular membrane. They bind to estrogen receptors that are present in the nucleus.

Breast cancer is the most common malignancy in women. About 33% of women who have this disease will die of disseminated breast cancer. The growth of breast epithelial cells is dependent on estrogen stimulation to induce

progesterin receptor expression. Two-thirds of breast carcinomas express ERs. It has also been established that the ER status of the tumor is an important prognostic indicator in breast cancer (1). Women with ER-positive breast tumors have a better prognosis than women with ER-negative tumors in terms of responsiveness to anti-estrogen treatment. ER content in breast cancer was assessed by receptor binding assays, which suffer from inter-assay variability and are also limited by intrinsic receptor heterogeneity of the tumor.  $16\alpha$ - $[^{18}\text{F}]$ Fluoro- $17\beta$ -estradiol ( $[^{18}\text{F}]$ FES) was proven to be a valuable tracer for the studies of the ER status of primary and metastatic breast cancer (2).

## Synthesis

[PubMed]

$[^{18}\text{F}]$ FES was first synthesized by nucleophilic displacement of the aliphatic triflate of 3,16 $\beta$ -bis(trifluoromethanesulfonyloxy)estrone using tetrabutylammonium  $[^{18}\text{F}]$ fluoride, followed by hydrolysis and ketone reduction. High-performance liquid chromatography (HPLC) purification provided a 30% radiochemical yield of  $[^{18}\text{F}]$ FES in about 90 min (3). On the basis of this method, an automated robotic synthesis was developed to give an overall yield of 6% in 80 min (4). A one-pot synthesis of  $[^{18}\text{F}]$ FES was synthesized by nucleophilic fluorination of 3-methoxymethyl-16 $\beta$ ,17 $\beta$ -epiestriol-*O*-cyclic sulfone.  $[^{18}\text{F}]$ FES was isolated to provide radiochemical yields of 30-45% with a specific activity of about 37 GBq/ $\mu\text{mol}$  (1 Ci/ $\mu\text{mol}$ ) in 60-120 min (5). Automated modules were developed for the synthesis of  $[^{18}\text{F}]$ FES to give ~50% radiochemical yields in 50-80 min (6, 7). Recently, automated synthesis procedure has been developed for clinical large-scale production of  $[^{18}\text{F}]$ FES in good yields (15-35%) with high radiochemical purity (>99%) (8).

## In Vitro Studies: Testing in Cells and Tissues

[PubMed]

ER binding affinity was assessed by competitive binding with  $[^3\text{H}]$ estradiol in MCF-7 cells. The binding affinity of FES was about 57% of estradiol (9). FES showed little binding to sex hormone-binding globulin as compared to estradiol.

## Animal Studies

### Rodents

[PubMed]

It was demonstrated that  $[^{18}\text{F}]$ FES uptake by target tissues (uterus and ovary) in immature female rats is highly specific (10). The uptake in liver and kidneys was lower than the uterus and nonspecific. There was also a significant depression of  $[^{18}\text{F}]$ FES uptake by the target tissues after pretreatment with the anti-estrogen, tamoxifen.  $[^{18}\text{F}]$ FES uptake by rat 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced breast tumors correlated well with the ER concentration (11). In another study, it was found that metabolism of  $[^{18}\text{F}]$ FES was rapid in rats bearing DMBA-induced breast tumors within 1-2 h after injection. Most of the radioactivity in the blood and non-target tissues was  $[^{18}\text{F}]$ FES metabolites, which did not bind to the target tissues and breast tumors (12).

Different animal models of estrogen-positive tumors using  $[^{18}\text{F}]$ FES were evaluated for their suitability to follow tumor response after various treatment protocols, using small-animal positron emission tomography (PET) (13). ER-positive human breast cancer cell lines MCF-7 and T-47D and murine mammary carcinomas MC4-L2, MC4-L3, and MC7-L1 were compared for their *in vivo* growth rate and retention of ER-positive status. Tumor metabolic activity was estimated from  $[^{18}\text{F}]$ fluorodeoxyglucose ( $[^{18}\text{F}]$ FDG) uptake, whereas ER content was determined from  $[^{18}\text{F}]$ FES uptake. The human cell lines grew at a slower rate in nude mice and failed to

accumulate [<sup>18</sup>F]FES; in contrast, the MC7-L1 and MC4-L2 carcinomas grew well in mice and showed good uptake of both [<sup>18</sup>F]FDG and [<sup>18</sup>F]FES. Chemotherapy and hormone therapy delayed the growth of MC7-L1 and MC4-L2 tumors, confirming their suitability as an ER-positive model for therapeutic interventions. The murine MC7-L1 and MC4-L2 tumors are suitable models for the monitoring of ER-positive breast cancer therapy using small-animal PET imaging.

## Other Non-Primate Mammals

[PubMed]

No publication is currently available.

## Non-Human Primates

[PubMed]

No relevant publication is currently available.

## Human Studies

[PubMed]

Thirteen patients with primary breast lesions were studied with [<sup>18</sup>F]FES PET (14). PET images demonstrated uptake of the tracer at sites of primary tumors and in several axillary lymph node metastases, as well as in one distant metastatic lesion. There was an excellent correlation between uptake within the primary tumor measured on the PET images and the tumor ER concentration measured by *in vitro* receptor binding assays after excision ( $r = 0.96$ ). In a study with 15 breast cancer patients (15), [<sup>18</sup>F]FES was cleared from the blood and metabolized in 20 min with only 20% of intact [<sup>18</sup>F]FES, most of which was bound to plasma proteins. Liver uptake of [<sup>18</sup>F]FES was rapid, and [<sup>18</sup>F]FES metabolites appeared in the blood as early as 5 min. The major, labeled metabolites in the blood and urine were sulfate and glucuronidate conjugates of [<sup>18</sup>F]FES, as measured by HPLC.

Human dosimetry of [<sup>18</sup>F]FES was determined from blood samples and PET images in 49 patients after intravenous injection of [<sup>18</sup>F]FES (16). The effective dose equivalent was 0.022 mSv/MBq (80 mrem/mCi). The organ that received the highest dose was the liver (0.13 mGy/MBq (470 mrad/mCi)), followed by the gallbladder (0.10 mGy/MBq (380 mrad/mCi)) and the urinary bladder (0.05 mGy/MBq (190 mrad/mCi)).

Uptake of [<sup>18</sup>F]FES in a series of patients with primary breast lesions and recurrent/metastatic breast tumors was compared with *in vitro* ER content and tumor uptake of [<sup>18</sup>F]FDG (17). There was no correlation between tumor ER status and [<sup>18</sup>F]FDG uptake or between tumor [<sup>18</sup>F]FES and [<sup>18</sup>F]FDG uptake in these patients. However, the [<sup>18</sup>F]FES PET assessments were in agreement with the *in vitro* ER binding assays. Anti-estrogen therapy decreased [<sup>18</sup>F]FES uptake in patients with ER-positive lesions (18), and patients with high initial uptake of [<sup>18</sup>F]FES were more likely to respond favorably to hormonal therapy (19). Peterson et al. (20) studied seventeen patients with primary or metastatic breast cancer with dynamic [<sup>18</sup>F]FES PET. For each tumor, partial-volume-corrected standardized uptake values (SUVs) of [<sup>18</sup>F]FES uptake were compared with ER expression measured by 3 different ER scoring methods: qualitative scoring, the Allred score, and a computerized immunohistochemistry (IHC) index. There was excellent agreement ( $r = 0.99$ ) between observers using IHC as well as the different methods of measuring ER content ( $P < 0.001$ ) with the best correlation being between the IHC index and [<sup>18</sup>F]FES SUVs. Tumor imaging with [<sup>18</sup>F]FES PET is useful in the determination of ER status and prognosis of therapy in breast cancer patients [PubMed].

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