Molecular imaging of estrogen receptors
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Assessment of estrogen receptor expression in epithelial ovarian cancer patients using 16α-18F-fluoro-17β-estradiol PET/CT. *Journal of Nuclear Medicine* 2015;56: 50-55.
ABSTRACT

The estrogen receptor (ER) α is expressed in ~70% of ovarian cancer tumors. Positron emission tomography (PET) of tumor ERα expression with the tracer 16α-18F-fluoro-17β-estradiol (18F-FES) may be valuable to select ovarian cancer patients for endocrine therapy. The aim of this study was to evaluate the feasibility of 18F-FES-PET to determine tumor ERα expression non-invasively in epithelial ovarian cancer patients.

18F-FES-PET/CT was performed shortly before cytoreductive surgery. Tumor 18F-FES uptake was quantified for all lesions ≥10 mm on CT and expressed as maximum standardized uptake value (SUV_{\text{max}}). 18F-FES-PET/CT findings were compared to histology and immunohistochemistry for ERα, ERβ, and progesterone receptor (PR). Receptor expression was scored semi-quantitatively using H-scores (percentage of positive tumor cells x staining intensity). The optimum threshold to discriminate ER positive and negative lesions was determined by receiver operating characteristic analysis.

In the 15 included patients with suspected ovarian cancer, 32 measurable lesions >10 mm were present on CT. Tumor 18F-FES uptake could be quantified for 28 lesions (88%), four lesions were visible but non-quantifiable due to high uptake in adjacent tissue. During surgery, histology was obtained of 23 out of 28 quantified lesions (82%). Quantitative 18F-FES uptake correlated with the semi-quantitative immunoscore for ERα (\rho=0.65, P<0.01), weakly with PR expression (\rho = 0.46, P = 0.03) and was not associated with ERβ expression (\rho=0.21, P=0.33). The optimal threshold to discriminate ERα positive and ERα negative lesions was a SUV_{\text{max}} >1.8, which provided a 79% sensitivity, 100% specificity, and area under the curve of 0.86 (95% CI 0.70-1.00). In two of seven patients with cytology/histology available at primary diagnosis and at debulking surgery immunohistochemical ERα expression had changed over time. 18F-FES-PET was in accordance with histology at debulking surgery, but not at primary diagnosis, indicating that 18F-FES-PET can provide reliable information about current tumor ERα status.

18F-FES-PET/CT can reliably assess ERα status in epithelial ovarian cancer tumors and metastases non-invasively. Evaluation of the predictive value of 18F-FES-PET/CT for endocrine therapy in epithelial ovarian cancer patients is warranted.
INTRODUCTION

Epithelial ovarian cancer is the second most common and most lethal gynecologic malignancy. Therefore, new therapeutic strategies are urgently needed. The estrogen receptor alpha (ERα) is expressed in ~70% of the epithelial ovarian cancer patients and presents a potential drug target for these tumors. Other hormone receptors, such as ERβ and progesterone receptor (PR) are expressed in ~75% and 20% respectively. In phase II studies in ovarian cancer patients unselected for ERα expression, endocrine therapy generated objective responses in up to 19% and clinical benefit in up to 51% of the patients.

Given the relatively low response rate, predictive biomarkers would be valuable to select those patients that are most likely to benefit from endocrine therapy. In breast cancer the ERα is a good predictor for response to endocrine agents. It therefore seems reasonable to select also ovarian cancer patients for endocrine therapy based on tumor ERα expression. Surprisingly however, it is currently unknown whether tumor ERα expression is predictive for treatment response in ovarian cancer. In breast cancer patients, the ERα can be heterogeneously expressed among lesions within individuals and ERα expression can change during the course of disease. In a retrospective study, ERα expression was discordant in 32% of 67 ovarian cancer patients with histology from both the primary tumor and a synchronous omental metastasis. A non-invasive method to quantify ERα expression in multiple metastases and at different time points might therefore be a valuable asset.

Whole-body imaging of tumor ERα expression could provide such information. It can be performed by positron emission tomography (PET) with the tracer 16α-18F-fluoro-17β-estradiol (18F-FES). 18F-FES-PET can predict response to endocrine therapy in breast cancer, and support patient-tailored therapy. It is however unknown whether 18F-FES-PET can also be used to evaluate ERα expression in ovarian cancer tumors and whether 18F-FES-PET can predict response to endocrine therapy in ovarian cancer patients. Visualization and quantification of 18F-FES uptake in ovarian cancer lesions may be impaired by the high physiological uptake in liver, gut, uterus, and bladder. We therefore evaluated the feasibility of 18F-FES-PET/CT to accurately determine ER density in lesions of patients with epithelial ovarian cancer.

MATERIALS AND METHODS

Patients

Patients diagnosed or with high clinical suspicion of epithelial ovarian cancer were eligible when they had tumor lesions ≥ 10 mm on diagnostic CT. Additional eligibility criteria were
Eastern Cooperative Oncology Group performance score ≤ 2, and a postmenopausal status. Patients with a history of ER positive malignancy (breast cancer, endometrial cancer), and patients using (anti)estrogenic drugs were excluded. All patients underwent 18F-FES-PET/CT. Tumor tissue for histology was prospectively collected during surgery performed shortly after 18F-FES-PET/CT imaging. Patients were allowed to have received neoadjuvant chemotherapy consisting of carboplatin/paclitaxel prior to 18F-FES-PET/CT imaging. In these patients, 18F-FES-PET/CT was performed after the last cycle of neoadjuvant chemotherapy and just prior to surgery. The Committee on Ethics of the University of Groningen approved this study and all subjects signed a written informed consent. The study is registered in the ClinicalTrials.gov database (NCT01439490).

CT and 18F-FES-PET/CT imaging
All patients underwent a diagnostic CT scan to identify tumor lesions. 18F-FES was produced as previously described. Patients received approximately 200 MBq 18F-FES intravenously. Whole body 18F-FES-PET/CT was performed 60 min after tracer injection, using a Siemens Biograph 64 slice mCT (PET/CT) camera (Siemens CTI) with 2 mm reconstructed spatial resolution and an emission acquisition time of 3 min per bed position. Low dose CT-scan (for attenuation and scatter correction), and PET imaging were performed sequentially within one procedure. Patients in whom the diagnostic CT-scan was ≥6 weeks old at the moment of the 18F-FES-PET/CT also underwent a new diagnostic CT in the same procedure. CT scans were evaluated by an experienced radiologist and used to allocate tumor lesions ≥ 10 mm. This threshold was chosen to limit partial volume effects and resolution-limitations during quantification of 18F-FES uptake. Tumor 18F-FES uptake was quantified by a nuclear medicine physician experienced in 18F-FES-PET imaging and according to the European Association of Nuclear Medicine guidelines in tumor lesions ≥ 10 mm, using fused PET/CT images. In line with previous studies we used the maximum standardized uptake value (SUV\text{max}) to calculate tumor 18F-FES uptake.\textsuperscript{63,64} As an explorative analysis we also measured the mean standardized uptake value (SUV\text{mean}) using a 70% isocontour of the hottest pixel.\textsuperscript{214} Concurrent with 18F-FES-PET/CT, venous blood was collected from the infusion site (prior to 18F-FES-injection) to evaluate serum estradiol, and sex hormone binding globulin, since these have been reported to negatively affect tumor 18F-FES uptake in breast cancer studies.\textsuperscript{40,149}

Tumor histology
All patients were scheduled for cytoreductive surgery aimed at complete debulking of all macroscopic tumor lesions. The locations of resected tumor lesions were recorded to allow comparison between pathology and imaging results. All tumor lesions and macroscopic diameters at pathologic examination were listed in a database. Slides for histological
examination were prepared from all parts with suspected tumor. Hematoxylin/eosin staining was used to evaluate the presence of tumor cells in the resected tissue and tumors were typed and graded. From all tumor lesions ≥ 10 mm of which quantitative $^{18}$F-FES uptake was available, additional immunohistochemistry was performed. Paraffin-embedded-formalin-fixed tumor blocks were sliced and mounted on 3-aminopropyltriethoxysilane-coated glass slides. Immunohistochemistry was performed as previously described. Briefly, ERα was stained using the clinical-grade SP1 monoclonal rabbit anti-ERα antibody (Ventana), and PR using 1E2 monoclonal rabbit anti-PR antibody (Ventana) in the automated slide stainer with an iView DAB Detection kit. ERβ was stained using a monoclonal mouse anti-ERβ1 clone PPG5/10 (Serotec).

Immunohistochemical analysis

Two independent observers scored the slides. The percentage of positive cells was scored (0-100%) as well as the staining intensity (0=none, 1=weak, 2=moderate, 3=strong). For dichotomous classification of receptor positivity, ≥ 10% of tumor cells with moderate or strong staining was used as cut-off point in reference to other studies in ovarian cancer. For semi-quantitative analysis, the percentage of positive cells and staining intensity scores were multiplied to obtain the H-score (range 0–300). To allow correction for tumor cell density, the percentage tumor and stromal tissue were estimated in a 1 cm² field of view. Dichotomous immunohistochemistry results, H-scores and ER density were compared to dichotomous and quantitative tumor $^{18}$F-FES uptake. Additionally, the association between serum CA-125, estradiol and sex hormone binding globulin with tumor $^{18}$F-FES uptake was evaluated.

Statistical analysis

In this pilot study we aimed to enroll ~15 patients to assure the inclusion of at least 8 patients with ERα positive histology. A sensitivity of $^{18}$F-FES-PET/CT ≥85% was anticipated. A stopping-rule was therefore applied when ≥ four out of eight patients with ER positive histology did not show tumor $^{18}$F-FES uptake (SUV$_{max}$ < 1.5), since this results in a 95% confidence interval below 85% sensitivity. Receiver operating characteristic analysis was done to identify the optimal threshold to differentiate between ERα positive and ERα negative lesions. Sensitivity, specificity and 95% confidence intervals were calculated. Mann-Whitney U test was performed to evaluate differences in $^{18}$F-FES uptake between receptor (ERα, ERβ, PR) positive and negative tumors. A Spearman’s correlation coefficient was determined to evaluate the correlation between quantitative tumor $^{18}$F-FES uptake and semi-quantitative measures of receptor expression, as well as the correlation with serum estradiol, and sex hormone binding globulin.
RESULTS

Patient characteristics
Fifteen patients were included between October 2011 and October 2013. One patient had a carcinosarcoma at pathological examination and was therefore excluded from further analyses. Of the remaining 14 patients, 13 had serous carcinoma, and one carcinoma of the transitional cell type. Patients had FIGO stage III (n=11), IV (n=2) and recurrent ovarian cancer (n=1). Nine (64%) of the 14 patients received 3 cycles of neoadjuvant chemotherapy prior to $^{18}$F-FES-PET/CT imaging. $^{18}$F-FES-PET/CT imaging was performed at a median of 9 days prior to cytoreductive surgery (range 1 – 22 days). All patients had postmenopausal serum estradiol levels at the time of $^{18}$F-FES-PET/CT (median 0.04 nmol/L, range 0.02–0.06 nmol/L) in accordance with the inclusion criteria. Serum CA-125 levels varied greatly at the time of $^{18}$F-FES-PET/CT (median 138, range 18–1771 kU/L). Patient characteristics are shown in table 1.

Table 1: Patient Characteristics

<table>
<thead>
<tr>
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<tr>
<td>Age (y)</td>
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<td>IV</td>
<td>2</td>
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<tr>
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<td>Serum tumor marker Ca-125, kU/L</td>
<td>Median (range)</td>
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<tr>
<td>Serum estradiol (nmol/L)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Serum sex hormone binding globulin, nmol/L</td>
<td>Median (range)</td>
</tr>
</tbody>
</table>

$^{18}$F-FES-PET/CT findings
All patients had a diagnostic contrast-enhanced CT scan available. All patients underwent $^{18}$F-FES-PET with co-registration of a low-dose CT. Of the 14 patients, two patients underwent a new diagnostic CT at the time of $^{18}$F-FES-PET/CT imaging, the remaining 12 patients had a diagnostic CT scan available that was made less than 6 weeks (median 28, range 7–41 days) prior to $^{18}$F-FES-PET/CT imaging.
On $^{18}$F-FES-PET/CT 12 out of 14 patients had lesions with $^{18}$F-FES uptake. A total of 32 lesions $\geq$ 10 mm were identified on $^{18}$F-FES-PET/CT. Four additional lesions were larger than 10 mm on earlier diagnostic CT, but could not be identified on the low-dose CT at the time of $^{18}$F-FES-PET/CT imaging. These four lesions were however present in patients that had received three cycles of neo-adjuvant chemotherapy at the time of $^{18}$F-FES-PET/CT, and all four lesions were confirmed to have become $< 10$ mm due to neodjuvant chemotherapy at pathological examination. Finally, four lesions were visible on $^{18}$F-FES-PET/CT but $^{18}$F-FES uptake could not be reliably quantified due to high physiological background uptake in the close proximity of the lesion (e.g. in liver, uterus and intestines). Therefore, a total of 28 lesions, consisting of 12 ovarian tumors and 16 intra abdominal metastases, were used for $^{18}$F-FES-PET/CT analysis. Examples of positive $^{18}$F-FES-PET/CT images of abdominal metastases are provided in figure 1. There were no new lesions discovered on $^{18}$F-FES-PET/CT that had not yet been recorded on diagnostic CT. One patient had newly diagnosed pleural effusion which harbored increased $^{18}$F-FES uptake. Mean tumor SUV$_{\text{max}}$ of all quantified lesions was 2.4 (range 1.1–5.1). It was noted that $^{18}$F-FES uptake was absent in cystic parts of the tumor lesions (figure 2). Although not a primary aim of our study, it was noted that fusion of PET with the diagnostic CT was crucial for identification of the tumor lesions, since tissue surrounding the lesions, such as uterus, bladder and intestines harbored high physiological uptake.

Figure 1. Imaging of a patient with metastatic lesions between stomach and spleen. (A) CT scan; (B) $^{18}$F-FES-PET/CT.

Figure 2. CT-scan (A) and $^{18}$F-FES-PET/CT (B) findings of the same patient as shown in Fig. 3. ERα expression was high and tumor $^{18}$F-FES uptake (SUV$_{\text{max}}$) was 5.1. $^{18}$F-FES uptake was absent in cystic parts of the tumor lesion (arrow head) when compared to solid parts (arrow).
Concordance between $^{18}$F-FES-PET/CT and pathology

Concurrent histology was available for 23 (82%) of 28 lesions quantified on $^{18}$F-FES-PET/CT. Histology was not available of the remaining lesions due to inability to perform a complete debulking during surgery. ERα was positive in 19 of 23 lesions (83%) with a median H-score of 101 (range 0–300), ERβ was positive in 13 lesions (57%) with a median H-score of 84 (range 0–300), and PR was positive in 10 lesions (43%) with a median H-score of 65 (range 0–188). Examples of ERα, ERβ, and PR immunostaining are provided in figure 3.

Figure 3. Representative examples of hematoxylin/eosin (A), ERα (B), ERβ (C) and PR (D) staining. In this patient ERα expression was high, ERβ was moderately expressed, and PR was heterogeneously expressed.

Tumor $^{18}$F-FES uptake was higher in ERα positive lesions than in ERα negative lesions (mean SUV$\text{max}$ 2.8 ± 1.3 vs. 1.4 ± 0.3, $P=0.03$). The optimum threshold for quantitative $^{18}$F-FES-PET imaging to discriminate between ERα positive and ERα negative lesions, as determined by receiver operating characteristic analysis, was a SUV$\text{max}$ of 1.8. Application of this threshold resulted in a 100% specificity (4 of 4 lesions with uptake < 1.8 were ERα negative) and 79% sensitivity (15/19 lesions with uptake > 1.8 were ERα positive). Also, using this threshold, one patient had both $^{18}$F-FES positive as well as $^{18}$F-FES negative lesions.

Mean tumor $^{18}$F-FES uptake did not differ significantly between ERβ positive and ERβ negative lesions (2.9 ± 1.4 vs. 2.1 ± 1.0, $P=0.19$), and between PR positive and PR negative lesions (3.1 ± 1.5 vs. 2.1 ± 0.8, $P=0.17$). As expected, $^{18}$F-FES-PET/CT was not suitable to differentiate between ERβ positive and ERβ negative lesions with a calculated sensitivity of 77% and specificity of 50%. The calculated sensitivity and specificity of $^{18}$F-FES-PET/CT for PR positive lesions were 70% and 38%. The use of SUV$\text{mean}$ instead of SUV$\text{max}$ did not affect the sensitivity and specificity of $^{18}$F-FES-PET for ERα positive lesions, with an optimum threshold
to discriminate between ERα positive and ERα negative lesions for a SUV$_{\text{mean}}$ $\geq$ 1.3.

In seven patients with histology at primary diagnosis, and at debulking surgery after neoadjuvant chemotherapy, paired samples were available to evaluate temporal discordance in ERα expression. In two patients (29%), there was discordant ERα expression. Both patients had ERα negative immunohistochemistry at diagnosis, 18F-FES-PET/CT showed 18F-FES positive lesions, and subsequent histology obtained during debulking surgery shortly thereafter was ERα positive.

**Correlation between quantitative 18F-FES-PET/CT and receptor expression**

Quantitative tumor 18F-FES uptake (SUV$_{\text{max}}$) correlated well with the H-score for ERα ($\rho=0.65$, $P<0.01$, figure 4A). 18F-FES uptake showed a weak correlation with PR expression ($\rho=0.46$, $P=0.03$, figure 4B) and was not associated with ERβ expression ($\rho=0.21$, $P=0.33$, figure 4C). The weak correlation observed between 18F-FES uptake and PR expression can likely be explained by the fact that increased ERα expression correlated with increased PR expression ($\rho=0.54$, $P<0.01$) as PR is an ERα-mediated estrogen-responsive gene. Indeed median SUV$_{\text{max}}$ was 3.8 in PR positive tumors that were also ERα positive (n=8 lesions) and only 1.2 in PR positive tumors that were ERα negative (n=2 lesions).

Using SUV$_{\text{mean}}$ instead of SUV$_{\text{max}}$ provided a slightly better correlation between quantitative tumor 18F-FES uptake and ERα expression ($\rho=0.75$, $P<0.01$). Also PR correlated with tumor SUV$_{\text{mean}}$ ($\rho=0.55$, $P<0.01$), while ERβ expression did not correlate with tumor 18F-FES uptake using SUV$_{\text{mean}}$ ($\rho=0.30$, $P<0.01$).

It was noted that in four lesions of two patients treated with neoadjuvant chemotherapy quantitative tumor 18F-FES uptake was low, while tumor cells were clearly ERα positive. In these two patients, however, the tumors had a relatively low percentage of vital tumor cells.
The lower ER density per cm² therefore likely explains these false-negative findings (figure 5).

**Figure 5.** Example of a patient with false-negative ¹⁸F-FES-PET/CT findings (upper panels) and true-positive ¹⁸F-FES-PET/CT findings (lower panels). (A) 1 cm² overview of ERα staining; (B) 1 mm² overview of ERα staining of the indicated area in (A); and (C) corresponding ¹⁸F-FES-PET/CT findings. The arrows indicate the tumor mass. ¹⁸F-FES uptake (SUV<sub>max</sub>) was 1.3 in the tumor shown in the upper panel and 4.9 in the lower panel. The low tumor cell density in the upper panel likely explains the negative findings on ¹⁸F-FES-PET/CT.

**Correlation between quantitative ¹⁸F-FES-PET/CT and serum estradiol and sex hormone binding globulin**

All patients had postmenopausal serum estradiol levels. Within the postmenopausal range, there was no trend towards lower ¹⁸F-FES uptake in individuals with higher serum estradiol levels (p=0.06, P=0.56). Increased sex hormone binding globulin levels were reported to negatively affect tumor ¹⁸F-FES uptake in larger breast cancer studies.⁴⁰ In our study high serum sex hormone binding globulin levels did not correlate with lower tumor ¹⁸F-FES uptake (p=-0.18, P=0.59).

**DISCUSSION**

This is the first study that showed that ¹⁸F-FES-PET/CT can reliably assess tumor ERα-status in patients with epithelial ovarian cancer. Twelve out of 14 patients had tumor lesions with an increased ¹⁸F-FES uptake.

To the best of our knowledge, no earlier studies describing ¹⁸F-FES-PET/CT in ovarian cancer are available apart from one preliminary case report of ¹⁸F-FES-PET in a patient with ovarian
cancer and leiomyoma in a review article that indicated that $^{18}$F-FES uptake can be observed in ovarian cancer.$^{16}$

In our feasibility study, we learned several aspects that can be of relevance for future $^{18}$F-FES-PET studies in ovarian cancer patients. First of all, we showed that $^{18}$F-FES uptake was absent in the cystic parts of lesions, and therefore a sufficiently large (e.g. >10 mm) solid component is required for quantification of tumor $^{18}$F-FES uptake. Secondly, in contrast to breast cancer where $^{18}$F-FES positive lesions can usually readily be observed also without concurrent CT-scan,$^{50}$ in this study, ovarian cancer lesions had to be allocated using a concurrent or recent contrast-enhanced diagnostic CT. This is the consequence of the fact that the far majority of lesions develop in the abdominal cavity where visualization is hampered by high physiological background tracer levels in liver, gallbladder, intestines, uterus, kidneys and bladder.$^{65}$ Finally, our study design allowed the inclusion of patients that had received neoadjuvant chemotherapy, which has potentially affected tumor $^{18}$F-FES uptake. The inclusion of neoadjuvant treated patients with high-stage disease allowed us to obtain both $^{18}$F-FES-PET/CT data and concurrent histology of multiple lesions from the same patient, which was also one of the strengths of our study. In two of nine of neoadjuvant treated patients, however, all lesions larger than 10 mm on earlier diagnostic CT, were reduced in size < 10mm due to chemotherapy effects precluding the assessment at the time of $^{18}$F-FES-PET. In two other neoadjuvant-treated patients, four lesions >10 mm harbored only few vital tumor cells at pathological examination. Thus, antitumor effects in patients treated with neoadjuvant chemotherapy may have impacted $^{18}$F-FES-PET sensitivity.

To date, most $^{18}$F-FES-PET studies have used SUV$_{\text{max}}$ to quantify tumor $^{18}$F-FES uptake.$^{149}$ This method of quantification has several advantages among which its easy reproducibility. As an explorative analysis we also measured SUV$_{\text{mean}}$ using an arbitrary 70% isocontour. Although this slightly increased the correlation between tumor $^{18}$F-FES uptake (SUV$_{\text{mean}}$) and ER$\alpha$ expression, it did not result in a better sensitivity and specificity. The most optimum way to quantify tumor $^{18}$F-FES uptake, using SUV$_{\text{max}}$ or SUV$_{\text{mean}}$ with a percentage isocontour, with or without correction for background physiological $^{18}$F-FES uptake needs to be addressed in future studies.

The current golden standard to determine hormone receptor expression is immunohistochemistry. This standard has some limitations in patients with metastatic disease. For example it may be difficult to obtain a biopsy due to e.g. the location of the lesion. Also, determining the current ER status of the patient on stored tissue samples can be unreliable due to changes in ER expression over time. Finally, a biopsy may not always reflect actual ER status due to intra-tumor and inter-tumor heterogeneity. These issues have especially been shown to play a role in breast cancer,$^{9,25}$ but may also apply to ovarian
cancer. Specifically, we showed previously that heterogeneous ER expression among lesions within the same individual does also exist in ovarian cancer.\textsuperscript{211} In the current study, in two of seven patients with biopsies at diagnosis and at surgery several months later, discordant ER\textalpha expression was observed. Since the first biopsy was performed as diagnostic procedure prior to inclusion in the study we were unable to precisely determine which lesion was biopsied. Therefore, the discordance might be explained by heterogeneity between lesions, or by changes in ER expression, \textit{e.g.} due to neoadjuvant chemotherapy effects. Either way, this illustrates that a single tumor biopsy may not always reliably reflect ER\textalpha-status during the course of disease.

\textsuperscript{18}F-FES-PET has previously been evaluated to assess ER status in breast cancer metastases, which showed a good sensitivity of 84\% and excellent specificity of 98\%.\textsuperscript{10,16,70,71,149} In addition, \textsuperscript{18}F-FES-PET showed to be as predictive biomarker for response to antihormonal therapy in various studies in metastatic breast cancer patients.\textsuperscript{57,63,64} In ovarian cancer patients, the role of endocrine therapy is limited. Objective tumor responses to endocrine agents are observed in 8-19\% of heavily pretreated patients in several phase II studies.\textsuperscript{4-7,206} But surprisingly, these studies did generally not select patients based on ER expression by their tumor. In a retrospective study in 26 patients with ovarian cancer treated with the pure ER antagonist fulvestrant, higher levels of ER expression by the tumor were associated with clinical benefit.\textsuperscript{207}

\textbf{CONCLUSION}

\textsuperscript{18}F-FES-PET/CT can reliably assess ER\textalpha status in epithelial ovarian cancer tumors and metastases non-invasively, with a 79\% sensitivity and 100\% specificity. Based on the findings of this study, exploration of the value of \textsuperscript{18}F-FES-PET to predict treatment response to endocrine agents is warranted. Ideally, patients with ovarian cancer presenting with especially solid tumor lesions larger than 10 mm seem candidate to evaluate the potential of \textsuperscript{18}F-FES-PET/CT as predictive imaging biomarker.

\textbf{CONFLICT OF INTEREST}

The authors declare no potential conflicts of interest.