[18F]FDG and [18F]FES PET/CT Imaging as a Biomarker for Therapy Effect in Patients with Metastatic ER+ Breast Cancer Undergoing Treatment with Rintodestrant
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Purpose: PET with 16α-[18F]-fluoro-17β-estradiol ([18F]FES) allows assessment of whole body estrogen receptor (ER) expression. The aim of this study was to investigate [18F]-fluorodeoxyglucose ([18F]FDG) and [18F]FES PET/CT imaging for response prediction and monitoring of drug activity in patients with metastatic ER-positive breast cancer undergoing treatment with the selective estrogen receptor downregulator (SERD) rintodestrant.

Experimental Design: In this trial (NCT03455270), PET/CT imaging was performed at baseline ([18F]FDG and [18F]FES), during treatment and at time of progression (only [18F]FES). Visual, quantitative, and mutational analysis was performed to derive a heterogeneity score (HS) and assess tracer uptake in lesions, in relation to the mutation profile. The primary outcome was progression-free survival (PFS).

Results: The HS and PFS in the entire group did not correlate (n = 16, Spearman’s rho, P = 0.06), but patients with a low HS (≤ 25.0%, n = 4) had a PFS of > 5 months whereas patients with no [18F]FES uptake (HS 100.0%, n = 3) had a PFS of < 2 months. [18F]FES uptake was not affected by estrogen receptor 1 (ESR1) mutations. On-treatment [18F]FES PET/CT scans showed no [18F]FES uptake in any of the baseline [18F]FES-positive lesions. At progression, [18F]FES uptake remained blocked in patients scanned ≤ 1–2 half-lives of rintodestrant whereas it restored in patients scanned ≥ 5 days after end of treatment.

Conclusions: Absence of ER expression on [18F]FES PET is a predictor for no response to rintodestrant. [18F]FES uptake during treatment and at time of progression is useful to monitor the (reversible) effect of therapy and continued mode of action of SERDs.

See related commentary by Linden and Mankoff, p. 2015

Introduction

Endocrine therapy is the mainstay of treatment for patients with metastatic estrogen receptor (ER)-positive (ER+), HER2-negative (HER2-) breast cancer (1). It includes drugs that reduce estradiol levels in blood, i.e., aromatase inhibitors such as anastrozole or letrozole, or drugs that reduce ER availability, i.e., selective ER modulators (SERM) such as tamoxifen and selective ER downregulators (SERD), like fulvestrant (1, 2). While endocrine therapy has improved patient survival, 0% to 40% of the tumors will acquire resistance over a period of time (2, 3). Therefore, several new SERMs and SERDs are under development to improve efficacy and overcome resistance, including the novel oral SERD rintodestrant (2, 4).

The primary biomarker for selecting patients that are candidates for endocrine therapy is the ER status, as determined by IHC on a biopsy of tumors (18). Therefore, several new SERMs and SERDs are under development to improve efficacy and overcome resistance, including the novel oral SERD rintodestrant (2, 4).

Several studies have investigated the predictive value of [18F]FDG and [18F]FES PET/CT (separately and combined). In general, it was found that for [18F]FDG high tracer uptake is associated with shorter efficacy and overcome resistance, including the novel oral SERD rintodestrant (2, 4).

Several studies have investigated the predictive value of [18F]FDG and [18F]FES PET/CT (separately and combined). In general, it was found that for [18F]FDG high tracer uptake is associated with shorter survival (19) whereas for [18F]FES responders to endocrine therapy had higher baseline [18F]FES uptake than those of nonresponders (13, 15). In cases where patients were treated with SERDs, [18F]FES uptake decreased (≥70.0%) during treatment indicating
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Translational Relevance
PET with 16a-[18F]-fluoro-17ß-estradiol ([18F]FES) can provide information on whole body estrogen receptor (ER) expression. The ER status is currently the primary biomarker for predicting response to endocrine therapy [specifically for selective estrogen receptor downregulators (SERD)] in patients with advanced ER-positive breast cancer. This prospective clinical trial showed that [18F]FES PET can serve as a biomarker for response prediction as the absence of ER expression, as measured on [18F]FES PET, is a predictor for no response to SERD treatment. This biomarker can also be applied in patients with estrogen receptor 1 (ESR1) mutated tumors for which novel SERDs have been developed as active drugs, as these mutations do not affect [18F]FES uptake. Moreover, [18F]FES PET imaging during treatment and at time of progression can be used to monitor the (reversible) effect of therapy and continued mode of action of SERDs, making it a useful tool in the development of these novel endocrine drugs.

Materials and Methods

Patients
Postmenopausal female patients (pre-/perimenopausal patients were allowed if on ovarian suppression) with histologically proven metastatic ER+/HER2- breast cancer were included in this study (sub-study of a phase I trial: NCT03455270) at the Amsterdam University Medical Centers – location VUMc, University Medical Center Groningen and Institute Jules Bordet (Brussels). Patients that underwent an [18F]FDG PET and [18F]FES PET within the phase II trial were selected for this sub-study. Patients were included in the phase I trial when they had progressive disease after having received a maximum of 3 lines of cytotoxic chemotherapy and 3 lines of endocrine therapy in the metastatic setting (4, 26). Patients were excluded when they were treated with SERMs (i.e., tamoxifen) or SERDs (i.e., fulvestrant) ≤ 5 weeks prior to inclusion as these drugs interfere with the availability of the ER (https://www.richtlijndatabase.nl/gerelateerde_documenten/f/17259/18F-20FES%20PETCT%20in%20oncology.pdf). For each participating center, the study was approved by the Medical Ethics Review Committee and conducted in accordance with recognized ethical guidelines (Declaration of Helsinki). All patients provided written informed consent for their participation.

Treatment and clinical outcome
Patients received rintodestrant orally once a day. In the phase I study, a 3+3 dose escalation design was used to determine the recommended phase II dose (4, 26). The starting dose in the first cohort was 200 mg which could be escalated up to maximally 2,000 mg/day, as previously described (26). Patients continued treatment until they had progressive disease (clinically or radiographically) or there was unacceptable toxicity. For response measurement, patients underwent a diagnostic CT scan of the thorax/abdomen/pelvis at baseline and initially every 8 weeks. After 48 weeks, these scans were performed every 12 weeks, unless clinically indicated to do this earlier. Investigator-determined response according to RECIST version 1.1 was the primary outcome measure used to determine tumor response in the main study. Progression-free survival (PFS), as determined by the time from treatment initiation to disease progression or death from any cause, was the main outcome measurement in this sub-study.

Mutational analysis
Within the scope of the phase I trial, peripheral blood samples were evaluated at baseline for assessment of the mutational status by analyzing cell-free DNA (27). Samples were processed and analyzed using the Guardant360 panel at Guardant Health, Inc. It was investigated whether the presence of estrogen receptor 1 (ESR1) mutations correlated with [18F]FES uptake and PFS.

PET imaging
PET scans were performed on an Ingenuity TF or Vereos PET/CT scanner (Philips Medical Systems, Cleveland, OH), a Biograph mCT 40 or 64-slice PET/CT scanner (Siemens/CTI, Knoxville, TN, and a Discovery 690 PET/CT scanner (GE Healthcare, Chicago, OH). Scans were acquired according to the guidelines of the European Association of Nuclear Medicine (EANM) and reconstructed according to EARL for quantitative purposes (28, 29). Imaging was performed at 3 time-points: whole body [18F]FDG and [18F]FES PET/CT scans were performed at baseline (with a minimum of 24 hours between both scans), followed by an [18F]FDG PET/CT scan performed during 4 weeks of treatment with rintodestrant and at the time of progression (within 10 days of the last dose of rintodestrant). For [18F]FDG PET/CT imaging, patients were asked to fast 6 hours prior to the scan. Before each scan, patients received a venous cannula for tracer administration of [18F]FDG (dose 3 MBq/kg according to EANM guidelines; ref. 29) or [18F]FES (fixed dose of 200 MBq ± 10%, molar activity: >19.8 GBq/μmol, maximum molar dose: 10 nanomole to a patient, radiochemical purity: >95%; synthesis described in Suppl. Dat; ref. 30). One hour after tracer administration, patients underwent a whole body low-dose CT scan for attenuation correction and anatomic correction followed by the PET scan (field of view: skull to mid-thigh).
Data analysis

Visual scoring

Scans were uploaded in the IntelliSpace Portal (v5.0.0.20030, Philips Healthcare, the Netherlands). At baseline, lesions were identified on the diagnostic CT, [18F]FDG, and [18F]FES PET/CT scans. The diagnostic CT and [18F]FDG PET/CT scans were evaluated according to standard of care by radiologists and nuclear medicine physicians of the various sites. The [18F]FES PET/CT scans were evaluated by two nuclear medicine physicians (DO, GG) for identification of malignant lesions. A head-to-head comparison was performed between [18F]FDG and [18F]FES PET/CT scans. Each identified lesion was indicated as [18F]FDG positive/negative ([18F]FDGpos/neg) and [18F]FES PET/CT positive/negative ([18F]FESpos/neg). Brain and liver metastases were excluded as they are difficult to identify due to high physiologic [18F]FDG uptake in the brain and high [18F]FES uptake in the liver, respectively. The size (<1.5 cm or ≥1.5 cm) and location of all identified lesions was taken into account. On the basis of the number of lesions present on the [18F]FDG and [18F]FES PET/CT scan, a HS—comparing and combining outcomes of these two different PET tracers —was calculated using the following equation:

\[
HS = \left(1 - \frac{\text{concordant FDG}^+ \text{ and FES}^+ \text{ lesions}}{\text{FDG}^+ \text{ lesions}}\right) \times 100\%
\]

For monitoring the effect of rintodestrant, [18F]FES PET/CT scans performed during 4 weeks of treatment and at time of progression were visually evaluated. On these scans [18F]FES uptake in known lesions as observed on the baseline [18F]FES PET scan was evaluated. In addition, the change in [18F]FES uptake (%) on the on-treatment scan (compared with the baseline scan) was assessed quantitatively (taking into account the background uptake in the same tissue).

Lesional analysis and quantification

On both [18F]FDG and [18F]FES PET/CT (independent of each other), 5 lesions with highest tracer uptake were identified using a threshold of SUV ≥ 4.0 for [18F]FDG and SUV ≥ 1.5 for [18F]FES according to literature (16). In case, there were more than 5 lesions with a SUV ≥ 4.0/1.5, then the best delineable lesions with the largest volume (as assessed visually) were selected. In case, there were no lesions with high tracer uptake visible (at the threshold), then the threshold was lowered until lesions become visible to be selected. Initial lesion selection was done independently on each scan. Subsequently, the lesions were matched on the other PET scan, in total selecting up to 10 lesions per patient. Volumes of interests (VOI) were then defined on PET images using a 40% iso-contour of the max voxel value using in-house developed software (Accurate tool, R. Boellaard; ref.s 26, 31). Furthermore, a fixed size VOI of 1.5 cm was placed in 5 consecutive axial planes within the lumen of the ascending aorta on both [18F]FDG and [18F]FES PET to calculate tumor-to-blood ratios (TBR). The low-dose CT scan was used as a reference for anatomic localization. Quantitative parameters, including max, peak and mean standardized uptake values (SUVmax, SUVpeak, SUVmean), mean TBRs, total lesion glycolysis (TLG) and total lesion ER expression (TL-ER) were obtained from this analysis.

Total tumor burden

The total tumor burden (in mL) comprises the volume of [18F]FDG positive lesions and [18F]FDG negative lesions with positive [18F]FES uptake. The [18F]FDG positive tumor volume (MTV) and [18F]FES positive tumor volume (ERTV) were calculated using the fixed threshold of a SUV ≥ 4.0 and SUV ≥ 2.0, respectively. From these collective VOIs, non-tumorous tissues and tumor lesions in tissues with high physiologic [18F]FDG and [18F]FES uptake (i.e., brain, liver, kidneys, urinary bladder) were excluded. Lesions that met the SUV threshold but were not automatically included in the VOI, were added manually.

Assuming that the number of [18F]FDG negative lesions would be small compared with the total number of lesions, it is possible to estimate the total tumor burden using MTV. In addition, the ERTV in relation to MTV was calculated using the following equation:

\[
\%\text{ERTV} = \left(\frac{\text{ERTV}}{\text{MTV}}\right) \times 100\%
\]

Statistical analysis

Statistical analyses were performed using SPSS Statistics 26 (IBM Corp., Armonk, NY). Median and interquartile range (IQR) were reported and nonparametric tests (including Mann–Whitney U, Kruskal–Wallis and Spearman’s correlation) were applied. The relationship between the HS and PFS, mutational profile and PFS, change in [18F]FES uptake between the baseline and on-treatment scan and the dose and PFS, lesional uptake and PFS and total tumor burden and PFS was investigated. For the various comparisons, correction for multiple testing was performed using the Benjamini–Hochberg test.

Data availability

The data generated in this study are available within the article and its Supplementary Data file. For further information regarding raw data, please contact the corresponding author.

Results

Patients

In this sub-study of NCT03455270 (4), 16 patients with a median (IQR) age of 63.0 years (59.3–70.8) were included (Supplementary Tables S1 and S2). The patients received different doses of rintodestrant, ranging from 200 mg to 1,000 mg, depending on the study cohort they were included in. There was no difference between the different doses and PFS, ranging from 200 mg to 1,000 mg, depending on the study cohort they were included in. There was no difference between the different doses and PFS, ranging from 200 mg to 1,000 mg, depending on the study cohort they were included in. There was no difference between the different doses and PFS (Kruskal–Wallis test, P = 0.17; after correction for multiple testing, P = 0.19) and the different doses and clinical response (Kruskal–Wallis test, P = 0.61). Almost all patients discontinued treatment due to progressive disease with an overall median (IQR) PFS of 1.9 (1.7–6.7) months (Supplementary Table S3).

At baseline, all patients (n = 16) underwent a [18F]FDG- and a [18F]FES PET/CT scan. Fifteen and 11 patients underwent a [18F]FES PET/CT scan during treatment with rintodestrant and at time of progression, respectively. Mutation profiling was performed in 10 of 16 (62.5%) patients (panel of 25 genes (Supplementary Table S4). Patients with an ESR1 mutation (n = 5) had a prolonged PFS of > 5 months (Spearman’s rho, P = 0.02; after correction for multiple testing, P = 0.04; Supplementary Table S4).

Visual scoring using [18F]FDG and [18F]FES PET/CT scans

In total, 1,051 lesions have been identified, mostly located in osseous (n = 893) and subcutaneous tissue (n = 69; Fig. 1). Liver lesions were present in 6 of 16 patients (patient 4, 8, 11, 12, 15, 16) but were not included in the analysis. The HS per patient varied between 0.0% and 100.0% (Table 1; Fig. 2). Three patients had no [18F]FES positive lesions. A total of 29 lesions showed [18F]FES uptake but no [18F]FDG uptake (in 8 patients). Overall, the HS and PFS (Spearman’s rho, P = 0.06; after correction for multiple testing, P = 0.08; Fig. 2) did not correlate. There was, however, a trend:

\[
\text{Spearman’s correlation (PFS) = } -0.17; \text{ after correction for multiple testing, } P = 0.08; \text{ after correction for multiple testing, } \rho = -0.19
\]
Figure 1.
The number of lesions identified by means of visual analysis using the baseline diagnostic CT, [18F]FDG, and [18F]FES PET/CT scans. Lesions have been classified per tissue type per patient. Brain and liver metastases were excluded because of the high physiologic background uptake of [18F]FDG and [18F]FES, respectively.

Table 1. Number of [18F]FES+, [18F]FDG+ lesions and lesions identified on CT per patient, with their corresponding HS, dose of rintodestrant, and PFS.

<table>
<thead>
<tr>
<th>Patient</th>
<th>[18F]FES+ lesions</th>
<th>[18F]FDG+ lesions</th>
<th>Lesions identified on CT</th>
<th>[18F]FES and [18F]FDG concordant lesions</th>
<th>HS</th>
<th>Dose of rintodestrant (mg)</th>
<th>PFS (months)</th>
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aData have been sorted in ascending order based on PFS.

bIn patient 12, more lesions have been identified on the CT scan compared with the [18F]FDG PET/CT scan. This patient had predominantly sclerotic bone metastases that could be identified on the CT scan. Many of these bone metastases were [18F]FDG negative, which is most likely a sign of response to the previous treatments that patient had received, explaining the discrepancy in number of lesions identified on the CT and the [18F]FDG PET/CT scan. Besides bone metastases, this patient also had lymph node metastases that were positive on the [18F]FDG and [18F]FES PET/CT scan.
patients with a low heterogeneity (<25.0%) score had a long PFS of >5 months whereas absence of [18F]FES uptake (HS of 100.0%; n = 3) at baseline led to a short PFS of < 2 months (Figs. 2, 3A and B). ESR1 status was known for all patients in the group with a low HS (< 25.0%). ESR1 mutations did not affect visualization of tumor lesions with [18F]FES as all these patients had a low HS, consistent with [18F]FES binding to ER in (nearly) all tumor lesions identified on [18F]FDG PET. Unfortunately, for patients with 100% heterogeneity, the ESR1 status was unknown as it was not performed.

The on-treatment [18F]FES PET/CT scan performed in 15/16 (93.8%) patients showed no visible [18F]FES uptake in any lesions identified on the baseline scan (Fig. 4A and B). Quantitative analyses showed a decrease in [18F]FES uptake during treatment from 75.3% up to 98.3%, unrelated to the dose of rintodestrant (Spearman’s rho, P = 0.65) and PFS (Spearman’s rho, P = 0.98; after correction for multiple testing; P = 0.98; Supplementary Table S5).

At time of progression, 11 of 16 (68.8%) patients underwent an [18F]FES PET/CT scan. Seven of them (63.6%) were scanned late after end of treatment (EoT), i.e., ≥ 5–16 days after the last dose of the drug. In all these patients, with [18F]FES uptake at baseline, [18F]FES uptake returned in tumor lesions. In 2 patients no [18F]FES uptake was found, in accordance with their [18F]FES negative baseline scan, despite having an ER+ tumor based on IHC. The remaining 4/14 (28.6%) patients were scanned shortly after EoT, i.e., within ≤ 24 hours, and in these patients no [18F]FES uptake was found in the tumor lesions (Fig. 4B), supporting continued selective downregulation of ER by still available rintodestrant (half-life in blood of rintodestrant: ≈ 16 hours; ref. 26).

Lesional analysis and total tumor burden

For the 80 lesions with highest uptake on [18F]FDG and/or [18F]FES PET, the majority of these had high uptake on both scans (n = 50),
versus 20 and 10 lesions that had only high uptake on [18F]FDG and [18F]FES PET/CT, respectively. Lesions were predominantly located in bone (n = 63) and the remainder in lymph nodes (n = 8), lung (n = 1), adrenal glands (n = 2), ovaries (n = 2), subcutaneous tissue (n = 2), and soft tissue (n = 2; Supplementary Fig. S1). SUV\text{max} and SUV\text{peak} of both tracers showed a moderate correlation with an $R^2$ of 0.5 and 0.6, respectively (Supplementary Fig. S2). Quantitative parameters (volume, SUV\text{max}, SUV\text{peak}, SUV\text{mean}, TBR, TLG, TL–ER) showed a trend that patients with a PFS $\geq$ 2.0 months had lesions with higher [18F]FDG and [18F]FES uptake than patients with a PFS of < 2.0 months (Mann–Whitney U test, $P < 0.04$, after correction for multiple testing, $P < 0.04$; Fig. 5A and B; Supplementary Fig. S3; Supplementary Table S6). Overall, quantitative parameters were not affected by the presence of ESR1 mutations (Mann–Whitney U test, $P > 0.05$; Supplementary Fig. S4). However, a trend could be observed showing higher tracer uptake in patients with an ESR1 mutation than in patients with an ESR1 wild-type.

MTV correlated with PFS (Spearman’s rho, $P = 0.02$; after correction for multiple testing, $P = 0.03$) while %ERTV did not (Spearman’s rho, $P = 0.28$; after correction for multiple testing, $P = 0.29$; Fig. 6A and B). However, regarding %ERTV, 2 groups could be distinguished (Fig. 6B): patients with a large range of %ERTV with a very short PFS and patients with a high %ERTV and long PFS.

**Discussion**

In this study, we found that patients with ER+ metastatic breast cancer with no uptake on [18F]FES PET/CT imaging at baseline do not respond to rintodestrant. In addition, patients with a high HS, i.e., low concordance between [18F]FDG and [18F]FES positive lesions, have a
short PFS. This is in line with previous studies showing that patients with partial or complete discordant scans have a higher risk of progressive disease and a shorter time to progression (8, 12, 22, 32). Potentially ER is still expressed (as identified on IHC), but it is likely that it is afunctional and therefore these patients will not respond to ER-targeted therapy. On the other hand, patients with a low HS, i.e., more concordance between $^{18}$F-FDG- and $^{18}$F-FES uptake in tumor lesions, have a prolonged PFS. These scan results may indicate a more homogeneous ER+ disease responsive to endocrine therapy, which is supported by previous studies (8, 12, 22). Prospective data of the IMPACT-MBC (NCT01957332) and the SONImage trial (NCT04125277), including patients with ER+ metastatic breast cancer who have undergone $^{18}$F-FDG PET/$^{18}$F-FES PET imaging at baseline and who have received endocrine treatment, are eagerly awaited to confirm that $^{18}$F-FES PET/CT imaging (in combination with $^{18}$F-FDG PET) can be used as a predictor for response to ER-targeted therapy and patient selection.

An interesting finding is that the presence of ESR1 mutations did not affect $^{18}$F-FES uptake. ESR1 mutations stabilize ER in an active conformation in the absence of ligand which results in constitutive activity, increased basal activity, and proteolytic stability, enhancing cancer growth, metastasis and resistance (33). However, (pre-)clinical investigations demonstrated that the most common ER mutations (including Y537S/N/C) do not directly affect the estradiol binding site.

**Figure 5.**
Relationship between the SUV$_{peak}$ values (median of all lesions per patient) and PFS for $^{18}$F-FDG (A) and $^{18}$F-FES (B). Data show that patients with a PFS $\geq$2.0 months have lesions that are metabolically more active and have higher ER expression than patients with a PFS of $<2.0$ months (Mann-Whitney U test). * P < 0.01.

**Figure 6.**
Relationship between MTV and PFS (A) and %ERTV and PFS (B). MTV correlated with PFS (Spearman’s rho, $P = 0.02$) while %ERTV did not (Spearman’s rho, $P = 0.30$).
As demonstrated in this trial, \(^{[18]}\text{F}\)FES PET retains its capacity to identify ER+ disease regardless of the ESR1 mutation status (8, 34). Importantly, in our study it was found that patients with ESR1 mutations respond well to rintodestrant. Various clinical trials (including the FERGI, SoFEA, EFFECT and PALOMA-3) have shown that ESR1 mutations do not predict poor response to SERDs such as fulvestrant (33). Our results support further development of rintodestrant as one of the novel SERDs that have been developed to retain effectivity despite ESR1 mutations (33).

Regarding uptake, patients with high \(^{[18]}\text{F}\)FES uptake at baseline have a longer PFS (≥ 2 months) compared with patients with low/absent \(^{[18]}\text{F}\)FES uptake. Indeed, high \(^{[18]}\text{F}\)FES uptake is consistent with high ER expression (35), which is a prerequisite for a (better) response to endocrine treatment. For \(^{[18]}\text{F}\)FDG uptake most publications report an association with high uptake and a worse prognosis in ER+ breast cancer (6, 36, 37). In our cohort patients with a PFS ≥ 2 months appeared to have a higher \(^{[18]}\text{F}\)FDG uptake than those with a short PFS, however the reported cutoffs for poor versus good prognosis for \(^{[18]}\text{F}\)FDG uptake vary largely, i.e., SUVmax from 2.2 to SUVmax of 10.35 (6, 36, 37). Regarding the reported lowest cutoff of SUVmax 2.2 (6), 3 of 5 patients with a \(^{[18]}\text{F}\)FDG SUVmax < 2.2 did (almost) not have \(^{[18]}\text{F}\)FES uptake thus no response could be expected. One of the other patients had heavily pretreated ductolobular carcinoma. Also the highest cutoff of 10.35 was not informative, as only 2 patients in our cohort had higher \(^{[18]}\text{F}\)FDG uptake. Investigating potential confounding factors, \(^{[18]}\text{F}\)FES uptake was (nearly) absent in 4 of 8 patients in the PFS < 2 months group, which is a strong predictor of endocrine therapy-resistant disease. In 3 of the 4 other patients with PFS < 2, the tumor type (ductal invasive) tumor which often has lower \(^{[18]}\text{F}\)FDG uptake than lobular breast cancer (38). Other confounding factors including tumor heterogeneity, pretreatments, histologic tumor characteristics (tumor subtype, PR), mutation status, number of lesions, location of lesions and presence of liver lesions, could not explain our results. Future larger prospective studies in a homogeneous population are awaited to further elucidate the relation of \(^{[18]}\text{F}\)FDG uptake. In combination with \(^{[18]}\text{F}\)FES PET uptake to outcome.

To understand how the total tumor burden is related to PFS, it is important to note that the tumor burden is determined accurately. However, the volumes for different tracers (in this case \(^{[18]}\text{F}\)FDG and \(^{[18]}\text{F}\)FES are by definition different due to differences in distribution, binding characteristics and applied thresholds. In case a matching threshold can be defined, correct volume determination would require accurate co-registration and warping of \(^{[18]}\text{F}\)FDG and \(^{[18]}\text{F}\)FES lesions. In addition, the volumes defined by threshold of a tracer signal do not match the anatomic volume (in case of \(^{[18]}\text{F}\)FDG and \(^{[18]}\text{F}\)FES negative lesions). For \(^{[18]}\text{F}\)FDG, it was found that the number of \(^{[18]}\text{F}\)FDG negative lesions was relatively low (29 of 1,051 lesions) and that MTV correlated with PFS, which is contrary to our hypothesis and what is known from previous studies (23–25). These results are in line with the lesional analysis. Regarding \(^{[18]}\text{F}\)ERTV, some patients with a high \(^{[18]}\text{F}\)ERTV responded well to rintodestrant with a long PFS, consistent with ER pathway depending disease that can effectively be treated with endocrine treatment. The extent of ER+ tumor burden does not seem to preclude effectivity. Other patients with a very short PFS had a large range of \(^{[18]}\text{F}\)ERTV, potentially indicating patients that do not respond to rintodestrant due to reduced ER expression or resistance due to previous treatments received.

\(^{[18]}\text{F}\)FES PET/CT imaging can also be used during SERM/SERD treatment to visualize mode of action and completeness of the ER blockade (7, 17, 20, 21). One study showed a decrease in \(^{[18]}\text{F}\)FES uptake > 87% in patients who received the novel SERD SAR439859 (20). For the novel SERD elacestrant, either 200 mg or 400 mg per day, led to a median reduction in tumor \(^{[18]}\text{F}\)FES uptake of up to 90.0%, regardless of the dose (21). This is in line with our study as we found an overall decrease of > 75.0% in \(^{[18]}\text{F}\)FES uptake during treatment with ≥ 400 mg of rintodestrant. As we did not observe any \(^{[18]}\text{F}\)FES uptake above background with visual analyses, the results are consistent with complete inactivation of functional ER by dose levels of 400 mg and above.

To better understand the mode of action and resistance to rintodestrant, \(^{[18]}\text{F}\)FES PET/CT imaging was also performed at the time of radiographically proven progressive disease. Patients were scanned ≤ 24 hours (within the first half life of the drug: ∼16 hours) to investigate whether the drug was still active. Indeed, none of the \(^{[18]}\text{F}\)FES positive lesions identified at baseline could be visualized in these patients. As these patients had progressive disease despite the fact that rintodestrant still interfered with ER, it is likely that other ER independent resistance pathways were activated in these patients causing disease progression. The remaining patients were scanned ≥ 7 half-lives after the last dose of drug (presumably no significant amount of drug remained in circulation), demonstrating the reversibility of the ER downregulation/blocking, as \(^{[18]}\text{F}\)FES uptake in the lesions returned on the \(^{[18]}\text{F}\)FES PET. Thus, despite a relatively low number of patients, consecutive imaging allows gaining a better understanding of the mode of action of rintodestrant.

To conclude the outcomes of this study, the data shows that absence of ER expression as measured with \(^{[18]}\text{F}\)FES PET is a predictor for no response to endocrine treatment such as rintodestrant. ESR1 mutations did not affect \(^{[18]}\text{F}\)FES uptake which is of special interest as a biomarker for SERDS which have been developed as active drugs in ESR1 mutated tumors. \(^{[18]}\text{F}\)FES uptake during treatment and at time of progression can be used to monitor the (reversible) effect of therapy and continued mode of action of SERDs, making it a useful tool in the development of these novel endocrine drugs.

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Conceptualization, software, formal analysis, investigation, methodology, writing-review and editing, C.W. Menke-van der Houwen van Oordt: Conceptualization, data curation, supervision, methodology, writing-review and editing.

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References


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Note

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