Whole-body PET imaging in metastatic breast cancer with a focus on hormone receptors

J. Boers, MSc, PhD
July 5, 2023
Rijksuniversiteit Groningen

Promotors:
C.P. Schröder, MD, PhD
Prof. G.A.P. Hospers, MD, PhD
Prof. A.W.J.M. Glaudemans, MD, PhD
Prof. E.F.J. de Vries, PhD

Introduction

Breast cancer is the most common type of cancer diagnosed in women; a women's lifetime risk of breast cancer is about 1 in 7. Approximately 5-6% of women present with metastatic breast cancer at diagnosis, and still 26% of women diagnosed with breast cancer develop distant metastases. The clinical course and prognosis of metastatic breast cancer depends on many factors, with hormone receptor expression being one of the most important ones. Nowadays, a biopsy is considered the 'gold standard' for determining hormone receptor expression profiles in metastatic breast cancer. However, this technique has limitations: it cannot always be performed safely due to the location of the lesion, may lead to sampling errors, and may not be predictive for all lesions, since heterogeneity of receptor expression exists between tumor lesions. Whole-body positron emission tomography (PET) imaging does not have these limitations.

Hormone receptors can be visualized by whole-body PET imaging, for example the estrogen receptor (ER). ER is expressed by the large majority of breast cancers, and can be visualized by means of 16α-[^{18}F]-fluoro-17β-estradiol ([^{18}F]FES)-PET. Whole-body information of ER expression in all tumor lesions within a patient may play an increasingly important role in clinical practice in the near future, when heterogeneity is taken into consideration in an optimized treatment plan for patients. In the Netherlands, [^{18}F]FES-PET scans can be performed in clinical practice for patients with ER-positive breast cancer with a remaining clinical dilemma despite standard workup.
In this thesis, we evaluated several aspects of whole-body PET imaging in patients with metastatic breast cancer. We focused on hormone receptor imaging, which is on the brink of implementation into clinical care. This thesis covers technical validation, clinical research as well as real life clinical practice aspects of whole-body PET imaging.

Technical validation of [^{18}F]FES-PET

Optimal interpretation of [^{18}F]FES-PET images is essential in clinical care. However, this can sometimes be challenging due to high physiological [^{18}F]FES uptake in the liver, gall bladder and gastrointestinal tract. All radiolabeled estrogens are rapidly metabolized in the liver and excreted via the bile ducts into the gastrointestinal tract. High physiological [^{18}F]FES uptake in the abdomen is a limitation of this PET tracer. Therefore, we investigated the effect of food intake prior to PET acquisition on abdominal background activity in [^{18}F]FES-PET scans. We hypothesized that eating a fatty meal before [^{18}F]FES-PET would lead to faster excretion, resulting in less disturbing physiological [^{18}F]FES uptake in the upper abdominal region. We investigated in an exploratory study whether abdominal [^{18}F]FES uptake was different between patients who had eaten a chocolate bar (fatty meal) between tracer injection and [^{18}F]FES-PET acquisition, had fasted before PET acquisition, or had no dietary restrictions before tracer injection (1). We found that eating chocolate decreased physiological [^{18}F]FES uptake in the gall bladder and stomach lumen, when compared to fasting. This might be caused by accelerated passage of the tracer. However, eating chocolate did not significantly decrease [^{18}F]FES uptake further compared to a normal diet. It is important to bear in mind that a fasting protocol is less patient-friendly compared to the other two protocols. The high physiological [^{18}F]FES uptake of the liver also complicates the evaluation of the ER status of liver metastases by means of [^{18}F]FES-PET. Consequently, liver metastases are often excluded from the analysis of [^{18}F]FES-PET studies. Therefore, we investigated whether [^{18}F]FES-PET/CT can be used to determine the ER status

of liver metastases in patients with breast cancer (2). We found that the ER status in most liver metastases can be determined with [^{18}F]FES-PET/CT, if correction for background and separate thresholds for ER-positive and ER-negative metastases are applied. Visual analysis is an important first step in detecting liver metastases on [^{18}F]FES-PET/CT and as a second step, quantitative analysis is needed. Although it is not clear yet whether our methodology would be clinically useful, our results at least provide guidance for the classification of a part of the liver metastases with [^{18}F]FES-PET/CT.

[^{18}F]FES-PET in clinical practice

[^{18}F]FES-PET can be used in clinical practice to support treatment decision-making, particularly for patients with breast cancer presenting with a clinical dilemma. A clinical dilemma may arise when a metastasis biopsy to determine the ER status cannot be performed safely or when ER heterogeneity is suspected between tumor lesions. Therefore, we assessed the value of [^{18}F]FES-PET in a large retrospective patient cohort (100 [^{18}F]FES-PET scans performed in 83 patients with (suspected) ER-positive metastatic breast cancer) by evaluating if the physician's clinical dilemma that remained after standard workup was solved by the [^{18}F]FES-PET scan (3). We showed that the [^{18}F]FES-PET scan can help to solve most of these clinical dilemmas (87%), in particular: 1) inability to determine the extent of (suspected) metastatic disease with standard workup (n=52), 2) unclear ER status of the tumor (n=31), and 3) inability to determine which primary tumor caused metastases (n=17). The clinical dilemma was solved more frequently if the scan showed [^{18}F]FES-positive disease than [^{18}F]FES-negative disease. We found that [^{18}F]FES-PET improves the physician's understanding of the disease status in patients with breast cancer and provides information for personalized treatment decision-making. [^{18}F]FES-PET can be a good alternative tool if a biopsy is not possible or does not solve the dilemma. These findings can potentially support further clinical implementation of [^{18}F]FES-PET.

Tumor response prediction using whole-body PET imaging

In recent years, cyclin-dependent kinase (CDK) 4/6 inhibitors in combination with endocrine treatment have proven to be a powerful treatment for patients with ER-positive

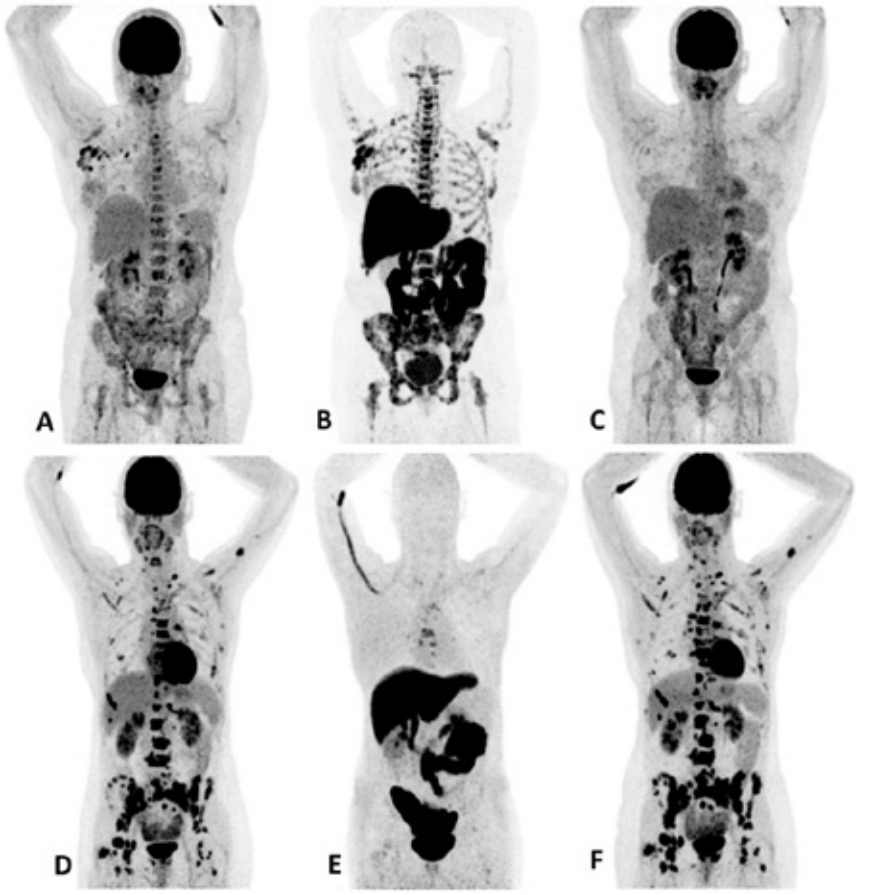

Figure 1. Examples of PET images of a metastatic breast cancer patient that responded to palbociclib plus letrozole (A, B, C) and one patient that did not respond (D, E, F). *Upper row responder:* Baseline FDG-PET (A) shows pathological uptake in axillary lymph nodes (right side) and in nearly all vertebrae and pelvic bones. Image B shows the baseline FES-PET with pathological ER expression in the axial skeleton (including vertebrae, pelvic bones, proximal humeri and femora) and in axillary lymph nodes (right side). After 8 weeks the FDG-PET (C) showing almost complete metabolic response (just some slightly elevated uptake in the axillary lymph nodes). The patient has been on treatment for more than 70 weeks. *Lower row non-responder:* Baseline FDG-PET (D) shows pathological uptake in multiple skeletal lesions. Image E shows the baseline FES-PET with only some increased ER expression in thoracic vertebrae. After 8 weeks the FDG-PET (F) showing no metabolic response, even some increase in the pathologic uptake in the multiple skeletal lesions.

metastatic breast cancer. Although the addition of CDK 4/6 inhibitors to endocrine treatment improves survival compared to endocrine treatment alone, in a subset of patients the combination is not wanted (due to non-response) or not needed (due to excellent response to endocrine treatment alone). Also in light of toxicity and high costs of the combined treatment, biomarkers for response are clearly needed. A biopsy cannot rule out ER heterogeneity, however, whole-body [^{18}F]FES-PET can solve this by assessment of ER expression of all the tumour lesions. Therefore, we assessed whether [^{18}F]FES-PET could serve as potential biomarker to identify patients with ER-positive metastatic breast cancer most likely to benefit from the combination regimen. We explored in a feasibility study whether the tumor ER heterogeneity percentage, as determined by [^{18}F]FES- and [^{18}F]FDG-PET/CT, was related to response to the treatment with the aromatase inhibitor letrozole and the CDK 4/6 inhibitor Palbociclib (4). We found that patients with 100% concordance (i.e. metastases were detected by both [^{18}F]FES- and [^{18}F]FDG-PET/CT) had a longer time to progression than patients with heterogeneous ER-positive disease or patients without ER-positivity. This is the first study exploring the concept of ER heterogeneity in relation to response to this combined treatment. These data suggest that this heterogeneity may be a biologically relevant entity to be considered in the management of breast cancer, which may potentially support identification of patients who benefit most (or least) from adding CDK 4/6 inhibitors to endocrine treatment. Whether ER heterogeneity is optimally assessed with molecular imaging, and whether it can be validated as biomarker for response, is currently investigated in larger studies. We are currently exploring FES/FDG-PET heterogeneity further in the SONImage study *(NCT04125277)*, a side study to the randomized Dutch SONIA trial in which patients with ER-positive metastatic breast cancer are treated with 1st line endocrine treatment +/- CDK 4/6 inhibition. For an example of the response to treatment with different combinations of [^{18}F]FDG-PET/CT and [^{18}F]FES findings in patients, see figure 1.

The androgen receptor

Like the ER, the androgen receptor (AR) is another potential endocrine target in breast cancer. This receptor is frequently expressed in ER-positive breast cancer but is also observed in triple-negative breast cancer. Whole-body PET with 16β-[^{18}F]-fluoro-5α-dihydrotestosterone ([^{18}F]FDHT) can be used for non-invasive visualization of AR. AR occupancy can be measured with [^{18}F]FDHT-PET, and a reduction in [^{18}F]FDHT uptake during AR-targeting therapy might be predictive for treatment response in patients with prostate cancer. This makes [^{18}F]FDHT-PET during AR-targeting treatment a potentially interesting tool for response prediction in patients with breast cancer as well. In a feasibility study of patients with AR-positive metastatic breast cancer, regardless of ER status, we studied the tumor uptake of [^{18}F]FDHT assessed by serial PET imaging before and during treatment with the AR antagonist bicalutamide (5). We found that it was feasible to detect a decline in [^{18}F]FDHT uptake during treatment, which was most pronounced in ER-negative metastases, but could not predict response to treatment. In ER-positive breast cancer AR agonists rather than antagonists may be more effective. We are currently exploring AR-targeting treatment further in the T&T trial, adding testosterone (an androgen agonist) to tamoxifen in male patients with metastatic breast cancer.

Conclusion

In this thesis we evaluated the opportunities of whole-body PET imaging in metastatic breast cancer, with a particular focus on hormone receptor imaging. We described essential steps towards clinical implementation, discussed solutions for high physiological tracer uptake, and showed in studies that whole-body PET imaging may potentially identify breast cancer subgroups who benefit from treatment, which can lead to more personalized medicine in patients with metastatic breast cancer. ♦

References

1. Boers J, Giatagana K, Schröder CP, Hospers GAP, de Vries EFJ, Glaudemans AWJM. Image quality and interpretation of [^{18}F]FES-PET: is there any effect of food intake? Diagnostics. 2020;10:756
2. Boers J, Loudini N, de Haas RJ, Willemsen ATM, van der Vegt B, de Vries EGE, et al. Analyzing the estrogen receptor status of liver metastases with [^{18}F]FES-PET in patients with breast cancer. Diagnostics. 2021;11:2019
3. Boers J, Loudini N, Brunsch CL, Koza SA, de Vries EFJ, Glaudemans AWJM, et al. Value of ^{18}F-FES PET in solving clinical dilemmas in breast cancer patients: a retrospective study. J Nucl Med. 2021;62:1214-20
4. Boers J, Venema CM, de Vries EFJ, Glaudemans AWJM, Kwee TC, Schuuring E, et al. Molecular imaging to identify patients with metastatic breast cancer who benefit from endocrine treatment combined with cyclin-dependent kinase inhibition. Eur J Cancer. 2020;126:11-20
5. Boers J, Venema CM, de Vries EFJ, Hospers GAP, Boersma HH, Rikhof B, et al. Serial [^{18}F]-FDHT-PET to predict bicalutamide efficacy in patients with androgen receptor positive metastatic breast cancer. Eur J Cancer. 2021;144:151-61