Imaging hormone receptors in metastatic breast cancer patients
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Chapter 1

General introduction and outline of the thesis
Breast cancer is still the most common cancer in women in the Western World and the most frequent cause of cancer-related death.\textsuperscript{1} For prognostic and therapeutic purposes knowledge of the expression levels of different receptors in the tumor is important. The estrogen receptor (ER) is expressed in about 70\% of breast cancer tumors. Patients with ER positive breast cancer have a more favorable prognosis compared to patients with ER negative breast cancer, and are likely to respond to antihormonal therapy.\textsuperscript{2} However not all ER positive patients do respond to antihormonal therapy.

Prediction of response and non-response is essential for optimal treatment and for the clinical development of new (combinations of) compounds. In breast cancer, the golden standard for determination of tumor ER expression is by immunohistochemistry on biopsy samples or surgically removed tissue. This technique has proven its value as predictive biomarker to select patients for hormone therapy.\textsuperscript{3} As tumor receptor status can change over time, current guidelines advise to perform biopsies when a lesion is first suspected, and in the metastatic setting to confirm receptor status, before initiating a new therapy.\textsuperscript{4} In ER-positive breast cancer, performing a biopsy is a particular challenge. First it is not always safe to biopsy a location or the lesion is difficult to access. And when a lesion is biopsied, sampling errors and complications can occur. Second, response to anti-hormonal treatment can be predicted by tumor ER status, but in the era of known disease heterogeneity, a single biopsy does not necessarily reflect the ER status of all lesions in the body. An alternative way to determine hormone expression is by whole body positron emission tomography (PET) imaging with tracers such as $16\alpha$-$[^{18}\text{F}]$fluoro-$17\beta$-estradiol (FES). This tracer has previously shown its ability to visualize and quantify ER-expression in all lesions within an individual patient, but to date is still considered experimental.\textsuperscript{5}

Not only the ER plays a vital role in the development and progression of breast cancer but also the androgen receptor (AR) seems to have a role in breast cancer. Several studies have shown that the AR is present in the majority of breast cancer patients and can be an attractive drug target.\textsuperscript{6,7} Based on preclinical studies, this offers a potential new treatment strategy.
The function of AR has mostly been described in prostate cancer, and multiple studies with the 16β-[¹⁸F]-fluoro-5α-dihydrotestosterone (FDHT) PET tracer have been performed in patients with prostate cancer to visualize the occupancy of AR during AR-targeted therapy⁸,⁹. In breast cancer patients no studies have been performed with FDHT PET. If FDHT-PET can determine the AR status in metastatic breast cancer patients, this technique has the potential to select patients eligible for AR-targeted therapies.

The aim of this thesis is to determine the feasibility of hormone receptor imaging via FES PET and FDHT PET in breast cancer patients and to evaluate the ability of these PET tracers to predict therapy response.

**Outline of the thesis**

FES is a PET tracer that has been used in a variety of preclinical and clinical studies to detect ER expression, mainly in breast cancer, but also in other oncological indications. Chapter 2 gives an overview of the main indications of FES PET in oncology and provides recommendations on the correct use of this imaging technique. This includes precautions that have to be taken for patient preparation, procedures for the acquisition of the scans, the physiological distribution of the tracer, factors that might influence tracer uptake and guidance for image analysis, quantification of tracer uptake and reporting of the scans.

With increasing experience in performing FES PET scans, also awareness of atypical, non cancer related FES uptake in the lungs of some patients was raised. This uptake is possibly related to previous radiation therapy. We investigated whether radiation therapy could cause enhanced pulmonary tracer uptake on the FES PET scan. While uptake of FES is considered to be ER specific, the influence of radiation therapy on FES PET is still unknown. Chapter 3 describes findings on FES PET scans after radiation therapy in 70 patients who have received radiation therapy and these findings were compared to 39 patients who did not receive radiation therapy prior to their FES PET. The results of this study could guide the interpretation of FES PET scans by nuclear medicine physicians.
Chapter 1

In Chapter 4 we retrospectively analyzed FES PET scans in patients with lobular breast cancer in 4 patients with a clinical dilemma. Lobular breast cancer is the second most common type of invasive breast cancer, accounting for almost ten percent of the invasive lesions. Lobular breast cancer lesions are often difficult to detect with conventional imaging. FES PET may have added value in relation to conventional staging in patients with lobular breast cancer and may support in clinical decision making.

In February 2015, the U.S. Food and Drug Administration granted accelerated approval to palbociclib for the use of palbociclib in combination with letrozole in postmenopausal women with ER positive, Human Epidermal Growth factor Receptor 2 (HER2) negative breast cancer as initial endocrine-based therapy. Palbociclib plus letrozole has improved both progression free survival and overall response rate in patients with measurable disease. However, it is still difficult to predict response to this treatment combination. It is presumed that the best biomarker for response to palbociclib is ER expression. In Chapter 5 we describe a feasibility study where we evaluate whether baseline FES PET results can predict treatment response to palbociclib plus letrozole. We hypothesized that lesions with low uptake on FES PET will not respond to the combination of letrozole plus palbociclib.

Chapter 6 comprises preclinical and clinical data on the androgen receptor in breast cancer. We summarized the role of the AR as a potential therapeutic target and performed in addition an in silico analysis of overexpression of AR with mRNA profiles of 7,270 primary breast tumors. As AR expression is not routinely assessed in breast cancers it is difficult to compare survival data. With this dataset we were able to get more uniform data in a large group of patients. In Chapter 7 we investigated whether assessment of AR and ER tumor receptor status by FDHT and FES PET is feasible in metastatic breast cancer patients. We quantified FDHT and FES uptake and correlated this with respectively AR and ER expression on immunohistochemistry of a fresh biopsy of a metastatic lesion. In Chapter 8 we described the effects on FDHT PET scans after treatment of bicalutamide, in AR-positive metastatic breast cancer patients. Bicalutamide is an oral, nonsteroidal AR antagonist, and part of standard of care in
patients with metastatic prostate cancer but not in breast cancer patients. In a phase II study in patients with metastatic breast cancer, a clinical benefit rate at 6 months was seen in 19% of the patients treated with bicalutamide.\textsuperscript{10} Although this rate is comparable to other treatment options in triple negative metastatic breast cancer patients, further improvement is clearly wanted. FDHT PET is able to visualize the AR-expression in metastatic breast cancer lesions, and uptake can be blocked by the addition of the AR antagonist flutamide and enzalutamide in prostate cancer patients.\textsuperscript{8,9} The AR occupancy, as reflected by the reduction in FDHT uptake during treatment with bicalutamide may be predictive of response, similar to change of ER uptake in relation to selective ER degrader therapy.\textsuperscript{11} The purpose of our study therefore was to evaluate whether FDHT PET imaging in metastatic breast cancer can be used to predict early treatment response to bicalutamide.

Not only FES PET and FDHT PET imaging have been performed in breast cancer patients, but also more PET data is available from other tracers. \textbf{Chapter 9} describes the process from development of PET tracers to the level of evidence for the use of these tracers in breast cancer. Several breast cancer trials have been performed with the PET tracers FDG, 3-\textsuperscript{[18F]}-3-deoxythymidine and FES. We studied them to assess how to optimize introducing novel tracers in clinical practice. After defining the gap between a good rationale for a tracer and implementation to the clinic, we propose solutions to fill the gap in order to try to bring more PET tracers to daily clinical practice.

The findings of this thesis are summarized in Chapter 10 followed by future perspectives with regard to the role of molecular imaging of hormone receptors in breast cancer. \textbf{Chapter 11} contains the Dutch summary.
References
