Molecular imaging of estrogen receptors
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Chapter 1

General introduction and outline of the thesis
INTRODUCTION

The majority (approximately 75%) of breast tumors express the estrogen receptor (ER). The ER functions as a transcription factor. When estrogen binds to the ER, the ER undergoes a conformational change, forms a dimer, and subsequently binds to DNA.\(^1\) At the DNA, under the influence of several co-regulatory proteins, the transcription of estrogen-responsive genes takes place. In breast cancer, transcription of estrogen-responsive genes results in proliferation and cell survival. Endocrine therapy can be used to interfere with this process by depleting circulating estrogens (via inhibition of aromatase), by competitive antagonism (\textit{e.g.} tamoxifen), or by decreasing ER expression (\textit{e.g.} fulvestrant). Aside from breast cancer there are several other tumor types in which the ER can be expressed, among which endometrial cancer, ovarian cancer and prostate cancer.\(^2\)

In endometrial cancer ER-targeted therapies are incorporated in clinical guidelines for recurrent and metastatic disease of the endometrioid subtype,\(^3\) and in ovarian cancer responses to ER-targeted therapies are reported in various clinical trials.\(^4-7\) Clearly, not all patients benefit from ER-targeted therapy. Therefore predictive markers are needed to select those patients that are most likely to respond to these therapies. Determination of tumor ER expression by immunohistochemistry is the standard procedure to evaluate ER status and has proven its value as predictive biomarker to select patients for endocrine therapies. In the past, ER expression was determined only at diagnosis. When metastatic disease would develop, the tumor characteristics were assumed to have remained the same in all lesions. There is currently emerging evidence that tumor ER status can change during disease progression and differ across lesions within a patient.\(^8,9\)

A novel way to determine ER expression is by positron emission tomography (PET) imaging of the ER with the tracer \(16\alpha-[^{18}\text{F}]\text{fluoro-17β-estradiol (}^{18}\text{F-FES)}\).\(^10\) This tracer has the potential to visualize and quantify ER expression in all lesions within an individual patient non-invasively.

The aim of this thesis is to address the clinical potential of \(^{18}\text{F-FES-PET imaging in patients with breast cancer and ovarian cancer.}\)

OUTLINE OF THE THESIS

In \textit{chapter 2}, we review the potential of PET imaging of the ER in breast cancer patients and discuss factors that can influence the uptake of \(^{18}\text{F-FES. Literature was searched to evaluate the different tracers that were developed for imaging of the ER. So far, all clinical studies have been performed with }^{18}\text{F-FES. The results of these studies were summarized to provide}}\)
an overview of the use of $^{18}$F-FES-PET 1) as a diagnostic tool, 2) to predict response to endocrine therapy, 3) to evaluate the heterogeneity of ER expression, and 4) to evaluate ER binding of endocrine drugs. Data were pooled to provide estimates of $^{18}$F-FES-PET sensitivity and specificity as well as its predictive value for response to endocrine therapy. Additionally, we evaluated the data on potential factors that can affect $^{18}$F-FES uptake in the tumor and which should therefore be taken into account in future clinical studies.

In chapter 3 we evaluate whether $^{18}$F-FES-PET can be used as an add-on diagnostic tool in case of clinical dilemmas. In 33 patients with an earlier ER positive breast tumor that presented with a clinical dilemma unresolved by standard work-up, $^{18}$F-FES-PET was performed. Referring physicians were required to fill in questionnaires before, shortly after and 3 months after $^{18}$F-FES-PET imaging to evaluate the contribution of $^{18}$F-FES-PET on diagnostic understanding and treatment decisions. In addition, $^{18}$F-FES-PET results were compared to conventional imaging, such as CT and bone scan in order to describe the number of lesions visualized, the distribution of the lesions per organ, quantitative tumor $^{18}$F-FES uptake, and the heterogeneity of $^{18}$F-FES uptake among lesions.

Also in other tumor types, such as endometrial stromal sarcoma (ESS), $^{18}$F-FES-PET could be valuable to guide treatment choices. In a case report (chapter 3A) concerning this rare tumor, $^{18}$F-FES-PET was performed in a patient with metastatic ESS to support treatment with the ER down-regulator fulvestrant. $^{18}$F-FES-PET was repeated after 6 months of therapy to evaluate the effects of fulvestrant on the availability of the ER. CT was used to determine treatment efficacy. In addition, a review of the literature is provided on the use of endocrine therapy in endometrial stromal sarcoma.

In metastatic breast cancer, the use of fulvestrant is approved since 2004. Although preclinical studies have shown that fulvestrant can completely abolish ER levels in cell lines and xenografts, it is unknown whether the dose currently given in the clinic is sufficient to completely abrogate the availability of ER. The aim of the study reported in chapter 4 is to evaluate residual ER availability during fulvestrant therapy by measuring the relative changes in $^{18}$F-FES uptake before and during treatment. Fifteen patients with metastatic breast cancer were treated with fulvestrant 500 mg intramuscularly on day 1, 14, 28 and every 4 weeks thereafter. $^{18}$F-FES-PET was performed prior to treatment initiation and after 28 and 84 days. A relative reduction of $\leq 75\%$ in tumor $^{18}$F-FES uptake with an absolute standardized uptake value ($\text{SUV}_{\text{max}}$) of $\geq 1.5$ was predefined as incomplete reduction in available ER. Additionally, plasma fulvestrant levels were determined by liquid-chromatography-tandem-mass-spectrometry to evaluate the correlation between plasma drug levels and effects on ER availability.
Whereas the most commonly used endocrine therapies in breast cancer focus on inhibition of ER signaling, also agonists such as estradiol can produce anti-tumor effects. Preclinical research has shown that long-term estrogen deprivation leads to adaptation of breast cancer cells by increasing ER expression. Although this adaptation allows the breast cancer cells to survive in an environment with a low estrogen concentration, higher doses of estradiol can now induce apoptosis of estrogen-deprived cancer cells. We therefore hypothesized that $^{18}$F-FES-PET could be a valuable predictive marker to select patients that would benefit from estradiol therapy by giving insights in tumor ER expression levels before treatment. In chapter 5, we describe a study in nineteen patients with metastatic breast cancer that underwent $^{18}$F-FES-PET imaging and were subsequently treated with estradiol. The treating physician and patients were blinded for $^{18}$F-FES-PET results. The positive and negative predictive value of $^{18}$F-FES-PET for clinical benefit (non-progression ≥ 24 weeks) was determined after final response classification of each patient. In addition, other potential markers of efficacy of estradiol treatment were measured, among which tumor markers and bone turnover markers.

In contrast to breast cancer, systemic endocrine therapy is not part of standard treatment in epithelial ovarian cancer, although ovariectomy is usually performed as part of debulking surgery. In clinical trials in recurrent disease, responses of ~15% have been noted for several ER-targeted drugs. There is however no know-how on how to select those patients that are most likely to respond. Most strikingly, despite the rationale to select patients based on ER expression, most studies have been performed in unselected groups of patients. In chapter 6 we evaluate the expression of two ER isoforms, the ERα and ERβ, as well as the expression of the progesterone receptor and androgen receptor (AR) in ovarian cancer patients. Tissue micro arrays were constructed from tissue of 121 ovarian cancer patients that were uniformly treated with docetaxel plus carboplatin in a prospective multicenter study. Hormone receptor expression was determined by immunohistochemistry and scored by two independent observers while blinded for patient survival data. Hormone receptor expression was thereafter compared with progression-free and overall survival to determine the prognostic value of hormone receptor expression. Also, heterogeneity in hormone receptor expression was evaluated in 69 patients from whom both primary ovarian tumor as well as omental metastasis tissue was available.

Aside from standard immunohistochemistry on surgical excised archival tissue, $^{18}$F-FES-PET may be of interest to select patients with ovarian cancer for endocrine therapy. The aim of chapter 7 was to evaluate whether it is feasible to visualize and quantify ER expression in ovarian cancer patients by means of $^{18}$F-FES-PET. A pilot study was performed in 15 ovarian cancer patients that would undergo debulking surgery. $^{18}$F-FES-PET was performed shortly
before surgery. CT was used to allocate and measure the size of tumor lesions. $^{18}$F-FES uptake was quantified for all lesions larger than 10 mm. Tissue was obtained at debulking surgery, which allowed the assessment of ER$\alpha$, ER$\beta$ and PR expression by immunohistochemistry in multiple lesions. Quantitative tumor $^{18}$F-FES uptake was compared to semi-quantitative immunohistochemistry scores.

The findings of this thesis are summarized in chapter 8. Current developments and future perspectives with regard to endocrine therapy and the role of molecular imaging of hormone receptors are discussed in the future perspectives.