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PET-CT Imaging in Breast Cancer Patients: New Tracers, Future Directions

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Abstract

Positron Emission Tomography using ^{18}F-fluoro-deoxi-glucose (FDG-PET) is giving a new perspective in disease staging and therapeutic response evaluation in daily oncological practice. To understand better the biological behavior and therapeutic response of breast cancer, new tracers and targets of molecular imaging are under investigation. These tracers may lead to non-invasive evaluation of the main, leading therapeutic decision-maker properties of metastatic breast cancer such as receptor status, proliferation activity and therapy resistance, and could also become predictive markers in the early measurement of therapeutic response in the neoadjuvant treatment of locally advanced breast cancer. However, these new agents are currently not available in the daily practice; the preliminary results are promising.

Keywords: PET-CT, breast cancer; FLT-PET, FES-PET; therapeutic response

Introduction

In the western world breast cancer is the most common malignancy and cause of cancer death in women second only to lung cancer [1]. Even though the incidence of breast cancer is rising in the last few decades, mortality appears to be declining [2], indicating a probable benefit from earlier detection and more effective treatments. Modern imaging techniques are excellent tools to reach this goal. Positron Emission Tomography (PET) is one of the imaging modalities which become successful not just in the staging of the disease, but in the therapeutic response evaluation, as well. The hybrid PET-CT imaging is a unique tool in the field of diagnostic imaging modalities: its main advantage is the ability to measure not just morphological, but also metabolical properties and even biological behavior of the tissues. These benefits increase the role of PET-CT diagnostics in oncology, especially in breast cancer diagnostics.

In PET-CT imaging the most widely used radiotracer is the 18F-fluoro-deoxi-glucose (FDG). FDG is a radio-labeled glucose analogue molecule which acts like a regular glucose until intracellular uptake via the glucose transporters (GLUTs) of the cell membrane. As the hexokinase enzyme phosphorylates the FDG, it is stuck in the cell, accumulating and reflecting the higher metabolic rate and glucose consumption of tumor tissues (the Warburg effect itself) [3]. With the additional CT imaging technique the sensitivity and specificity of FDG-PET-CT imaging is become remarkable in the staging of the disease, the detection of distant metastases and tumor recurrence as well [4-8].

Although in most countries in the daily clinical practice only FDG is available for PET-imaging, but the evolving new PET-CT tracers can give a new perspective in the determination of stage and in the evaluation of therapeutic response of tumors [9,10].

In our paper we review these new pathways of radiotracer researches in PET-imaging. To understand the mainstream of these researches, the tracers were divided into three main groups:

• Tracers in connection to the unique therapeutic agents of breast cancer, such as hormonal or anti-HER2 (Human Epidermal Growth Factor Receptor 2) therapies–specific breast cancer tracers

• Tracers which are–like FDG itself–related to cell proliferation and metabolism non-specifically for breast cancer, and

• Tracers linked to other pathways of tumor metabolism, such as the markers and inhibitors of angiogenesis, or to growth factor receptor families. (mostly under investigation)

Hormone receptor imaging with PET-CT

As Oude Munning et al. [11] suggested hormone receptor imaging could become a reasonable choice in the diagnosis and evaluation of recurrent and/or metastatic hormone positive breast cancer due to the fact that hormone receptor expression can vary between primary tumor and its recurrence in nearly 30% of the cases or even more [12-14]. Although it is possible to sample recurrent or metastatic tumors, in most cases sampling is troublesome or even impossible. For these patients a specific estrogen imaging method could be determinative for the later therapy giving the chance to analyze the whole tumor tissue with one imaging technique, avoid sampling errors and unnecessary delay in the appropriate treatment of cancer patients [15]–these are the guiding light of present and future researches with hormone receptor imaging techniques.

Estrogen receptor imaging

16-α-[^{18}F]-fluoro-17-β-estradiol (FES) is a suitable tracer for these goals. This radio-labeled ligand of the estrogen receptors (ER) was investigated since 1988 [16,17] and has been successful in the evaluation of hormone receptor status in breast carcinomas [18-20]. Further researches focused on the optimization of the imaging with FES PET by analyzing the blood clearance and its interactions with

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sex hormone binding globulins (SHBGs) [21,22]. Peterson et al. [23] recently demonstrated the significance of lean body mass adjusted FES-SUV calculations (SUV=Standardized Uptake Value) and also underlined the importance of the SHBG levels to optimize FES imaging techniques. In therapy monitoring Dehdashti et al. [24] also found interesting correlations between the therapeutic response to the endocrine treatment and FES-uptake: patients who were responding to tamoxifen treatment showed higher initial FES uptake (and also metabolic flare phenomenon with FDG tracers after the initiation of the therapy) than non-responders [19,24-26]. Linden et al. [27] found similar results with 6 months of hormonal treatment (i.e., tamoxifen), but the connection between FES-uptake and response to treatment was higher in patients with luminal A molecular subtype (only ER positive) tumors than with luminar B (both HER2 and ER positive) ones. Moreover, Linden et al. further analyzed the efficiency of FES imaging during different ER-blocking treatments. With tamoxifen and fulvestran treatment the eventually detected decline of FES caused by the treatment were higher than the treatment-related decline due to estrogen-depleting aromatase-inhibitor therapies [28]. In conclusion–as van Kruchten et al. [29] pointed out correctly–whole-body imaging of ER expression with FES-PET can become a valuable diagnostic modality but only if standard work-up is inconclusive, due to the possible variations and known limitations of FES scans [30]. A new agent, 4-fluoro-11β-methoxy-16α-[^{18}F]-fluoro-estradiol (4FMFES) developed by Paquette et al. achieved higher specific tumor uptake and also better contrast, i.e. tumor-to-background ratio than FES [31].

Progesterone receptor imaging

21-[^{18}F]fluoro-16-α-ethyl-19-norprogesterone (FENP) and 4-[^{18}F] fluoropropyl-tanaproget (FPTP) are developed to characterize the progesterone status of breast cancer patients [15]. Clinical studies with FENP [32] were not successful due to the high metabolism of the tracer (high hepatic uptake and non-specific bindings), but new agents, such as FPTP may overtake these difficulties [33]. Tanaproget is a non-steroidal progestin, binding highly specifically and sensitively to progesterone receptors which made it suitable as a potential agent for radio-labeling and using in PET imaging. Zhou et al. [34] investigated this agent *in vitro* and *in vivo*, and the early results indicated a potential benefit of FPTP in progesterone receptor imaging [35].

Moreover, Dehdashti et al. [36] also studied the uptake of a new agent, 21-[^{18}F]-fluoro-16a, 17a-[(R)-(19-a-furylmethylidene)dioxy]-19-norpregn-4-ene-3,20-dione (FFNP), a fluoro-labeled progesterone analogue.

They also found promising results with this agent, showing its safety and sensitivity to assess progesterone receptor status of women with newly diagnosed breast cancer.

Growth Factor Receptor Imaging

HER-2 receptor imaging

HER-2 is a member of the Epidermal Growth Factor Receptor (EGFR) family, which contains 4 transmembrane tyrosine kinase receptors. HER-2 receptor is over expressed in approximately 20% of all breast cancers. HER-2 over expression was identified as an indicator of poor prognosis and more aggressive disease [37-40]. HER-2 amplification and receptor over expression is extremely important in the treatment decision of breast cancer patients: to select the suitable patients for the targeted treatment of HER-2 with the monoclonal antibody, trastuzumab. To identify and quantify these receptors with imaging modalities is a highly investigated area due to the same reasons mentioned earlier with hormone receptor imaging: i.e., that HER-2 expression can vary during treatment and differ across metastatic lesions [11]. The main conception of the PET imaging of HER-2 receptors is to label trastuzumab and its fragments with positron emitting isotopes [41].

From the experiments of Smith-Jones, who used Hsp90 (heat shock protein 90) inhibitors to decrease HER-2 expression in mice and to monitor the changing, ^{68}Ga-DOTA-F(ab')$_2$-herceptin fragment PET was applied, successfully [42]. The ^{89}Zr-labeled trastuzumab revealed to be also a suitable agent for HER2-imaging [43,44], and also seemed to be advantageous in metastatic, HER2-positive breast cancer patients. The feasibility study of Dijkers et al. [45]–performed in 14 metastatic breast cancer patients–demonstrated the good visualization of HER-2 positive lesions with an appropriate 50 mg dose of ^{89}Zr-labeled trastuzumab in trastuzumab-naïve and 10 mg in pretreated patients.

After the first preliminary results with zirconium labeled trastuzumab PET, the researchers of the ZEPHIR study [46] also chose to apply ^{89}Zr-trastuzumab PET to measure the HER-2 expression before and after 3 cycles of T-DM1 treatment. T-DM1 is a trastuzumab-emtasin conjugate which contains trastuzumab and a maytansin derivate, a potent cytotoxic agent from the Vinca-alkaloid family, an effective, but expensive drug in anti-HER2 treatment. The rationales for this interventional, open-label study were the facts that the early identification of non-responder patients to T-DM1 could be cost-effective and help to avoid unnecessary side-effects by using ^{89}Zr-trastuzumab PET. The preliminary results of this study are expected to be published in the autumn of 2013, the end of the study will be in 2015 [46].

A new molecule, a fluorine-18 labeled HER2-binding affibody, the N-(2-(4-[^{18}F]fluoro-benzamido)ethyl)maleimide ([^{18}F]FBEM) conjugated $Z_{HER2:342}$-*Cys* is also a promising agent in HER2 imaging. Affibodies are highly stable proteins smaller than regular monoclonal antibodies, therefore easier penetrate in solid tumors with a rapid clearance from the blood-stream. Moreover the binding is unaffected by pretreatment with trastuzumab. This enables to use them as suitable carriers of radioisotopes. According to the preclinical studies [^{18}F] FBEM conjugated $Z_{HER2:342}$-*Cys* could be an optimal candidate for clinical applications [47-50]. However other randomized studies with larger number of enrolled patients will also be required to further analyze the significance of HER2-imaging in treatment planning and daily oncological practice.

HER-1 (EGFR) and IGF-1 receptor imaging

Other members of the epidermal growth factor receptor family are also showing significant correlations with the behavior of breast cancers, like HER1 (EGFR) over expression, which is more frequent in triple negative (estrogen, progesterone and also HER-2 negative) tumors [51,52]. The contribution of the over-expressed HER1 (EGFR) in the enhanced cell-proliferation in breast cancer by binding to the epidermal growth factor (EGF) or the transforming growth factor alpha (TGFα) was also reported by Meng et al. Therefore, antibody-based, affibody-based, or EGF-based molecular probes for EGFR imaging of breast cancer have been under investigation [53].

Type 1 insulin-like growth factor receptor (IGF-1R) is a transmembrane tyrosine kinase receptor which plays an important role in signaling cell survival and proliferation. Some preliminary studies also showed that IGF-1R-targeted therapy in breast cancer can be monitored by imaging of IGF-1R expression [53,54].

Tumor proliferation imaging–"beyond FDG"

FDG is highly specific for increased glucose metabolism and measurement of the presence of viable tumor tissues in the body. Although to measure the exact proliferation of the tumors more specific tracers are also under investigation. These special tracer molecules are currently available to study therapeutic response and tumor proliferation by measuring the rate of the cell membrane synthesis, or increased amino-, and nucleic-acid usage.

Amino-acid metabolism radiotracers

The pioneer of these molecules was the ^{11}C-methionine [55], an essential amino-acid molecule used by every cell of the human body, especially tumor cells to nourish their enhanced protein synthesis. ^{11}C-methionine incorporates in the newly synthesized proteins, allowing the imaging of the increased protein metabolism of cancers. ^{11}C-methionine uptake correlates fairly with the tumor proliferation in breast cancer patients and seemed to be useful in the measurement of therapeutic response. Based on the studies of a Finnish group we can conclude that metabolic changes in the amino-acid metabolism detected by ^{11}C-methionine-PET precede the clinical response [56,57].

Moreover, during the investigation the glutamine and glutamate metabolism of the tumors, the cystine/glutamate exchanger (xC-transpoter, xCT) also becomes a target for radiotracer imaging. Koglin et al. [58] found excellent tumor visualization and high tumor-to-backgorund ratios by using (4S)-4-(3-[18F]fluoropropyl)-L-glutamate (BAY 94-9392, also named [^{18}F]-FSPG) in preclinical tumor models. In Baek et al. study, [^{18}F]-FSPG showed promising results in the detection of breast tumors, however, the number of the examined patients (n=5) is limiting the value of these results [59]. Although we must underline the significance of these studies, due to the reason that [^{18}F]-FSPG is also developed to quantify glutathione-based drug resistance and oxidative stress-induced signaling pathways in which system xCT plays an important role by exchanging and transporting cystein to the cell [59].

DNA-synthesis radiotracers

Pyrimidine analogues–like ^{11}C-thymidine and ^{18}F-fluoro-deoxi-L-thymidine (FLT)–are also promising agents in PET imaging based on detecting cellular proliferation and enhanced nucleic acid usage of tumor cells which is believed to be more specific for tumor tissue than FDG. FLT-PET is already proved its suitability in the visualization of breast cancers [60,61] and evaluating the early changes after chemotherapy [62].

Moreover FLT-PET seems to be useful for predicting therapeutic response. Dittman et al. found promising results with FLT in response evaluation in their *in vitro* study [63], and–according to Pio et al.–FLT-PET was also a successful imaging method for the response evaluation after one administered cycle of chemotherapy and was also predictive for the long-term efficacy of the therapy by showing correlation with the late changes of tumor markers [64]. Recently Jolles et al. [65] are investigating the role of dynamic FLT-PET in the neoadjuvant treatment of breast cancer in their ongoing phase II study–FLT-PET is performed before the initiation of therapy, after 1 cycle and also after the completion of the treatment, the recruitment for the study is nearly ended [15]. Furthermore, Lubberink et al. [66] in their similarly structured study with dynamic FLT-PET imaging in locally advanced breast cancer patients treated with neoadjuvant chemotherapy, compared the effectiveness of tumor-to-whole blood ratio (TBR) measurements with the semi quantitative SUV (Standardized Uptake Value) results and suggested that TBR may be preferred to SUV when using FLT-PET imaging [67]. In conclusion FLT-PET may play a role in prediction of response to therapy in breast cancer patients, but further investigations are needed [11].

Phospholipid synthesis radiotracers

^{18}F-fluoro-ethyl-choline (FEC) and ^{11}C-choline which are integrated in the membrane phospholipid synthesis and ^{11}C-acetate, a marker of the lipid synthesis are currently used in the imaging of prostate cancer [68,69] and hepatocellular carcinomas [70].

The first study with ^{11}C-choline PET in breast cancer was performed by Contractor et al. to detect and separate clinically aggressive tumor phenotypes in patients with ER positive breast cancer. With ^{11}C-choline PET these tumors were visualized with good tumor-to-background ratio and the choline-uptake also correlated well with tumor grade [71]. These results were confirmed by Kenny et al. and also revealed that tumor response to trastuzumab therapy could be early assessed with choline-imaging only after one month treatment [72]. Contractor et al. [73] also found significant correlation between tumor proliferation and choline-uptake during PET scans, not just by investigating the correlations with the widely used pathological marker, the Ki-67 labeling index, but the ^{11}C-choline-uptake also correlated well with the proliferation measured by ^{18}F-fluoro-thymidine PET [73]. Tateishi et al. also examined the correlation between FDG-uptake and ^{11}C-choline-uptake in breast cancer patients. Although ^{11}C-Choline showed higher specificity for the detection of aggressive disease (the degree of mitosis was the only marker which was independently associated with higher SUV and TBR of ^{11}C-choline-PET/CTs), but by any other pathological and biological properties of the tumors FDG and choline tracer showed similar uptake-profile [74]. Eventually we can conclude that now FDG should still be preferred in daily clinical practice than choline, due to its easier production and wider availability.

Angiogenesis imaging

Angiogenesis is the physiological process of forming new blood vessels which is the key of tumor growth; therefore it could be a potential target for PET imaging.

VEGF-receptor

Radio-labeled anti-VEGF and Fab-fragments–like the earlier described tracers containing trastuzmuab–have been used for development of anti-angiogenesis imaging. ^{89}Zr-labeled bevacizumab showed clear and specific tumor localization in human ovarian cancer models [75]. Nagengast et al. reported similar results with ^{18}F-labeled ranibizumab, a Fab-fragment binding to VEGF [76,77], and also found good correlation between ^{89}Zr-bevacizumab uptake and therapeutic response to anti-angiogenic treatment *in vivo* in mouse-model with ovarian cancer xenografts [78]. The early experiences in breast cancer are also promising with ^{89}Zr-bevacizumab-PET-CT imaging, Gaykema et al. found significant correlation between VEGF-A levels and ^{89}Zr-bevacizumab uptake in 26 breast cancer patients [79].

Integrins

Integrins are cell adhesion receptors which are important in cell-cell interactions. Integrin $\alpha_v\beta_3$ has been shown to strongly correlate with tumor angiogenesis, and it has over expression on both endothelial and tumor cells in breast cancer. Integrin imaging originally based on the use of argininge-glycine-aspartic acid (RGD) based radioligands. McParland et al. [80] tested first the [^{18}F]-fluciclatide, also named [^{18}F]-AH111585 (AH111585 is a cyclic peptide containing RGD motif that

binds directly to integrin receptors such as $\alpha_v\beta_3$ with high affinity) in healthy volunteers to assess the safety and biodistribution of intergrin-tracers, with encouraging results. Beer et al. examined the tumor uptake of $\alpha_v\beta_3$-selective PET tracer ^{18}F-galacto-arginine-glycine-aspartic-acid (^{18}F-galacto) RGD in sixteen patients with primary (n=12) or metastatic breast cancer (n=4) and they found that all the primary tumors and metastases were clearly identified [53,81].

Other potential molecular imaging tracers

To investigate the chemo resistance and metastatic potential of tumors further PET-tracers are also under investigation. The earlier mentioned role of (*4S*)-4-(3-[^{18}F]fluoropropryl)-L-glutamate ([^{18}F] FSPG) [59] in the quantification of glutathione-based drug resistance is still under investigation. 1-[^{18}F]fluoroelacridar could be a suitable tracer for P-glycoprotein and breast cancer resistance protein detection, and also have potential benefits in the better understanding of the blood-brain barrier and ATP-driven efflux transport mechanisms [82]. Moreover, there are under consideration tracers against markers of the cell proliferation and metastatic potential such as radio-labeled agents against tumor growth factor-β receptor, platelet-derived growth factor-β receptor etc., which are currently under development or tested *in vitro* [11].

Conclusions

Development of new tracers in PET imaging could open a door for better understanding of the biological behavior of breast cancer, especially metastatic lesions and evaluate the heterogeneity and evolution of metastatic disease, due to the fact that biological behavior of breast cancer can differ between primary tumor and the metastases. The main advantage of PET imaging is the chance to avoid sampling errors of metastatic disease and spare the patient from unnecessary treatment and side-effects due to the chance of evaluating the whole-tumor with one single imaging test. PET imaging could enable repeated assessment of receptor status, proliferation activity and tumor viability in the near future. Subsequent imaging with different tracers could also be promising methods for these patients, but to apply these methods in the daily clinical practice, further investigations are needed.

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