

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

Tímea Tőkés^{1*}, Kornélia Kajáry², László Torgyik¹, Zsolt Lengyel², Tamás Györke^{3,4}, Magdolna Dank Med. Habil¹¹Department of Internal Medicine, Semmelweis University, Oncology Division, Budapest, Hungary²Pozitron-Diagnosztika Kft. Budapest, Hungary³Scanomed Kft. Budapest, Hungary⁴Department of Nuclear Medicine, Semmelweis University, Budapest, Hungary

Abstract

Positron Emission Tomography using ¹⁸F-fluoro-deoxy-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 metabolic 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-deoxy-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

¹⁶α-^{[18}F]-fluoro-¹⁷β-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

*Corresponding author: Tímea Tőkés M.D, Department of Internal Medicine, Oncology Division Semmelweis University, Faculty of Medicine, Budapest, Hungary, E-mail: tokes.timea@med.semmelweis-univ.hu

Received June 27, 2013; Accepted July 23, 2013; Published July 28, 2013

Citation: Tőkés T, Kajáry K, Torgyik L, Lengyel Z, Györke T, et al. (2013) PET-CT Imaging in Breast Cancer Patients: New Tracers, Future Directions. J Mol Imaging Dynam 2: 111. doi:10.4172/2155-9937.1000111

Copyright: © 2013 Tőkés T, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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 luminal 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-11 β -methoxy-16 α -[¹⁸F]-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-[¹⁸F]fluoro-16- α -ethyl-19-norprogesterone (FENP) and 4-[¹⁸F]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-[¹⁸F]-fluoro-16 α , 17 α -[(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, ⁶⁸Ga-DOTA-F(ab')₂-herceptin fragment PET was applied, successfully [42]. The ⁸⁹Zr-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 ⁸⁹Zr-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 ⁸⁹Zr-trastuzumab PET to measure the HER-2 expression before and after 3 cycles of T-DM1 treatment. T-DM1 is a trastuzumab-emptasin 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 ⁸⁹Zr-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-[¹⁸F]fluoro-benzamido)ethyl)maleimide ([¹⁸F]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 [¹⁸F] 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 (TGF α) 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 ¹¹C-methionine [55], an essential amino-acid molecule used by every cell of the human body, especially tumor cells to nourish their enhanced protein synthesis. ¹¹C-methionine incorporates in the newly synthesized proteins, allowing the imaging of the increased protein metabolism of cancers. ¹¹C-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 ¹¹C-methionine-PET precede the clinical response [56,57].

Moreover, during the investigation the glutamine and glutamate metabolism of the tumors, the cystine/glutamate exchanger (xCT) also becomes a target for radiotracer imaging. Koglin et al. [58] found excellent tumor visualization and high tumor-to-background ratios by using (4S)-4-(3-[¹⁸F]fluoropropyl)-L-glutamate (BAY 94-9392, also named [¹⁸F]-FSPG) in preclinical tumor models. In Baek et al. study, [¹⁸F]-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 [¹⁸F]-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 cysteine to the cell [59].

DNA-synthesis radiotracers

Pyrimidine analogues–like ¹¹C-thymidine and ¹⁸F-fluoro-deoxy-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

¹⁸F-fluoro-ethyl-choline (FEC) and ¹¹C-choline which are integrated in the membrane phospholipid synthesis and ¹¹C-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 ¹¹C-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 ¹¹C-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 ¹¹C-choline-uptake also correlated well with the proliferation measured by ¹⁸F-fluoro-thymidine PET [73]. Tateishi et al. also examined the correlation between FDG-uptake and ¹¹C-choline-uptake in breast cancer patients. Although ¹¹C-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 ¹¹C-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 trastuzumab–have been used for development of anti-angiogenesis imaging. ⁸⁹Zr-labeled bevacizumab showed clear and specific tumor localization in human ovarian cancer models [75]. Nagengast et al. reported similar results with ¹⁸F-labeled ranibizumab, a Fab-fragment binding to VEGF [76,77], and also found good correlation between ⁸⁹Zr-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 ⁸⁹Zr-bevacizumab-PET-CT imaging, Gaykema et al. found significant correlation between VEGF-A levels and ⁸⁹Zr-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 arginine-glycine-aspartic acid (RGD) based radioligands. McParland et al. [80] tested first the [¹⁸F]-fluciclatide, also named [¹⁸F]-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 integrin-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]fluoropropyl)-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.

References

1. <http://globocan.iarc.fr/>
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 365: 1687-1717.
3. Warburg O, Wind F, Negelein E (1927) THE METABOLISM OF TUMORS IN THE BODY. *J Gen Physiol* 8: 519-530.
4. Lin E, Alavi A (2009) PET and PET/CT: A Clinical Guide, 2nd ed. Thieme, New York, USA.
5. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, et al. (1993) Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. *J Clin Oncol* 11: 2101-2111.
6. Wahl RL (2001) Current status of PET in breast cancer imaging, staging, and therapy. *Semin Roentgenol* 36: 250-260.
7. Berriolo-Riedinger A, Touzery C, Riedinger JM, Toubreau M, Coudert B, et al. (2007) [^{18}F]FDG-PET predicts complete pathological response of breast cancer to neoadjuvant chemotherapy. *Eur J Nucl Med Mol Imaging* 34: 1915-1924.
8. Gennari A, Piccardo A, Altrinetti V, Corradengo D, Villavecchia G, et al. (2012) Whither the PET scan? The role of PET imaging in the staging and treatment of breast cancer. *Curr Oncol Rep* 14: 20-26.
9. Quon A, Gambhir SS (2005) FDG-PET and beyond: molecular breast cancer imaging. *J Clin Oncol* 23: 1664-1673.
10. Buck AK, Schirrmeyer H, Mattfeldt T, Reske SN (2004) Biological

characterisation of breast cancer by means of PET. *Eur J Nucl Med Mol Imaging* 31 Suppl 1: S80-S87.

11. Oude Munnink TH, Nagengast WB, Brouwers AH, Schröder CP, Hospers GA, et al. (2009) Molecular imaging of breast cancer. *Breast* 18 Suppl 3: S66-S73.
12. Spataro V, Price K, Goldhirsch A, Cavalli F, Simoncini E, et al. (1992) Sequential estrogen receptor determinations from primary breast cancer and at relapse: prognostic and therapeutic relevance. The International Breast Cancer Study Group (formerly Ludwig Group). *Ann Oncol* 3: 733-740.
13. Kuukasjärvi T, Kononen J, Helin H, Holli K, Isola J (1996) Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy. *J Clin Oncol* 14: 2584-2589.
14. Brunn Rasmussen B, Kamby C (1989) Immunohistochemical detection of estrogen receptors in paraffin sections from primary and metastatic breast cancer. *Pathol Res Pract* 185: 856-859.
15. Cintolo JA, Tchou J, Pryma DA (2013) Diagnostic and prognostic application of positron emission tomography in breast imaging: emerging uses and the role of PET in monitoring treatment response. *Breast Cancer Res Treat* 138: 331-346.
16. Mintun MA, Welch MJ, Siegel BA, Mathias CJ, Brodack JW, et al. (1988) Breast cancer: PET imaging of estrogen receptors. *Radiology* 169: 45-48.
17. McGuire AH, Dehdashti F, Siegel BA, Lyss AP, Brodack JW, et al. (1991) Positron tomographic assessment of 16 alpha-[^{18}F] fluoro-17 beta-estradiol uptake in metastatic breast carcinoma. *J Nucl Med* 32: 1526-1531.
18. Peterson LM, Mankoff DA, Lawton T, Yagle K, Schubert EK, et al. (2008) Quantitative imaging of estrogen receptor expression in breast cancer with PET and ^{18}F -fluoroestradiol. *J Nucl Med* 49: 367-374.
19. Mortimer JE, Dehdashti F, Siegel BA, Katzenellenbogen JA, Fracasso P, et al. (1996) Positron emission tomography with 2-[^{18}F]Fluoro-2-deoxy-D-glucose and 16alpha-[^{18}F]fluoro-17beta-estradiol in breast cancer: correlation with estrogen receptor status and response to systemic therapy. *Clin Cancer Res* 2: 933-939.
20. Dehdashti F, Mortimer JE, Siegel BA, Griffith LK, Bonasera TJ, et al. (1995) Positron tomographic assessment of estrogen receptors in breast cancer: comparison with FDG-PET and *in vitro* receptor assays. *J Nucl Med* 36: 1766-1774.
21. Mankoff DA, Tewson TJ, Eary JF (1997) Analysis of blood clearance and labeled metabolites for the estrogen receptor tracer [^{18}F]-16 alpha-fluoroestradiol (FES). *Nucl Med Biol* 24: 341-348.
22. Tewson TJ, Mankoff DA, Peterson LM, Woo I, Petra P (1999) Interactions of 16alpha-[^{18}F]fluoroestradiol (FES) with sex steroid binding protein (SBP). *Nucl Med Biol* 26: 905-913.
23. Peterson LM, Kurland BF, Link JM, Schubert EK, Stekhova S, et al. (2011) Factors influencing the uptake of ^{18}F -fluoroestradiol in patients with estrogen receptor positive breast cancer. *Nucl Med Biol* 38: 969-978.
24. Dehdashti F, Flanagan FL, Mortimer JE, Katzenellenbogen JA, Welch MJ, et al. (1999) Positron emission tomographic assessment of "metabolic flare" to predict response of metastatic breast cancer to antiestrogen therapy. *Eur J Nucl Med* 26: 51-56.
25. Dehdashti F, Mortimer JE, Trinkaus K, Naughton MJ, Ellis M, et al. (2009) PET-based estradiol challenge as a predictive biomarker of response to endocrine therapy in women with estrogen-receptor-positive breast cancer. *Breast Cancer Res Treat* 113: 509-517.
26. Mortimer JE, Dehdashti F, Siegel BA, Trinkaus K, Katzenellenbogen JA, et al. (2001) Metabolic flare: indicator of hormone responsiveness in advanced breast cancer. *J Clin Oncol* 19: 2797-2803.
27. Linden HM, Stekhova SA, Link JM, Gralow JR, Livingston RB, et al. (2006) Quantitative fluoroestradiol positron emission tomography imaging predicts response to endocrine treatment in breast cancer. *J Clin Oncol* 24: 2793-2799.
28. Linden HM, Kurland BF, Peterson LM, Schubert EK, Gralow JR, et al. (2011) Fluoroestradiol positron emission tomography reveals differences in pharmacodynamics of aromatase inhibitors, tamoxifen, and fulvestrant in patients with metastatic breast cancer. *Clin Cancer Res* 17: 4799-4805.
29. van Kruchten M, Glaudemans AW, de Vries EF, Beets-Tan RG, Schröder CP, et al. (2012) PET imaging of estrogen receptors as a diagnostic tool for breast cancer patients presenting with a clinical dilemma. *J Nucl Med* 53: 182-190.
30. Kurland BF, Peterson LM, Lee JH, Linden HM, Schubert EK, et al. (2011)

- Between-patient and within-patient (site-to-site) variability in estrogen receptor binding, measured *in vivo* by ¹⁸F-fluoroestradiol PET. J Nucl Med 52: 1541-1549.
31. Paquette M, Phoenix S, Ouellet R, Langlois R, van Lier JE, et al. (2013) Assessment of the Novel Estrogen Receptor PET Tracer 4-Fluoro-11β-methoxy-16α-[¹⁸F]fluoroestradiol (4FMFES) by PET Imaging in a Breast Cancer Murine Model. Mol Imaging Biol .
32. Verhagen A, Studeny M, Luurtsema G, Visser GM, De Goeij CC, et al. (1994) Metabolism of a [¹⁸F]fluorine labeled progestin (21-[¹⁸F]fluoro-16 alpha-ethyl-19-norprogesterone) in humans: a clue for future investigations. Nucl Med Biol 21: 941-952.
33. Jonson SD, Welch MJ (1998) PET imaging of breast cancer with fluorine-18 radiolabeled estrogens and progestins. Q J Nucl Med 42: 8-17.
34. Zhou HB, Lee JH, Mayne CG, Carlson KE, Katzenellenbogen JA (2010) Imaging progesterone receptor in breast tumors: synthesis and receptor binding affinity of fluoroalkyl-substituted analogues of tanaproget. J Med Chem 53: 3349-3360.
35. Lee JH, Zhou HB, Dence CS, Carlson KE, Welch MJ, et al. (2010) Development of [¹⁸F]fluorine-substituted Tanaproget as a progesterone receptor imaging agent for positron emission tomography. Bioconjug Chem 21: 1096-1104.
36. Dehdashti F, Laforest R, Gao F, Aft RL, Dence CS, et al. (2012) Assessment of progesterone receptors in breast carcinoma by PET with 21-18F-fluoro-16α,17α-[(R)-(1'-α-furylmethylidene)dioxy]-19-norpregn-4-ene-3,20-dione. J Nucl Med 53: 363-370.
37. Baselga J (2010) Treatment of HER2-overexpressing breast cancer. Ann Oncol 21 Suppl 7: vii36-40.
38. Slamon DJ (1987) Proto-oncogenes and human cancers. N Engl J Med 317: 955-957.
39. Slamon DJ, Clark GM (1988) Amplification of c-erbB-2 and aggressive human breast tumors? Science 240: 1795-1798.
40. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, et al. (1987) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235: 177-182.
41. Goldstein R, Sosabowski J, Vigor K, Chester K, Meyer T (2013) Developments in single photon emission computed tomography and PET-based HER2 molecular imaging for breast cancer. Expert Rev Anticancer Ther 13: 359-373.
42. Smith-Jones PM, Solit D, Afroze F, Rosen N, Larson SM (2006) Early tumor response to Hsp90 therapy using HER2 PET: comparison with 18F-FDG PET. J Nucl Med 47: 793-796.
43. Oude Munnink TH, Korte MA, Nagengast WB, Timmer-Bosscha H, Schröder CP, et al. (2010) (89)Zr-trastuzumab PET visualises HER2 downregulation by the HSP90 inhibitor NVP-AUY922 in a human tumour xenograft. Eur J Cancer 46: 678-684.
44. Dijkers EC, Kosterink JG, Rademaker AP, Perk LR, van Dongen GA, et al. (2009) Development and characterization of clinical-grade 89Zr-trastuzumab for HER2/neu immunoPET imaging. J Nucl Med 50: 974-981.
45. Dijkers EC, Oude Munnink TH, Kosterink JG, Brouwers AH, Jager PL, et al. (2010) Biodistribution of 89Zr-trastuzumab and PET imaging of HER2-positive lesions in patients with metastatic breast cancer. Clin Pharmacol Ther 87: 586-592.
46. Phase II Prospective Imaging Study Evaluating the Utility of Pre-treatment zr89 Labelled Trastuzumab PET/CT and an Early FDG-PET/CT Response to Identify Patients With Advanced HER2+ BC Unlikely to Benefit From a Novel antiHER2 Therapy: TDM1 /HER2 Imaging Study to Identify HER2 Positive Metastatic Breast Cancer Patient Unlikely to Benefit From T-DM1 (ZEPHIR).
47. Kramer-Marek G, Kiesewetter DO, Martiniova L, Jagoda E, Lee SB, et al. (2008) [¹⁸F]FBEM-Z(HER2:342)-Affibody molecule-a new molecular tracer for *in vivo* monitoring of HER2 expression by positron emission tomography. Eur J Nucl Med Mol Imaging 35: 1008-1018.
48. Kiesewetter DO, Krämer-Marek G, Ma Y, Capala J (2008) Radiolabeling of HER2 specific Affibody(R) molecule with F-18. J Fluor Chem 129: 799-805.
49. Lee SB, Hassan M, Fisher R, Chertov O, Chernomordik V, et al. (2008) Affibody molecules for *in vivo* characterization of HER2-positive tumors by near-infrared imaging. Clin Cancer Res 14: 3840-3849.
50. Puri A, Kramer-Marek G, Campbell-Massa R, Yavlovich A, Tele SC, et al. (2008) HER2-specific affibody-conjugated thermosensitive liposomes (Affisomes) for improved delivery of anticancer agents. J Liposome Res 18: 293-307.
51. Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, et al. (2004) Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res 10: 5367-5374.
52. Carey LA (2010) Directed therapy of subtypes of triple-negative breast cancer. Oncologist 15 Suppl 5: 49-56.
53. Meng Q, Li Z (2013) Molecular imaging probes for diagnosis and therapy evaluation of breast cancer. Int J Biomed Imaging 2013: 230487.
54. Majo VJ, Arango V, Simpson NR, Prabhakaran J, Kassir SA, et al. (2013) Synthesis and *in vitro* evaluation of [(18F)BMS-754807: A potential PET ligand for IGF-1R. Bioorg Med Chem Lett 23: 4191-4194.
55. Jansson T, Westlin JE, Ahlström H, Lilja A, Långström B, et al. (1995) Positron emission tomography studies in patients with locally advanced and/or metastatic breast cancer: a method for early therapy evaluation? J Clin Oncol 13: 1470-1477.
56. Leskinen-Kallio S, Nägren K, Lehtikoinen P, Ruotsalainen U, Joensuu H (1991) Uptake of 11C-methionine in breast cancer studied by PET. An association with the size of S-phase fraction. Br J Cancer 64: 1121-1124.
57. Huovinen R, Leskinen-Kallio S, Nägren K, Lehtikoinen P, Ruotsalainen U, et al. (1993) Carbon-11-methionine and PET in evaluation of treatment response of breast cancer. Br J Cancer 67: 787-791.
58. Koglin N, Mueller A, Berndt M, Schmitt-Willich H, Toschi L, et al. (2011) Specific PET imaging of xC- transporter activity using a [¹⁸F]-labeled glutamate derivative reveals a dominant pathway in tumor metabolism. Clin Cancer Res 17: 6000-6011.
59. Baek S, Choi CM, Ahn SH, Lee JW, Gong G, et al. (2012) Exploratory clinical trial of (4S)-4-(3-[¹⁸F]fluoropropyl)-L-glutamate for imaging xC- transporter using positron emission tomography in patients with non-small cell lung or breast cancer. Clin Cancer Res 18: 5427-5437.
60. Been LB, Elsinga PH, de Vries J, Cobben DC, Jager PL, et al. (2006) Positron emission tomography in patients with breast cancer using (18F)-3'-deoxy-3'-fluoro-L-thymidine ((18F)-FLT)-a pilot study. Eur J Surg Oncol 32: 39-43.
61. Smyczek-Gargya B, Fersis N, Dittmann H, Vogel U, Reischl G, et al. (2004) PET with [¹⁸F]fluorothymidine for imaging of primary breast cancer: a pilot study. Eur J Nucl Med Mol Imaging 31: 720-724.
62. Kenny L, Coombes RC, Vigushin DM, Al-Nahhas A, Shousha S et al. (2007) Imaging early changes in proliferation at 1 week post chemotherapy: a pilot study in breast cancer patients with 3'-deoxy-3'-[¹⁸F]fluorothymidine positron emission tomography. Eur J Nucl Med Mol Imaging 34: 1339-1347.
63. Dittmann H, Jusufoska A, Dohmen BM, Smyczek-Gargya B, Fersis N, et al. (2009) 3'-Deoxy-3'-[(18F)fluorothymidine (FLT) uptake in breast cancer cells as a measure of proliferation after doxorubicin and docetaxel treatment. Nucl Med Biol 36: 163-169.
64. Pio BS, Park CK, Pietras R, Hsueh WA, Satyamurthy N, et al. (2006) Usefulness of 3'-[¹⁸F]fluoro-3'-deoxythymidine with positron emission tomography in predicting breast cancer response to therapy. Mol Imaging Biol 8: 36-42.
65. Phase II Study of 3'-Deoxy-3'-¹⁸F Fluorothymidine (FLT) in Invasive Breast Cancer /ACRIN 6688 <http://www.acrin.org/TabID/597/Default.aspx/>
66. Lubberink M, Dierckx W, Emmering J, van Tinteren H, Hoekstra OS, et al. (2012) Validity of simplified 3'-deoxy-3'-[¹⁸F]fluorothymidine uptake measures for monitoring response to chemotherapy in locally advanced breast cancer. Mol Imaging Biol 14: 777-782.
67. Tehrani OS, Shields AF (2013) PET Imaging of Proliferation with Pyrimidines. J Nucl Med 54: 903-912.
68. Jadvar H (2011) Prostate cancer: PET with ¹⁸F-FDG, ¹⁸F- or ¹¹C-acetate, and ¹⁸F- or ¹¹C-choline. J Nucl Med 2011; 52 : 81-89.
69. Steiner Ch, Veas H, Zaidi H, Wissmeyer M, Berrebi O, et al. (2009) Three-phase ¹⁸F-fluorocholine PET/CT in the evaluation of prostate cancer recurrence. Nuklearmedizin 48: 1-9.
70. Ho CL, Yu SC, Yeung DW (2003) 11C-acetate PET imaging in hepatocellular carcinoma and other liver masses. J Nucl Med 44: 213-221.
71. Contractor KB, Kenny LM, Stebbing J, Al-Nahhas A, Palmieri C, et al. (2009)

- [11C]choline positron emission tomography in estrogen receptor-positive breast cancer. *Clin Cancer Res* 15: 5503-5510.
72. Kenny LM, Contractor KB, Hinz R, Stebbing J, Palmieri C, et al. (2010) Reproducibility of [11C]choline-positron emission tomography and effect of trastuzumab. *Clin Cancer Res* 16: 4236-4245.
73. Contractor KB, Kenny LM, Stebbing J, Challapalli A, Al-Nahhas A, et al. (2011) Biological basis of [^{11}C]choline-positron emission tomography in patients with breast cancer: comparison with [^{18}F]fluorothymidine positron emission tomography. *Nucl Med Commun* 32: 997-1004.
74. Tateishi U, Terauchi T, Akashi-Tanaka S, Kinoshita T, Kano D, et al. (2012) Comparative study of the value of dual tracer PET/CT in evaluating breast cancer. *Cancer Sci* 103: 1701-1707.
75. Nagengast WB, de Vries EG, Hospers GA, Mulder NH, de Jong JR, et al. (2007) In vivo VEGF imaging with radiolabeled bevacizumab in a human ovarian tumor xenograft. *J Nucl Med* 48: 1313-1319.
76. Nagengast W, De Vries E, Warnders F, Hospers G, Mulder N, et al. (2008) In vivo VEGF imaging with an anti-VEGF Fab-fragment in a human ovarian tumor xenograft model using MicroPET and MicroCT. *AACR Meeting Abstracts*; abstract #3161;pp: 42.
77. Nagengast WB, Lub-de Hooge MN, Hospers GA, Brouwers AH, Hoekstra JJ, et al. (2008) Towards clinical VEGF imaging using the anti-VEGF antibody bevacizumab and Fab-fragment ranibizumab. *J Clin Oncol*; 26: abstract #3547.
78. Nagengast WB, de Korte MA, Oude Munnink TH, Timmer-Bosscha H, den Dunnen WF, et al. (2010) 89Zr-bevacizumab PET of early antiangiogenic tumor response to treatment with HSP90 inhibitor NVP-AUY922. *J Nucl Med* 51: 761-767.
79. Gaykema SB, Brouwers AH, Lub-de Hooge MN, Pleijhuis RG, Timmer-Bosscha H, et al. (2013) 89Zr-Bevacizumab PET Imaging in Primary Breast Cancer. *J Nucl Med* 54: 1014-1018.
80. McParland BJ, Miller MP, Spinks TJ, Kenny LM, Osman S, et al. (2008) The biodistribution and radiation dosimetry of the Arg-Gly-Asp peptide 18F-AH111585 in healthy volunteers. *J Nucl Med* 49: 1664-1667.
81. Beer AJ, Niemeyer M, Carlsen J, Sarbia M, Nährig J, et al. (2008) Patterns of alphavbeta3 expression in primary and metastatic human breast cancer as shown by ^{18}F -Galacto-RGD PET. *J Nucl Med* 49: 255-259.
82. Dörner B, Kuntner C, Bankstahl JP, Wanek T, Bankstahl M, et al. (2011) Radiosynthesis and in vivo evaluation of 1- ^{18}F fluoroelacridar as a positron emission tomography tracer for P-glycoprotein and breast cancer resistance protein. *Bioorg Med Chem* 19: 2190-2198.

Citation: Tökés T, Kajáry K, Torgyik L, Lengyel Z, Györke T, et al. (2013) PET-CT Imaging in Breast Cancer Patients: New Tracers, Future Directions. *J Mol Imaging Dynam* 2: 111. doi:[10.4172/2155-9937.1000111](https://doi.org/10.4172/2155-9937.1000111)

Submit your next manuscript and get advantages of OMICS Group submissions

Unique features:

- User friendly/feasible website-translation of your paper to 50 world's leading languages
- Audio Version of published paper
- Digital articles to share and explore

Special features:

- 250 Open Access Journals
- 20,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.omicsonline.org/submission>

