Molecular imaging of breast cancer


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A R T I C L E I N F O 

Keywords: 
Breast cancer 
Staging 
Molecular imaging 
Positron emission tomography 
Single photon emission computed tomography 

S U M M A R Y 

Molecular imaging of breast cancer can potentially be used for breast cancer screening, staging, restaging, response evaluation and guiding therapies. Techniques for molecular breast cancer imaging include magnetic resonance imaging (MRI), optical imaging, and radionuclide imaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT). This review focuses on PET and SPECT imaging which can provide sensitive serial non-invasive information of tumor characteristics. Most clinical data are gathered on the visualization of general processes such as glucose metabolism with the PET tracer [18F]fluorodeoxyglucose (FDG) and DNA synthesis with [18F]fluoro-L-thymidine (FLT). Increasingly more breast cancer specific targets are imaged such as the estrogen receptor (ER), growth factors and growth factor receptors. Imaging of the ER with the PET tracer 16α-[18F]fluoro-17β-estradiol (FES) has shown a good correlation between FES tumor uptake and ER density. 111In-trastuzumab SPECT to image the human epidermal growth factor receptor 2 (HER2) showed that in most patients with metastatic HER2 overexpressing disease more lesions were detected than with conventional staging procedures. The PET tracer 89Zr-trastuzumab showed excellent, quantifiable, and specific tumor uptake. 111In-bevacizumab for SPECT and 89Zr-bevacizumab for PET-imaging have been developed for vascular endothelial growth factor (VEGF) imaging as an angiogenic marker. Lastly, tracers for the receptors EGFR, IGF-1R, PDGF-βR and the ligand TGFβ are under development. Although molecular imaging of breast cancer is still not commonly used in daily clinical practice, its application portfolio is expanding rapidly.

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Introduction 

Current screening and staging techniques for breast cancer give a non-perfect diagnostic yield.1 In addition, optimal treatment with targeted therapies often requires knowledge about the expression of their targets within the tumor lesions. Molecular imaging of tumor metabolism, proliferation and other more tumor specific targets may therefore be of additional value in breast cancer management. It can potentially be used for breast cancer screening, staging, restaging, response evaluation and guiding surgery, radiotherapy and systemic treatment. Additionally, molecular imaging can be a useful tool in targeted drug development and for translating breast cancer science.2,3 

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Molecular imaging has been defined by the Society of Nuclear Medicine as the visualization, characterization and measurement of biological processes at the molecular and cellular levels in humans and other living systems.4 Molecular imaging of breast cancer is an emerging field. It can be performed with various imaging modalities. Ligands used for this purpose can be labeled with either a contrast agent for magnetic resonance imaging (MRI), a fluorescent dye for optical imaging, a positron emitting radionuclide for positron emission tomography (PET) or a gamma emitting radionuclide for single photon emission computed tomography (SPECT) imaging. This review will focus on PET and SPECT molecular breast cancer imaging given the high sensitivity of nuclear imaging, with up to 1 million times more sensitivity in detecting molecular probes than other imaging modalities, and available results. Both PET and SPECT molecular imaging are based on the detection of radiolabeled (tumor specific) ligands. Radioisotopes are chosen based on the proposed imaging modality, PET or SPECT, and the physical half-life of the radioisotope ideally should match the biological half-life of the ligand. Radioisotopes used for PET imaging
Fig. 1. Schematic presentation of the (potential) targets for breast cancer molecular imaging.

(e.g. $^{18}$F, $^{11}$C, $^{15}$O, $^{13}$N, $^{64}$Cu, $^{124}$I, $^{89}$Zr) emit positrons during radioactive decay. After combining with an electron, the positron and electron are annihilated and their combined masses are converted into two gamma photons of 511 keV each, emitted in 180° opposite directions. The photons thus produced, are available for detection by a PET camera, in which two paired detectors both register a photon simultaneously (coincidence detection). Radioisotopes used in SPECT imaging ($^{111}$In, $^{99m}$Tc, $^{123/125}$I) emit single gamma photons which can be detected with a gamma camera. As single photons offer no information about the direction of travel, the direction of detected photons is fixed by using a collimating lead filter (collimator). This collimator has small parallel holes which reject the photons not traveling perpendicular to the detector surface. SPECT imaging uses rotating gamma camera heads for acquiring multiple 2D projections, and a computer algorithm for reconstruction to 3D images. The relatively limited sensitivity of SPECT reduces its statistical strength for quantitative interpretation. However in general, SPECT is a less expensive technique than PET and in addition, SPECT isotopes are more widely available than PET isotopes.

For breast cancer molecular imaging, several tumor characteristics are candidates for development of tumor specific tracers (Fig. 1). To target general phenomena one can visualize the tumor cell glucose metabolism or DNA synthesis, which are both increased in tumor cells compared to normal cells. Most breast cancers express hormone receptors in the tumor cell, making these receptors interesting targets for imaging in these subsets of patients. Also receptors present at the tumor cell membrane, such as Human Epidermal growth factor Receptor 2 (HER2), Epidermal Growth Factor Receptor (EGFR), Insulin-like Growth Factor–1 Receptor (IGF–1R) and Platelet Derived Growth Factor β Receptor (PDGF–βR), may be of interest for imaging. In addition, tumor cells excrete growth factors, like Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor β (TGF-β), in the tumor microenvironment and therefore are tracer target candidates. Finally, all targets involved in angiogenesis (VEGF-receptors, α5β3 integrin, fibronectin, endostatin) and hypoxia can be used, since both processes are key players in tumor growth generally not occurring in normal breast tissue.

FDG-PET breast cancer imaging

The best studied and clinically most used PET-tracer is [18F]fluorodeoxyglucose (FDG). FDG-PET visualizes glucose metabolism, which is often increased in tumor cells compared to normal cells. FDG is transported across the cell membrane by glucose transporter proteins and is phosphorylated by hexokinases to FDG-6-phosphatase. Because FDG-6-phosphate lacks a hydroxyl group in the 2-position, unlike glucose-6-phosphate, it is not further metabolized and thus ‘trapped’ in the cell. This results in a tumor accumulation of FDG, which is regulated by the activity of the glucose transporters and hexokinase. During the process of tumor accumulation, FDG is cleared from the blood by the kidneys resulting in low blood levels. Usually 45–90 minutes after FDG injection, the tumor uptake can be detected with a PET camera (Fig. 2A). Under physiological conditions, FDG predominantly accumulates in tissues with high glucose metabolism, such as the brain. Less uptake is seen in muscle, myocardium, liver, intestine and kidneys. Limited anatomical information by FDG-PET alone is increasingly improved by fusing the separately recorded PET images with computed tomography (CT) or magnetic resonance imaging (MRI), and by fusing the images recorded by integrated PET-CT cameras. FDG-PET has been evaluated for primary tumor detection and diagnosis, (re)staging of locoregional and distant metastases and monitoring therapy response. In a pre-operative setting, high FDG

Fig. 2. Examples of three breast cancer patients imaged with various PET tracers. (A) FDG-PET shows physiological FDG uptake in brain, bladder, kidneys, liver, intestine and muscles, and pathological FDG uptake in supraclavicular and mediastinal metastatic lesions. (B,C) FLT-PET shows physiological FLT uptake in liver and bone marrow, and pathological FLT uptake in primary tumor. (D) FES-PET shows physiological FES uptake in liver and intestine, and pathological FES uptake in numerous bone metastases.
tumor uptake was observed particularly in ductal carcinomas. The degree of FDG tumor uptake was positively correlated with grade, Ki-67 proliferation index, 8,9 mitotic index, Glut-1 expression, amount of necrosis, number of tumor cells/volume, hexokinase I expression and microvessel density. 11 However, FDG uptake itself is not tumor-specific, and the distinction between malignant and benign breast cells can be difficult, particularly in situations of breast hypermetabolism (breast feeding, mastitis). 12,13 Also, false positive results can be due to the accumulation of FDG in activated inflammatory cells such as granulocytes and macrophages. 14

For early breast cancer detection and diagnosis, the ability to detect non-palpable, small (<1.0 cm) malignancies is desirable. The spatial resolution of previous-generation clinical PET cameras is >7 mm, depending on positron range, and therefore whole body FDG-PET has not extensively been used for this purpose. 5,15 In the latest generation of PET/CT cameras, spatial resolution has improved to ≤4 mm for [18F].

High resolution, high sensitive positron emission mammography (PEM) has been developed for early stage breast cancer detection and diagnosis. This technique consists of two planar detectors placed opposite a gently compressed breast and is capable of detecting primary breast cancers lesions as small as 3 mm. 16 PEM results were correlated with histopathology for 92 lesions in 77 patients, and a sensitivity of 90% and a specificity of 86% for detecting primary breast cancers was found. In the same study, PEM detected 5 of 8 lesions smaller than 1 cm in patients with biopsy proven breast cancer or suspicious breast lesions. 17 Its clinical utility for screening or as adjunct to mammography has to be proven in larger series. 18,19

The role of FDG-PET for staging, including detection of tumor involvement in regional lymph nodes and distant metastases, has recently been reviewed. 20 It cannot replace histological staging for axillary staging, since its sensitivity varied from 20% to 94% in 20 studies with a specificity of 85–100%. 21,22

A number of studies addressed the role of FDG-PET for detecting distant metastases and disease recurrence. Specificity varied from 100% to as low as 20%, while sensitivity was consistently high, ranging from 78% to 100%. Overall acceptable and generally superior sensitivity is reported for FDG-PET compared to conventional imaging (mammography, ultrasonography, CT, MRI, radiography and bone scintigraphy) in the detection of local recurrence or distant metastatic disease. 19,23–26 For the detection of bone metastases, particularly osteolytic or mixed type, FDG-PET can perform better than conventional bone scintigraphy. 27 FDG-PET detects osteolytic metastases often missed by bone scintigraphy, while FDG-PET often misses osteoblastic metastases, for which bone scintigraphy has higher sensitivity. 28,29 It appears that FDG-PET is complementary to bone scintigraphy, which remains the standard for detecting bone metastases in breast cancer. 30 For patients with inflammatory breast cancer, it was suggested that FDG-PET/CT should be considered for initial staging because it provides additional information on distant metastases. 31

Guidelines in general advice a relatively modest use of FDG-PET. The National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology (v.1.2009) advice not to use FDG-PET for breast cancer staging in general, but apply it in case of those clinical situations with locally advanced or metastatic disease where other staging studies are equivocal or suspicious. 32 Others also do not recommended FDG-PET for routine breast cancer staging. 20 The “Recommendations on the use of FDG-PET in oncology” panel chaired by the American Society of Clinical Oncology (ASCO) concluded that it should be routinely added to the conventional work-up in detecting metastatic or recurrent breast cancer in those patients clinically suspected of metastases or recurrence. 5

Assessment of the change in tumor burden, either by tumor size or by tumor functionality, is important for the clinical evaluation of cancer therapeutics. In 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) guideline for the assessment of tumor size changes included imaging with X-ray, CT or MRI for response monitoring. 33 In the recently updated RECIST guideline (version 1.1), FDG-PET is included and mentioned to be able to complement CT to assess progression. In addition, it is now suggested to use FDG-PET in circumstances where it is difficult to distinguish residual disease from normal (scar) tissue. 34

Thresholds ranging from 20% to 70% decrease of the standardized uptake value (SU) are used for FDG tumor uptake as response evaluation. 35,36 The appropriate percentage SUV decrease threshold depends among others on technical and clinical factors differing between studies and institutions. 37 For early effect assessment on chemotherapy after one cycle for example, smaller SUV threshold values are used than for late assessment. There is no standardized protocol with a SUV cut-off value that is generally accepted to implicate a response. In the neo-adjuvant setting (n = 64), changes in FDG tumor uptake between baseline and after 1, 2, 3 and 6 cycles of chemotherapy were compared with pathologic response at surgery after the sixth cycle. In patients with a histological total or near-total therapeutic effect, decrease in FDG uptake increased after each cycle of chemotherapy. The average decrease in FDG uptake after 1, 2, 3 and 6 cycles was 59.6%, 78.7%, 86.3% and 90.2% in this group, respectively. In patients with histologically no or less than 50% therapeutic effect, FDG uptake was only decreased to an average of 53.2% after six cycles of chemotherapy. 38 In another neo-adjuvant study, FDG-PET was performed at baseline and after the first and second chemotherapy cycle. Twenty-four of 104 patients had a low baseline SUV (<3.0), and none of them experienced a histopathological response to chemotherapy, defined as minimal residual disease. In patients with a baseline FDG SUV >3.0, histopathological responders showed an average decrease of 51% in FDG uptake, while non-responders showed an average decrease of 37% (P = 0.01). 39 In addition, the FDG SUV decrease after the first cycle was a predictive factor for a pathologically proven complete response (pCR) as a SUV decrease <60% predicted the pCR with an accuracy of 87%. 40 Others showed similar results in 30 primary and metastatic breast cancer patients. 41 In a neo-adjuvant setting (n = 96), decrease in FDG uptake after chemotherapy in the subset of patients with low baseline FDG uptake (n = 57), could not predict histopathological tumor response. 42 In the subset of patients with high baseline FDG uptake (n = 39), there was a clear and significant difference between the FDG decrease for the high and low histopathological tumor response categories. 43 Increased metabolic activity, or ‘metabolic flare’, detected by FDG-PET in response to hormonal treatment was predictive for tumor response and overall survival. 44–46

A few small studies addressed the prognostic role of FDG-PET for chemotherapy outcome. A superior predictive value of complete metabolic response measured with FDG-PET before- and one month after completion of chemotherapy, as compared with conventional imaging techniques, has been reported. Mean survival was 10 months in patients without metabolic response (n = 13), versus 24 months in those with metabolic response (n = 34). In patients with response measured by conventional imaging (n = 31), median survival was 21 months, versus 10 months in non-responders. 47 Preoperative FDG tumor uptake after neo-adjuvant chemotherapy (n = 40) was inversely associated with disease free but not with overall survival. 48 FDG tumor uptake before primary breast surgery correlated with prognostic parameters such as tumor size, axillary lymph node status, histological type, histological grade, ER status, p53 and Ki-67 expression. 49,50

In conclusion: in clinical practice FDG-PET is not recommended as a standard procedure for breast cancer diagnosis and staging.
The use of FDG-PET in detection of breast cancer recurrence and metastasis can be of value, especially in patients at high risk. Information on its role in evaluation and prediction of treatment response is increasing, but FDG-PET is not recommended as a routine assessment yet.

FLT-PET breast cancer imaging

The pyrimidine analogue PET-tracer [18F]fluoro-L-thymidine (FLT) has been developed to image increased DNA synthesis, as FLT tumor uptake reflects the proliferation rate of tumor cells (Fig. 2B,C). Normal physiological uptake of FLT is seen in liver, bone marrow and the urinary tract. In breast cancer patients, small studies have been performed for staging and as early predictive marker of response to chemotherapy. FLT uptake was seen in 8 out of 10 primary breast tumors and some large axillary lymph node metastases, but small axillary lymph node metastases were not detected. Slightly better results were seen in another report in 12 patients, where 13 out of 14 primary breast tumors and 7 out of 8 axillary lymph node metastases could be detected. Experience with FLT-PET for early response prediction is limited.

Overall, FLT-PET is not regarded as a routine staging tool for breast cancer but may play a role in prediction of response to therapy.

Hormone receptor imaging

At diagnosis, 70% of breast cancer patients have tumors positive for hormone receptors, of which the majority are positive for estrogen receptor (ER). Furthermore, >95% of progesterone receptor (PR) positive tumors are also ER positive. Immunohistochemical determination of ER and PR expression at the time of primary diagnosis is part of standard care. Treatment strategies are based on hormone receptor expression, which is predictive of response to anti-hormonal treatment in up to 70% of patients with a new diagnosis of breast cancer. The guidelines of the PDQ, the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) indicate that new histology has to be considered at relapse, as hormone receptor expression can vary between primary tumor and recurrence in ~30% of cases.

In one study, the discordance between the ER status of the primary tumor and the distant metastases was 41% for bone marrow metastases, and 44% for liver metastases. Obtaining tumor tissue at relapse may be cumbersome. Also, sampling error may be a potential problem, as ER expression can differ between primary tumor and synchronous metastases. In addition, anti-hormonal treatment induces ER loss in a number of patients with acquired hormonal resistance.

The PET tracer 16-a-[18F] fluoro-17-β-estradiol (FES) was developed as a receptor ligand for ER (Fig. 2D) and binds to both subtypes ERα and ERβ, with a preference for ERα. Several studies with FES-PET have been performed in breast cancer patients. FES tumor uptake was shown to correlate with immunohistochemical ER tumor density. These studies pointed to the potential role of FES-PET in the assessment of ER status, especially in patients with multiple tumors or tumors that are difficult to biopsy, and in the guidance of anti-hormonal therapies. Comparison of FES and FDG tumor uptake with ER status in 43 patients, showed an 88% overall agreement between FES uptake and ER status. However, no correlation was found between FDG uptake and ER status or between FES and FDG uptake.

With regard to predicting and monitoring of response to anti-hormonal therapy, few data are available. FES-PET was evaluated in 47 patients with immunohistochemically ER positive recurrent or metastatic tumors. FES-PET was performed at baseline prior to, or shortly after the initiation of anti-hormonal therapy, consisting of tamoxifen, aromatase inhibitor or aromatase inhibitor with fulvestrant. FES tumor uptake at baseline was compared with the response after 6 months therapy, determined by a combination of clinical assessment and modified RECIST criteria. In patients with low FES tumor lesions uptake at baseline (n = 15), no response was shown. In the group with a high uptake at baseline, 11 of 32 patients responded to anti-hormonal therapy. Particularly patients with HER2 co-expression (n = 10) did not show an objective treatment response, in spite of high FES uptake at baseline.

With regard to the prognostic value of FES-PET, no data are available yet. So far, no validated tracer is available for imaging PR.

In conclusion, thus far FES-PET cannot be regarded as a routine imaging technique for the workup of a breast cancer patient. However, it is certainly a technique that deserves to be explored more extensively, particularly with regard to predicting treatment response.

HER2 imaging

HER2 is encoded for by the HER2 proto-oncogene (HER2/neu or c-erbB-2) and is involved in tumor cell survival, proliferation, maturation, metastasis and angiogenesis, and has anti-apoptotic effects. Overexpression of HER2, the result of HER2 gene amplification, is present in 25-30% of breast cancer patients. Trastuzumab is a recombinant IgG1 monoclonal antibody targeting the extracellular domain of HER2 and is widely used clinically in patients with HER2 overexpressing breast cancer.

HER2 tumor expression can vary during treatment and can differ across metastatic lesions within a patient. Therefore, there is a need for methods that are able to assess the HER2 status repeatedly, preferably in all lesions and non-invasively. HER2 imaging could potentially serve this aim. HER2 imaging starts with selecting a suitable HER2 targeting ligand. Currently available HER2 targeted ligands includes full length monoclonal antibodies, Fab-fragments, F(ab′)2-fragments, diabodies, minibodies, affibodies, scFv-Fc and peptides. When radiolabeling these HER2 targeted molecules, the physical half-life of the radio isotope ideally should suit the biological half-life of the HER2 targeting molecule to allow imaging at the optimal time-point. This implicates that full-length monoclonal antibodies are mostly radiolabeled with long-lived isotopes while the smaller HER2 targeting molecules, which have a more rapid clearance, are radiolabeled with shorter-lived isotopes. Full-length HER2 monoclonal antibodies have been labeled with 111In, 111In and 99mTc for HER2 SPECT/gamma camera imaging and with 124I, 86Y, 78Br and 89Zr for HER2 PET. The smaller HER2 targeting antibody fragments, proteins and peptides have been labeled with 111In, 111In and 99mTc for HER2 SPECT/gamma camera imaging and with 18F, 64Cu, 68Ga and 76Br for HER2 PET.

We have performed In-trastuzumab planar gamma camera and SPECT imaging in HER2 positive metastatic breast cancer patients. With this technique, 45% of single tumor lesions, detected with conventional imaging, could be shown. In addition, new tumor lesions were discovered in 13 of 15 patients. Since PET imaging provides a higher spatial resolution, a better signal-to-noise ratio and is potentially more quantitative than SPECT, we have developed...
VEGF imaging

The development of vascular supply, usually called angiogenesis, is important for the growth of tumors. One of the most important factors involved in angiogenesis is vascular endothelial growth factor (VEGF). In tumor cells there is an unproportional upregulation of VEGF production which leads to locally high VEGF levels, mainly located in the extracellular matrix.

In metastatic breast cancer the addition of bevacizumab, a humanized monoclonal antibody which neutralizes all isoforms of VEGF-A, to paclitaxel leads to an increased response rate and increased progression free survival. To select patients who could benefit from VEGF targeted therapies, and to follow up new treatment regimes, imaging of VEGF using specific tracers is of great interest. It is an important downstream protein produced as a result of multiple processes (hypoxia), activation of growth factor receptors (EGFR, HER2) and intracellular proteins (HIF-1α, mTOR etc.).

To date, several radiolabeled anti-VEGF antibodies and Fab-fragments have been used for the development of VEGF imaging namely 186Vg76e, HumMV833, bevacizumab and ranibizumab. 125I- and 124I-labeled Vg76e, an IgG1 mouse monoclonal anti-VEGF antibody, showed specific tumor targeting in a human HSP90 inhibitor NVP-AUY922 in a tumor xenograft.86 Treatment with HSP90 inhibitors results in HER2 downregulation. This rapid but transient HER2 downregulation has been shown in several preclinical reports, both in vitro and in vivo.87–89 The pharmacodynamics of HER2 downregulation induced by 17-AAG were visually and quantitatively evaluated by PET in an HER2 overexpressing xenograft model with a 125I labeled Fab-fragment of trastuzumab. HER2 PET imaging with this fragment was able to quantify the HER2 response as a 50% lower tracer tumor uptake after 17-AAG treatment,84 while FDG tumor uptake was unaffected during the 21 days follow-up period.85 We showed a 37% decrease of 89Zr-trastuzumab uptake by the new HSP90 inhibitor NVP-AUY922 in a tumor xenograft.86

In summary, preclinical results with HER2 imaging are abundant and promising but clinical experience is limited. Our findings with clinical HER2 SPECT and PET imaging with 111In-trastuzumab and 89Zr-trastuzumab in metastatic breast cancer advocate the further development and exploration of the possibilities of this technique.

Other targets for molecular breast cancer imaging

Breast cancers that are negative for ER, PR and HER2 immuno-histochemically, known as triple-negative breast cancer, have a poor prognosis.90–101 Much research is ongoing to identify the biological processes and targets that drive triple-negative breast cancer. Molecular imaging of these targets could have a role in target identification, drug development and response prediction and evaluation.

Overexpression of EGFR is seen in 57% of triple negative breast cancers. The EGFR-directed monoclonal antibody cetuximab is currently in clinical investigation for the treatment of triple-negative breast cancer.102 Several tracers have been developed for EGFR imaging, such as radiolabeled EGFR tyrosine kinase inhibitors and the EGFR ligand Epidermal Growth Factor or EGFR antibodies.103 Recently, also the IGF-1R has been identified as a possible target for treatment of triple-negative breast cancer because many of these tumors express IGF-1R and tracers for imaging IGF-1R are underway.105 In breast cancer, the crucial orchestrating role of TGF-β in the metastasising processes becomes more and more evident106 and TGF-β and TGF-βRs targeting therapies are currently in clinical trials. Imaging TGF-β could help to select patients most likely to benefit from TGF-β targeting therapies and to monitor TGF-β targeting therapies.

PDGFR-βR is commonly expressed in malignant breast tissue and surrounding peri-epithelial stromal cells.107 PDGFR-βRs are pivotal
in peritumoral vasculature, stroma and bone. The receptor and its downstream effectors trigger a cascade that regulates cell proliferation, differentiation, and survival. Increased PDGF-βR signaling is required for formation of breast cancer metastases. Therefore, the visualization of this receptor can possibly contribute to improved breast cancer staging. A possible strategy to perform this, is by radiolabeling a construct with the PDGF-βR homing peptide pPB.

Discussion and future direction

Although molecular imaging of breast cancer is still not commonly used in daily clinical practice, its application portfolio is expanding rapidly and it thereby holds promise for improving breast cancer management. We addressed results with the sensitive PET and SPECT techniques, but these techniques do have limitations, especially for screening purposes, caused by the exposure to ionizing radiation, limited capacity and the limited spatial resolution of currently used systems which hinders early tumor detection. Resolution of the latest-generation PET and SPECT cameras has improved and the introduction of combined systems with an integrated CT (and soon also MRI) system has led to a much better (anatomic) interpretation of the data. In addition to this integration of imaging modalities, also the indirect combination of nuclear imaging and optical imaging could serve shared purposes. Optical contrast agents (tracers) that target specific molecular changes associated with breast cancer formation as well as clinical optical breast imaging equipment are under development, primarily for breast cancer screening. In case of optical imaging, no ionizing radiation is needed and the technique is relatively inexpensive, which are significant advantages for breast cancer screening purposes. For clinical use, the optical tracer and its target have to be validated. In a combined setting, more sensitive PET and SPECT imaging can be used for target and tracer validation and if successful, the nuclear tracer can be converted to an optical tracer by replacing the radioisotope by a fluorescent label. Also an intermediate stage tracer validation can be performed with dual labeled tracers, for combined nuclear and optical imaging. This makes the integration of nuclear and optical imaging an attractive approach for developing an optical imaging breast cancer screening system capable of early tumor detection.

Competing interests: EGEvdV has received an investigational grant from Roche. The other authors have no conflict of interest to declare.

Funding: THOM: Dutch Cancer Society, WBN: Dutch Cancer Society. AHB: none to declare. CPS: none to declare. GAPH: grant support from Roche. MNLdH: none to declare. EvdW: none to declare. PjVd: none to declare. EGEvdV: Dutch Cancer Society; Pink Ribbon; Pink Ribbon Gala

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