Clinical Potential of Human Epidermal Growth Factor Receptor 2 and Human Epidermal Growth Factor Receptor 3 Imaging in Breast Cancer

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KEYWORDS

• PET • SPECT • CT • Radiotracers • HER2 • HER3 • Metastasis • Breast cancer

KEY POINTS

- The human epidermal growth factor receptor (HER) family members are of increasing interest to target by small molecules, affibody moieties, and monoclonal antibodies.
- Imaging can simultaneously assess HER expression of primary and metastatic sites, which may vary across lesions within any given patient.
- PET and SPECT imaging allows noninvasive diagnosis in breast cancer, has the ability to detect metastatic disease, and addresses the issue of tumor heterogeneity.
- Resistance against the epidermal growth factor receptor and HER2-targeting agents is a clinically relevant problem that requires optimization of targeting other members of the HER family.
- HER3 is strongly involved in the development and maintenance of many tumor types and is emerging to play a significant role in breast cancer.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, with approximately 12% of women in the United States developing invasive breast cancer in their lifetime.[1] Although breast cancer has come a long way with regard to treatment options and overall survival, there remain challenges that occur mostly from intratumoral heterogeneity[2] and metastatic disease.[3] Although significant research has emerged to identify biological processes leading to breast cancer,[4] selecting patients who would benefit from targeted therapies remains a major hurdle. Noninvasive tools to stratify patients and facilitate precision medicine are needed to address this issue.[5–7]

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Although breast cancer is typically diagnosed and staged via 3 main biomarkers, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2),[8] there are other biomarkers of interest that are relevant and may be beneficial to the clinical outcome of breast cancer. Reports of clinical benefit from HER2-targeted therapy in patients with a primary HER2$^-$ tumor have facilitated to spearhead the concept behind HER2-targeted molecular imaging for unsuspected metastases in breast cancer.[9,10] An additional biomarker of interest includes HER3.[11] HER3 overexpression has been linked with poor prognosis in multiple cancer subtypes, including breast, which has driven interest in HER3 as potential target for both imaging and therapy. Additionally, emerging resistance to HER2-targeted therapy has driven the need to explore additional targets for both imaging and therapy.[11] The HER family in general has been extensively studied in breast cancer,[12] and there are many HER2-targeted agents for therapy and molecular imaging,[13–15] and strategies to target HER3 are also increasing in clinical trials.[16,17]

Molecular imaging, particularly with tracers used in PET and single photon emission computed tomography (SPECT) have the ability to noninvasively detect heterogeneity between primary tumors and metastases in breast cancer.[6,18] PET- and SPECT-based measurement of the HER2 and HER3 expression in breast cancer offers several advantages over repeated biopsies in patient cohorts. Several groups have developed antibody, affibody, and nanoparticle-based radioligands for PET imaging preclinically and clinically,[19–22] many of which include radiotracers used to image HER2 and HER3 in breast cancer.[13,23] Pairing these targeting moieties with longer lived radioisotopes such as zirconium-89 (^{89}Zr; half-life ($t_{1/2}$) = 78 hours) for PET, along with lutetium-177 (^{177}Lu; $t_{1/2}$ = 6.7 days) and indium-111 (^{111}In; $t_{1/2}$ = 67 hours) for SPECT can be used to match the biological half-life of antibodies in vivo ($t_{1/2}$ ~72 hours for typical full-length antibodies).[24] Isotopes like copper-64 (^{64}Cu; $t_{1/2}$ = 12 hours) or technium-99m (^{99m}Tc; $t_{1/2}$ = 6 hours) can be used in PET and SPECT, respectively, for both full-length and antibody fragments, as well as affibodies.[25–27] Antibody fragments and affibody molecules are often labeled with shorter-lived isotopes such as gallium-68 (^{68}Ga; $t_{1/2}$ = 68 minutes) or fluorine-18 (^{18}F, $t_{1/2}$ = 110 minutes) to pair appropriately with shorter biological half-lives in vivo.[28–31]

Many of the PET and SPECT imaging tracers that have made it to the clinic (in phase I/II trials) to detect HER2$^+$ breast cancer and metastases, are summarized in our previous review.[15] This review seeks to communicate an update about the current clinical trials for both HER2- and HER3-targeted imaging, which are outlined in **Table 1**. The current clinical radiotracers used to image HER3$^+$ and HER2$^+$ breast cancers are reviewed herein.

PET AND SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY IMAGING WITH MONOCLONAL ANTIBODIES IN HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2$^+$ BREAST CANCER

An extensively studied target for imaging in breast cancer is HER2, because clinical trials using this target are being undertaken at cancer centers all over the world.[9,32,33] HER2 imaging can address the issue of tumor heterogeneity and reliably determine both the quantity and the functional status of tumor HER2 in individual lesions in a noninvasive manner. This technique is of critical importance to identify patients who would truly benefit from HER2-targeted therapy, and to monitor the change in HER2 status during immunotherapy.[34,35] We have previously reviewed HER2 targeted imaging,[15] and provide an update of more recent work here.

^{89}Zr-Trastuzumab

^{89}Zr-trastuzumab has been vastly studied across patient cohorts and clinical trials for both primary and metastatic breast cancer.[9,36–40] Ulaner and coworkers[9,41] have expanded the field with ^{89}Zr-trasuzumab to detect unsuspecting metastases in both HER2$^+$ and HER2$^-$ primary breast tumors. Multiple studies are being carried out at Memorial Sloan Kettering Cancer Center to image this HER2 expression discordance and guide biopsies.[41,42] Another current clinical trial using ^{89}Zr-trastuzumab is led by Laforest and coworkers[43] at Washington University in St. Louis. Twelve women were enrolled in the study, 6 with primary breast cancer and 6 with metastatic breast cancer. Eleven of these patients underwent ^{89}Zr-trastuzumab PET/CT during neoadjuvant or adjuvant therapy, and the remaining patient was imaged before neoadjuvant therapy. Laforest and colleagues found that increasing the dose to 62 $\pm$ 2 MBq (vs the average dose of 37 MBq, which was used in previous studies done by Dijkers and colleagues[38,44] in the ZEPHIR [HER2 Imaging Study to Identify HER2 Positive Metastatic Breast Cancer Patient Unlikely to Benefit From T-DM1] trial)[33] allowed for optimal images at later time points (**Figs. 1** and **2**). The dose-limiting organ was found to be the liver, with a