Immunoscintigraphy with Positron Emission Tomography: Gallium-68 Chelate Imaging of Breast Cancer Pretargeted with Bispecific Anti-MUC1/Anti-Ga Chelate Antibodies

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ABSTRACT

Pretargeting techniques that are based on the sequential administrations of bispecific antitumor/antimetale chelate antibodies (BS-MAbs), a blocker to saturate the anti-chelate binding sites of the BS-MAb still present in the circulation, and the radiolabeled chelate are suitable to increase tumor-to-normal tissue contrasts and enable positron emission tomography (PET) as an imaging method. As demonstrated in the nude mouse model, a combination of pretargeted immunoscintigraphy and PET markedly improved the detection of tumor xenografts. With the presented preliminary clinical trial, we attempted to assess the efficacy of pretargeting and PET for breast cancer localization in patients. The BS-MAb used for pretargeting was synthesized from the F(ab′)2 fragments of the anti-MUC1 MAb 12H12, which reacts with the vast majority of breast tumors, and the F(ab′)2 fragments of an anti-gallium (Ga) chelate MAb via a mixed functional chemical linker. For labeling of the Ga-chelate, we used the short-lived positron emitter Ga-68 (t1/2 68 min; β+, 88%). The dose and time schedule of pretargeting was deduced from previous animal experiments. Ten patients with biopsy-proven, primary breast carcinoma were infused with 10 mg of the BS-MAb. Eighteen h later, they received i.v. injections of 10.7 mg of a blocker and, 15 min later, 9.6 μg of the Ga chelate labeled with 230–300 MBq of 68Ga. PET imaging was started 60–90 min after injection of the 68Ga chelate. Average tumor-to-blood and tumor:normal breast tissue ratios were 0.9 and 3.0 at 1 h postinjection. Tumor uptake amounted to ~0.003% ID/g corresponding to a standard uptake value of ~2. Blood clearance of the 68Ga chelate showed a t1/2 β of ~100 min. Fourteen of 17 known lesions, averaging 25 ± 16 mm in size, were clearly visualized as foci of increased activity with PET. No false-positive but three false-negative readings were obtained. An enhanced, bilateral activity uptake in the whole breast parenchyma, found in 4 of the 10 patients, compromised the recognition of these tumor sites. Although the shedding of the MUC1 antigen and the comparatively low tumor affinity of the BS-MAb, common to all anti-mucin MAbs, proved not to be optimal for increasing tumor:tissue ratios with a pretargeting technique, PET imaging offered better sensitivity for the detection of breast cancer at low tumor contrasts than conventional immunoscintigraphy. This could be demonstrated by the clear visualization of tumor sites 10 mm in size, which contrasted only by a factor of 2 from surrounding normal breast tissue.

INTRODUCTION

Breast cancer is associated with high mortality during the first 10-year interval, attributable to disseminated disease. Despite progress in the morphological characterization of breast lesions with mammography, computed tomography, and ultrasonography, diagnostic specificity remains low and often requires an invasive, histopathological examination to demonstrate malignancy.

A higher specificity in the noninvasive characterization of breast lesions can be expected from IS2—2a:0:ZPICKFOOT:F3a2 with radiolabeled MAbs raised against breast cancer-associated antigens (1–3). However, IS frequently lacks sensitivity because of low radioactivity contrasts between tumor and the surrounding normal tissues caused by the physiological disadvantages of MAbs, including slow clearance from the circulation, high nonspecific liver uptake, and slow penetration into solid tumors (4, 5). An additional, technical restriction of IS is the need for longer-lived radionuclides with suitable high-photon intensities for MAb labeling. Because appropriate isotopes are seldom in the group of positron emitters, the use of PET with its inherently better contrast resolution and higher detection efficiency, compared with conventional gamma cameras, has not found wide application in IS.

To combine the specificity of immunoscintigraphic tumor localization with an improved sensitivity, we developed a three-step pretargeting technique that increases tumor-to-normal tissue contrasts and enables PET as an imaging method. For pretargeting, we injected a BS-MAb. After a waiting period, which allows the BS-MAb to localize in the tumor, a blocker was given to saturate the anti-Ga chelate-binding sites of the BS-MAb still present in the circulation. Tumor localization with PET was carried out 1 h after the administration of the 68Ga-labeled Ga chelate, which was given shortly after the blocker. 68Ga is a short-lived positron emitter (t1/2 68 min; β+, 88%) that is produced, independent from a cyclotron, by a 68Ge/68Ga generator. Using different antitumor MAbs for BS-MAb preparation, the sensitivity of tumor detection could be markedly enhanced in nude mice bearing rat pancreas carcinoma (6) and human colon carcinoma (7).

For breast tumor localization, we prepared an antimucin/anti-Ga chelate BS-MAb. In a previous investigation we have described the biokinetics of this BS-MAb in nude mice xenografted with a human mammary carcinoma (8). In this study, we present the first clinical results obtained with the BS-MAb, pretargeting, and PET in patients with primary breast cancer.

MATERIALS AND METHODS

BS-MAb and Blocker. MAB 12H12 is a mouse IgG1, which recognizes the carbohydrate-side chains of TAG 12, which differs in glycosylation from the MUC1 mucin on normal epithelial cells. TAG 12 is overexpressed by the vast majority of epithelial cell adenocarcinomas and is shed into circulation because of proteolytic cleavage from the cell membrane (9).

Anti-Ga chelate MAbs were raised by immunization of BALB/c mice with Ga-HBED-CC coupled to keyhole limpet hemocyanine. Because of the racemic nature and the high kinetic stability of the Ga chelate in vivo, hybridomas

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2 The abbreviations used are: IS, immunoscintigraphy; MAB, monoclonal antibody; PET, positron emission tomography; BS-MAB, bispecific antibody; Ga, gallium; Ga-HBED-CC, gallium-N,N′[2-hydroxy-5-(ethylenyl-β-carboxybenzyl)] ethylene diamine N, N′ diacetic acid; TAG, tumor-associated glycoprotein; IDC, invasive ductal carcinoma; IL-6, interleukin-6; CEA, carcinoembryonic antigen; FDG, fluorodeoxyglucose; EGFR, epidermal growth factor receptor; In, indium.
obtained secreted MAbs of high enantioselectivity for only one of the two Ga-HBED-CC enantiomers. Two MAbs, designated 3A10 (IgG3) and 8–16 (IgG1), of opposite enantioselectivity were selected (10).

BS-MAbs were synthesized by coupling the F(ab′)2 fragments of the 12H12 and the F(ab′)2 fragments of the 3A10 via a mixed functional clinical linker (6). The affinity of the BS-MAb toward the Ga chelate was 1.5 × 10^9 M^(-1) s^(-1) (11). To the eluate, containing 1.6 GBq of 68Ga in 0.5 ml of 0.5 M HCl, and 35 μl of 1 M NaCl carrier were added, and the mixture was evaporated to dryness. After redissolving in 200 μl of acetate buffer (pH 4.8), 40 μl of 1 M HBED-CC were added, and the mixture was kept for 15 min at 95° in a water bath. Uncomplexed 68Ga was separated from the 68Ga chelate by adsorption on a small cation exchange column (Chelex 100; Bio-Rad, Munich). Separation of the racemic Ga chelate into its enantiomers was achieved with an immunoadsorption column containing MAb 8–16 immobilized to Sepharose. The enantiomer reactive with the 12H12/3A10 BS-MAb appeared in the effluent, whereas the enantiomeric counterpart was retained on the column (6). The final solution contained ~16 nmol of Ga chelate in 0.01 M PBS with a specific activity of ~20 MBq 68Ga/1 nmol Ga chelate. The overall preparation time took ~70 min.

### Dose and Time Schedule of Pretargeting

Because of the limited number of patients, dose-finding was omitted. The BS-MAB dose selected corresponds to ~1 nmol/kg for a patient of 65 kg body weight. Similar doses were used successfully in pretargeting approaches with an anti-CEA/anti-In-diethylene-triaminepentaacetic acid BS-MAB (12, 13). The corresponding amounts of Ga chelate and BS-MAb, and for the experimental use of radiotracers (68 Ga).

**Patient Study.** Ten patients with biopsy-proven, primary breast carcinoma were examined. All patients gave written, informed consent before participating in the trial. The study was approved by the ethics committee of the University of Heidelberg. An investigational new drug application was filed with the federal authorities for the use of pharmaceuticals, sera, and vaccine (Ga chelate and BS-MAb), and for the experimental use of radiotracers (68 Ga).

Patients were infused i.v. with 10 mg (62.5 nmol) of 12H12 BS-MAb diluted with 250 ml of saline during a 2-h period. Eighteen to 19 h after the infusion of the BS-MAb, 10.7 mg (125 nmol) of blocker were injected i.v. in 5.0 ml of PBS and then, 15 min later, 9.6 μg (16 nmol) of enantiomeric 68Ga-HBED-CC (230–300 MBq) in 5.0 ml of PBS. Blood samples were drawn at 5, 10, 30, 60, and 90 min after 68Ga chelate injection and counted in a gamma counter together with aliquots of the injectate. Nine patients had surgery 0–4 days after scintigraphy. One patient, initially scheduled for a neoadjuvant chemotherapy, had surgery 4 months later. A histopathological examination (hematoxylin and eosin staining) of the resected tissues was available for all patients.

**PET Imaging.** Two PET scanners were used for imaging. Eight patients were examined with a Siemens ECAT EXACT HR scanner, which has an axial field of view of 15 cm and produces 63 axial slices of 2.3 mm in thickness. Images were taken in the three-dimensional mode, corrected for scatter and attenuation, and reconstructed iteratively for viewing transaxial, coronal, and sagittal planes (14). Transaxial resolution was 6 mm. In general, scans of two contiguous positions were obtained. A 25-min emission and a 10-min transmission scan of the mammary region was followed by a 35-min emission and 10-min transmission scan of the axillary region.

Two patients were examined with a Scanditronix PC 2048–7 WB scanner, which contains a two-ring detector system providing three transaxial slices, two primary and one cross-section, with thicknesses of 11, 8, and 11 mm, respectively. The scanner lacked three-dimensional acquisition capability. Images were corrected for scatter and attenuation and reconstructed iteratively; in-plane resolution was 6.5 mm. Five contiguous positions with a total axial field of 15 cm covering the mammary region were imaged by alternate emission and transmission scans of 15- and 10-min durations, respectively.

All patients had an i.v. injection of 230–300 MBq of 68Ga HBED-CC. The first emission scan was started between 60 and 90 min postinjection of the Ga chelate. Two patients were imaged in the supine position, the arms positioned along the body. Eight patients were examined in the prone position with raised arms and breasts dependent through cut-outs in a special support.

Tumor: blood and tumor:nor mal tissue ratios were determined from images reconstructed in a 128 × 128 matrix with a 4.2-mm pixel size. Regions of interest, comprising 3 × 3 pixels, were drawn within the highest uptake areas of the tumor and the heart chamber. Data of normal tissue uptake were averaged from regions in the ipsilateral and the contralateral breast.

**Immunohistology.** Antigen expression was assessed by immunohistochemical staining. Five μm sections of paraffin-embedded tumor tissue were incubated with the 12H12/3A10 BS-MAb for 60 min and subsequently stained with a standard ABC immunoperoxidase technique (Dako, Hamburg, Ger-

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### Table 1 Multistep targeting in patients with biopsy-proven breast carcinomas

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yrs)</th>
<th>pTNM stage*</th>
<th>Histopathology</th>
<th>No. of lesions/size [mm]</th>
<th>Immunohistochemistry*</th>
<th>PET-imaging ratios</th>
<th>Time postinjection (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>T4bN2L1G3</td>
<td>IDC multifocal</td>
<td>1/15^b</td>
<td>1-2</td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>T3N1bL1G3</td>
<td>IDC</td>
<td>1/100</td>
<td>2-3</td>
<td>3.8</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>T2N1bL1G3</td>
<td>ILC multifocal</td>
<td>1/25^b</td>
<td>3^d</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>T1bN1bL1G3</td>
<td>ILC</td>
<td>2/10, 10^b</td>
<td>3.0</td>
<td>0.8</td>
<td>2.0, 2.0</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>T2N0L1G3</td>
<td>ILC</td>
<td>1/15</td>
<td>NA^c</td>
<td>4.2</td>
<td>1.3</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>T2N0L1G3</td>
<td>IDC multifocal</td>
<td>2/22, 13^b</td>
<td>1</td>
<td>2.5, 1</td>
<td>0.9, 1.5</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>T1aN1aL1G3</td>
<td>IDC multifocal</td>
<td>2/18, 15^b</td>
<td>2-3</td>
<td>3.2, 2.8</td>
<td>1.5, 1.3</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>T2N1bL1G2</td>
<td>IDC multifocal</td>
<td>2/25, 12^b</td>
<td>2-3</td>
<td>4.1, 3.5, 3.3^d</td>
<td>0.9, 0.8</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>T3N1aL1G2</td>
<td>ILC</td>
<td>1/50</td>
<td>NA^c</td>
<td>2.5^e</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>T2N1bL1G3</td>
<td>ILC</td>
<td>1/50</td>
<td>NA</td>
<td>No increased uptake^c</td>
<td></td>
</tr>
</tbody>
</table>

* pTNM, postoperative histopathological classification.
* Size of the greatest nodule(s).
* Score 0–3.
* Also contains areas with much lower score.
* NA not assessed.
* Ratio of a sternal lymph node metastasis.
* Only an incomplete delineation was possible.
* Compared with surrounding parenchyma.
RESULTS

In the 10 patients with proven primary breast carcinoma, histopathology identified IDCs in 7 and ILCs in 3 cases (Table 1). Two patients had bilateral disease and 8 patients had unilateral disease, in some instances with multiple tumor sites. One patient with IDC had a large, solid intraductal component of the tumor and was lactating at the time of scintigraphy. Of the 17 histologically confirmed breast lesions with an average size of 25 ± 16 mm (range, 10–80 mm), PET clearly visualized 14 (82%) as foci of increased 68Ga chelate accumulation. Tumor:normal breast tissue and tumor:blood ratios were 3.0 ± 0.9 (range, 1.8–4.2) and 0.9 ± 0.3 (range 0.5–1.5), respectively. 68Ga chelate clearance from the circulation was biphasic with a \( t_{1/2a} \) (extravasation and renal excretion) of about 4.5 min and a \( t_{1/2b} \) (renal excretion) of 100 ± 15 min, which was similar to the values obtained in two volunteers not pretreated with BS-MAb (\( t_{1/2b} \approx 90 \) min). Blood clearance data and the tumor:blood ratios were used to estimate a tumor uptake of 0.0029 ± 0.0013% ID/g (range, 0.0012–0.0050) of the 68Ga chelate 60 min postinjection, which corresponds to a standard uptake value of ~2. 68Ga chelate uptake in lesions examined immunohistochemically with the BS-MAb and with an immunoperoxidase technique roughly correlated with the score of antigen expression. An exception was patient 6, who showed medium and high 68Ga chelate uptake but a score of only 1. Tissue sections of tumor foci with medium and high antigen expression and normal ductuli, some of which contain appreciable amounts of shed antigen, are presented in Fig. 1.

PET imaging identified two groups of patients, which differed in their radioactivity accumulation of normal breast parenchyma. One group, which included patients 1, 3, and 5–7 had a low parenchymal uptake that did not exceed that of surrounding adipose and fibrous tissues (Figs. 2–5), whereas in the second group of patients (patients 2 and 8–10), a 2- to 5-fold increase in uptake was noted. Lesion detection in patients with increased uptake was possible in two cases (patients 2 and 8), because tumor sites positively contrasted with increased parenchymal activity (Figs. 6 and 7). It was questionable in one patient with bilateral disease (patient 9) because the activity levels in both lesions and breast parenchyma were too similar, allowing a delineation of only one lesion, which was mainly surrounded by fibrous and adipose tissue (both lesions were classified as false-negative findings). A malignant lesion in patient 10, who showed the highest parenchymal uptake, was only suggested by a corresponding region of decreased parenchymal activity (false-negative finding: Fig. 8). A rare combination of malignant lesions and lactating breast tissue was found in one patient (patient 4). PET identified two invasive foci and a large, strongly accumulating intraductal tumor in the right breast as well as increased uptake in the nonmalignant contralateral breast, which was conspicuous because of its annular shape (Fig. 9).

Detection of axillary lymph nodes metastases was hampered by a high activity in large blood vessels located proximal to the lymph nodes. Positive results were obtained in patient 10 with proven axillary level I–III metastases (Fig. 8), and in patient 2 with axillary and infraclavicular metastases (Fig. 6). A parasternal lymph node of ~10 mm in size was visualized in patient 8 (Fig. 7) and subsequently confirmed by computed tomography.

DISCUSSION

PET is the most efficient imaging technique in nuclear medicine. Our study demonstrates that it is feasible to combine IS and PET via pretargeting with antitumor/anti-Ga chelate BS-MAb. The positron emitter 68Ga used for imaging was readily produced by a radionuclide generator. The estimated absorbed radiation dose for a patient proved to be similar for the 68Ga chelate and 18F-labeled fluorodeoxyglucose. The labeling step of our pretargeting technique, the 68Ga chelate binding to the anti-chelate part of the BS-MAb, proved to be of high affinity, providing a Ga chelate binding at subnanomolar levels of BS-MAb. A general applicability of this labeling step is suggested by...
animal experiments using different antitumor MAbs but the same anti-Ga chelate MAb for BS-MAb preparation. The efficacy of our pretargeting approach to detect breast cancer, however, predominantly depended on the physiological features of TAG 12 binding to the anti-MUC1 MAb 12H12, used as the tumor localization step. Pretargeting in breast carcinoma patients with the 12H12/3A10 BS-MAb resulted in an average 0.003% iD/g tumor uptake of the 68 Ga chelate and tumor:normal breast and tumor:blood ratios of 3.0 and 0.9, respectively. The tumor uptake in patients roughly corresponded to that extrapolated from mammary carcinoma-bearing nude mice (8). This comparatively low uptake in animals and patients reflects the fast tumor kinetics of the BS-MAb in relation to its low tumor affinity. The tumor contrasts with blood and normal breast tissue, however, were reduced by a factor of 3 compared with the animal data. This loss in contrasts seems to be a consequence of the slower $\beta$-component of 68 Ga chelate blood clearance in humans.

Compared with data reported previously from quantitative patient studies using the F(ab)2 fragments or the native anti-MUC1 MAb HMFG1, labeled either with the positron emitter $^{124}$I (16) or with $^{111}$In (17), the average tumor:blood ratio of the 68 Ga chelate 1 h postinjection was superior to that of the MAb and was similar to that of the $^{111}$In-labeled F(ab')2 at 48 h. Conventional gamma camera imaging with the $^{111}$In-labeled F(ab')2 detected three of seven primary lesions as foci of increased activity. This compares with 14 true-positive results of 17 with the 68 Ga chelate and PET, demonstrating the higher sensitivity of PET at low tumor contrast.

An increased, bilateral activity accumulation throughout the non-cancerous breast parenchyma, seen in 4 of 10 patients, resulted in the false-negative findings in this study. The homogeneous distribution of activity rules out focal benign breast diseases such as fibroadenoma or atypical hyperplasia. Additionally, no correlation with the blood levels of estrogens and progestins was observed (data not shown), which excludes an influence from menses, contraceptives, and hormone supplementation. It seems likely that this prominent parenchymal pattern arises from fibrocystic changes, which cause variable proliferation of the ductal epithelial cells leading to enhanced antigen expression and an increased accessibility for the BS-MAb. An additional contribution for the enhanced parenchymal uptake may be attributable to the shedding of the MUC1 antigen (9). Shedding into
this ductuli should result in antigen accumulation, as suggested by immunohistochemical staining (Fig. 1c). False-positive results, attributable to the prominent parenchymal activity described for conventional IS with anti-CEA MAbs (18), were not obtained. Similarly, the enhanced $^{68}$Ga chelate uptake in the contralateral breast of patient 4 (Fig. 9), attributed to an overexpression of the MUC1 antigen by lactating glandular cells (19), should not lead to false-positive readings because of its distinctive shape and the patient’s anamnesis.

Activity accumulation in those tumor lesions assessed histochemically approximately correlated with antigen density, but visualization of tumors could also be affected by antigen shedding. As described for the prominent $^{68}$Ga chelate accumulation in the parenchyma, antigen that is shed into the tumor surrounding ductuli may contribute to the high and homogeneous activity of the solid, intraductal tumor of patient 4 (Fig. 9). An opposite effect of antigen shedding on $^{68}$Ga chelate uptake might be obtained in infiltrating tumor lesions because of enhanced perfusion rates, which should result in a more rapid clearance of antigen shed from the tumor tissue and of BS-MAb bound to it. Because the pretargeting time of 18–19 h approximately corresponds to the half-life of MUC1 shedding (20), appreciable amounts of initially cell-bound BS-MAb might be cleared as free antigen/BS-MAb immune complex. Such an effect may explain the low tumor uptake found in patient 10 (Fig. 8). This patient was also examined with dynamic magnetic resonance imaging to access tumor microcirculation via gadolinium diethylenetriaminepentaacetic acid (21). Dynamic magnetic resonance imaging indicated a markedly increased perfusion of the tumor area and a much lower, but above normal, perfusion of parenchyma (data not shown). Because this patient had the highest parenchymal uptake, the moderately increased activity at the tumor site contrasted negatively with the parenchyma.

Detection of axillary lymph node metastases, not a primary goal of this study, remains inconclusive. Lamki et al. (22) reported a low sensitivity of antimucin MAbs for localizing axillary metastases. Tissue counts of resected lymph nodes were similar for both tumor-bearing and tumor-negative nodes. Larger lymph node metastases, 20–30 mm in size, were successfully imaged with the HMF1G1 (23). Pretargeting and PET visualized axillary metastases of similar size, but appeared to be more sensitive for the detection of internal mammary and parasternal metastases.

At the present stage of investigation, our pretargeting approach using an anti-mucin BS-MAb shows no general clinical advantage over $^{18}$F-FDG, which is presently evaluated for breast cancer characterization (24, 25). On the one hand, the specificity of the BS-MAb appears to be superior to that of FDG because no false-positive results were obtained, whereas FDG shows a specificity of 85–90% because of an accumulation in inflammatory and benign lesions. On the other hand, a general sensitivity of $\geq 90\%$ for detecting malignant lesions, as reported for FDG, might not be obtained with an antimucin BS-MAb because of the lower tumor contrasts and antigen shedding. However, an exception might be the sensitivity for detecting ductal carcinoma in situ. This tumor species often shows a lower FDG uptake than IDC (26), whereas the BS-MAb accumulates more strongly in intraductal tumor sites.

**Conclusions.** This study suggests, that a relatively complicated, three-step IS is feasible in a clinical setting and that the administered doses of the reagents are safe, because none of the 10 patients showed any signs of adverse reaction. Although it was shown that the PET-based IS has potential in clinical medicine, with obvious imaging advantages, the presented pretargeting approach using an anti-MUC1 BS-MAb for breast cancer detection did not prove to be optimal because of the fast tumor kinetics of the BS-MAb and the nonspecific distribution of shed antigen. Consequently, pretargeting of breast tumors with anti-CEA and anti-EGFR BS-MAbs, not affected by antigen shedding, should be more sensitive than with the antimucin BS-MAb. Because these MAbs are available with affinities of $>10^5 M^{-1}$, much higher than those described for antimucin MAbs (27), additionally increased tumor: tissue ratios compared with the present approach can be expected, as can be deduced from previous animal experiments using BS-MAbs of higher tumor affinity (6, 7). Bearing in mind that CEA and EGFR antigens are less frequently expressed by breast carcinomas than MUC1, pretargeting with the corresponding BS-MAbs might be less suitable for screening of breast abnormalities but should offer promise to those patients with antigen-positive tumors. Especially pretargeting with an anti-EGFR BS-MAb might contribute to a specific therapy monitoring because anti-EGFR MAbs show potential for an immunotherapy in 25–30% of human breast tumors. Finally, this study elucidates the prerequisites for a successful pretargeting with PET of other tumor entities.

**REFERENCES**


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