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Clinical Significance of HER2-Targeted PET/CT Imaging for Response Monitoring in Breast Cancer Patients

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Abstract

Breast cancer is characterized by marked variability in human epidermal growth factor receptor 2 (HER2) expression across and within tumors. In routine clinical practice, obtaining repeat tissue samples from recurrent or metastatic sites is often invasive, technically difficult, and sometimes infeasible. Therefore, alternative strategies capable of reliably characterizing HER2 status and tracking treatment efficacy are needed. This study investigated the clinical utility of HER2-targeted PET/CT imaging for noninvasive evaluation of HER2 expression and longitudinal assessment of therapeutic response in breast cancer. In this exploratory investigation, data were derived from a prospective clinical study involving adult breast cancer patients who underwent both ^{18}F-Al-NOTA-HER2-BCH PET/CT and ^{18}F-FDG PET/CT at Beijing Cancer Hospital between June 2020 and July 2023 (ClinicalTrials.gov identifier: NCT04547309).

A total of 59 patients with a median age of 55 years were included in the analysis. Among lesions classified as HER2 immunohistochemistry (IHC) 3+, uptake on HER2-targeted PET/CT was significantly higher prior to anti-HER2 therapy compared with post-treatment imaging (median SUVmax 19.9 [95% CI: 15.7–25.3] vs 9.8 [95% CI: 5.6–14.7]; P = .006). Pretreatment SUVmax values demonstrated a statistically significant positive association with HER2 IHC status (P = .034), with substantially greater tracer accumulation observed in HER2-positive lesions than in HER2-negative lesions (17.9 ± 13.2 vs 1.1 ± 0.3; P = .007). Imaging further revealed pronounced heterogeneity in HER2 expression, both between primary tumors and metastatic deposits (22.9%) and across distinct metastatic sites (26.7%). Notably, higher baseline SUVmax values were associated with improved therapeutic response. The HER2-targeted PET/CT protocol was safely completed by all participants without adverse events. HER2-targeted PET/CT represents a feasible, safe, and quantitative imaging modality for evaluating HER2 expression in breast cancer. By enabling whole-body, noninvasive assessment of receptor status and treatment response, this approach may support more precise and individualized therapeutic decision-making in clinical oncology.

Keywords: Tumor heterogeneity, HER2-targeted PET/CT, Response monitor, Breast cancer

Introduction

Prognostic outcomes in breast cancer vary considerably according to molecular subtype and disease stage, with approximately 20–30% of patients experiencing recurrence or metastasis after radical mastectomy [1, 2]. HER2 positivity is observed in roughly 15–20% of cases and is associated with poorer prognosis and reduced overall survival [3, 4]. Anti-HER2 therapies are therefore recommended throughout the disease course to improve survival in advanced HER2-positive breast cancer. HER2 expression exhibits considerable heterogeneity, reported in up to 34% of cases, which may manifest as intralesional (within a single tumor), interlesional (between primary and metastatic sites or among different metastases), and temporal variability over the course of treatment [5–8]. Such heterogeneity is a recognized negative predictor of response to HER2-targeted therapies [8]. Accurate assessment of HER2 status is therefore critical for selecting appropriate therapeutic strategies in advanced disease, with current guidelines

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advocating repeated biopsies of metastatic lesions to determine molecular subtypes [2–4]. Recent investigations have also highlighted the dynamic nature of HER2-low status in triple-negative breast cancer (TNBC), with serial biopsies showing an increased probability of HER2-low detection correlated with the number of biopsies performed [9]. However, repeated or multisite biopsies are clinically challenging and carry procedural risks. In the absence of metastatic biopsy data, treatment is typically guided by the molecular profile of the primary tumor, a practice that may be confounded by tumor heterogeneity.

PET/CT molecular imaging plays a multifaceted role in breast cancer, encompassing lesion detection, staging, heterogeneity evaluation, treatment response monitoring, and follow-up, while informing therapeutic decisions [10–12]. Additionally, PET/CT can assess estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, facilitating comprehensive molecular characterization of both primary and metastatic tumors [4]. Traditional PET/CT imaging with 18F-fluoro-2-deoxyglucose (18F-FDG) reflects tumor metabolic activity but has limited sensitivity in certain organs, such as the brain and liver [13]. In contrast, HER2-targeted probes specifically bind to HER2 receptors on tumor cells, enabling precise quantification of HER2 expression across systemic lesions [14–17]. This dynamic monitoring capability provides critical insights to optimize anti-HER2 therapy. Consequently, HER2-targeted PET/CT imaging offers a noninvasive, quantitative approach that addresses biopsy-related challenges and accounts for HER2 heterogeneity [18, 19].

At Beijing Cancer Hospital's Department of Nuclear Medicine, our team has developed and translated the use of Al18F-NOTA-HER2-BCH for clinical HER2-targeted PET/CT imaging in HER2-positive patients. This work has generated a robust collection of clinical data and established a strong research foundation [20, 21]. In this study, we evaluated the safety, feasibility, biodistribution, and tumor-targeting efficacy of Al18F-NOTA-HER2-BCH in breast cancer patients. We specifically aimed to clarify the clinical utility of HER2-targeted PET/CT by examining correlations between PET/CT-derived maximum standardized uptake values (SUVmax) and HER2 immunohistochemistry (IHC), as well as the relationship between SUVmax and tumor response amid heterogeneity. These results are expected to provide novel insights and practical guidance for refining anti-HER2 therapeutic strategies.

Materials and Methods

Study design and participants

This study represents an exploratory analysis nested within a prospective investigation carried out at Beijing Cancer Hospital from June 2020 to July 2023. Participants were selected based on their completion of both HER2-targeted and 18F-FDG PET/CT scans, aimed at comparing the diagnostic performance of Al18F-NOTA-HER2-BCH versus 18F-FDG in detecting HER2-positive breast cancer lesions. Ethical clearance was obtained from the Medical Ethics Committee of Beijing Cancer Hospital (Approval No. 2019KT114), and the study was registered on ClinicalTrials.gov (NCT04547309). Written informed consent was secured from all participants. Imaging and clinical data were independently reviewed by two board-certified oncologists.

Eligible patients were adults (≥18 years) with pathologically confirmed breast cancer of any stage, including early and advanced disease, and had documented HER2 status. Additional inclusion criteria comprised measurable or evaluable disease per RECIST version 1.1 [22], an ECOG performance status of 0–2, and a life expectancy exceeding three months. Patients had to consent to undergo both HER2-targeted and 18F-FDG PET/CT scans at the study center. Key exclusion criteria included a history of other primary malignancies, significant cardiac, hepatic, or renal dysfunction, PET/CT imaging performed during adjuvant therapy, pregnancy or lactation, and inability to tolerate supine positioning for over one hour.

All participants had at least one lesion confirmed via biopsy for HER2 assessment, predominantly from the breast. In patients with metastatic disease, only a subset of distant lesions was biopsied due to ethical considerations. HER2 positivity was defined according to ASCO/CAP guidelines as IHC 3+ or IHC 2+ with FISH-confirmed amplification. HER2-low status included IHC 1+ or IHC 2+ without FISH-confirmed amplification. Hormone receptor positivity was defined as ER and/or PR expression ≥1% in either primary or metastatic tumors.

HER2-targeted and 18F-FDG PET/CT imaging

Al18F-NOTA-HER2-BCH, synthesized in-house at Beijing Cancer Hospital, was administered intravenously at a dose of 222 ± 18.5 MBq. PET/CT scans were performed two hours post-injection. To reduce non-specific uptake in the liver, a co-injection of 1 mg unlabeled HER2-affibody was given [23]. Within a 7-day period, all participants also underwent 18F-FDG PET/CT imaging (3.7 MBq/kg) following a minimum 6-hour fast, with imaging acquired one hour after tracer injection.

Scans were performed using a Biograph mCT Flow 64 scanner (Siemens, Erlangen, Germany) covering the region from the skull apex to mid-thigh. PET images were acquired in 3D flow mode with a bed speed of 1 mm/s and an axial field of view of 21.6 cm. Image reconstruction employed the TrueX + TOF algorithm via the Siemens Multimodality Workplace platform, with attenuation correction using low-dose CT data.

Image evaluation

Two experienced radiologists analyzed all images. SUVmax values were calculated using an automatically generated 3D ROI encompassing 60% of the lesion volume. Lesions with SUVmax exceeding background tissue were considered suspicious. Semiquantitative evaluation deemed any focal accumulation of Al18F-NOTA-HER2-BCH or 18F-FDG above adjacent tissue as potentially malignant.

Assessment of treatment response

Tumor response was assessed using RECIST 1.1 criteria via CT or MRI. Responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients achieving CR or PR. Progression-free survival (PFS) was measured from the initiation of therapy to disease progression or death, whichever occurred first. Patients underwent evaluations every two treatment cycles, including physical examination, laboratory testing, and imaging via CT or MRI.

Statistical analysis

Patient demographics, clinical outcomes, and PET/CT imaging results were collected from medical records and summarized using descriptive statistics. Frequencies and percentages were used to report categorical data. Differences between groups were assessed using the chi-square test for categorical variables and the Mann-Whitney U test for nonparametric comparisons. The relationship between SUVmax values from PET/CT scans and HER2 expression by IHC was analyzed using Pearson correlation. Kaplan-Meier survival curves were generated to estimate progression-free survival (PFS), and differences between groups were tested using the log-rank method. All analyses were conducted using SPSS version 15.0 (SPSS Inc., Chicago, IL), and statistical significance was defined as a P value less than 0.05.

Results and Discussion

Patient characteristics

From the initial cohort of 86 breast cancer patients who underwent both Al18F-NOTA-HER2-BCH and 18F-FDG PET/CT scans, 59 women met the study criteria and were included in the analysis. Participant ages ranged from 30 to 88 years, with a median of 55 years. Among them, 50 patients (approximately 85%) were classified as HER2-positive, while 9 patients (15%) were HER2-negative.

PET/CT imaging was performed for initial tumor assessment in 15 patients (25%), with 9 of these scans conducted prior to neoadjuvant therapy and 6 shortly after therapy initiation. The remaining 44 patients (75%) underwent imaging in the context of recurrent or metastatic disease: 13 patients before starting first-line treatment and 31 after commencing therapy. A comprehensive summary of demographic and baseline clinical characteristics is presented in **Table 1**.

All participants tolerated the HER2-targeted PET/CT procedure without any adverse pharmacologic effects or physiological complications related to Al18F-NOTA-HER2-BCH administration.

Table 1. Demographic and baseline clinical features of female breast cancer patients (n = 59)

Characteristic	n (%)
Age, years [median (range)]	55 (30–88)
ECOG Performance Status	
2	1 (1.7)
1	14 (23.7)
0	44 (74.6)
Histopathological Subtype	
Invasive lobular carcinoma	7 (11.9)
Invasive ductal carcinoma	50 (84.7)
Metaplastic carcinoma	1 (1.7)
Micropapillary carcinoma	1 (1.7)

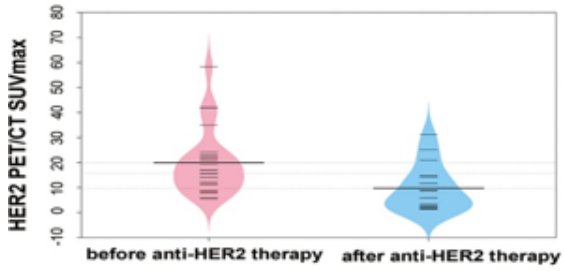
Hormone Receptor Status	
HR-negative	39 (66.1)
HR-positive	20 (33.9)
HER2 Expression	
HER2-negative	9 (15.3)
HER2-positive	50 (84.7)
Treatment Phase at Time of PET/CT	
Neoadjuvant therapy	15 (25.4)
Salvage/recurrence treatment	44 (74.6)
Sites of Metastasis in 44 Patients	
Lung	17 (38.6)
Bone	24 (54.5)
Liver	12 (27.3)
Chest wall	11 (25.0)
Brain	3 (6.8)

Abbreviations: ECOG= Eastern Cooperative Oncology Group; HR= hormone receptor; HER2= human epidermal growth factor receptor 2.

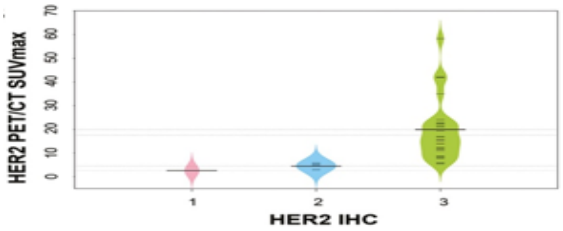
SUVmax in HER2-targeted PET/CT and HER2 IHC

In this analysis, 48 lesions were examined using both HER2-targeted PET/CT and pathological IHC assessment. Of these, 27 lesions (56.3 percent) were imaged before any anti-tumor therapy, whereas the remaining 21 lesions (43.8 percent) were evaluated while patients were receiving treatment. Among the lesions, 39 showed a HER2 IHC score of 3+. Prior to the initiation of anti-HER2 therapy, 23 of these lesions were scanned, while 16 were assessed after therapy had begun.

A notable difference in tracer uptake was observed between pre-treatment and on-treatment lesions. The median SUVmax for lesions imaged before therapy was 19.9 (95% CI: 15.7–25.3), compared with 9.8 (95% CI: 5.6–14.7) for lesions scanned during treatment, a statistically significant reduction (P = 0.006; **(Figure 1a)**).



a)



b)

Figure 1. (a) a comparison of maximum standardized uptake values (SUVmax) in 39 lesions classified as HER2 IHC 3+, showing values before versus after anti-HER2 treatment; and (b) the association between SUVmax on HER2-targeted PET/CT and HER2 status by immunohistochemistry (IHC) in 27 patients who underwent imaging prior to any anti-tumor treatment.

Recognizing that anti-HER2 treatment reduces SUVmax in lesions, we additionally investigated the link between SUVmax and HER2 expression (as assessed by IHC and FISH) in these 27 treatment-naïve patients. The results demonstrated a statistically significant association (P = .034; **(Figure 1b)**). Specifically, the 23 patients with HER2 IHC 3+ status before therapy had a mean SUVmax of 19.9. Overall, lesions with HER2-positive pathology (24/27, 88.9 percent) showed markedly higher SUVmax than those with HER2-negative pathology (3/27, 11.1 percent) (17.9 ± 13.2 versus 1.1 ± 0.3; P = 0.007).

As shown in **Figure 2a**, the tracer Al^{18}F-NOTA-HER2-BCH outperformed ^{18}F-FDG in identifying primary tumors and suspected lymph node metastases (detecting 20 versus 7 lesions). The axillary lymph nodes identified had an average diameter of 0.72 cm, including the smallest at just 0.29 cm. Notably, Al^{18}F-NOTA-HER2-BCH detected six lymph nodes measuring less than 0.50 cm. In HER2-negative lesions **(Figure 2b)**, Al^{18}F-NOTA-HER2-BCH displayed minimal uptake at tumor sites—consistent with low HER2 expression by IHC—while ^{18}F-FDG showed high uptake.

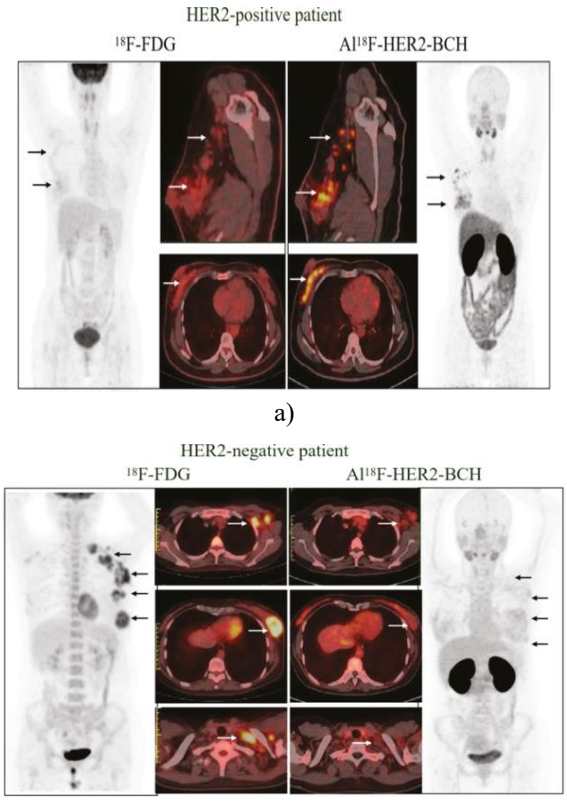


Figure 2. Scans from 18F-FDG PET/CT and Al18F-NOTA-HER2-BCH PET/CT in two breast cancer patients with differing HER2 status. (a) shows a 47-year-old woman diagnosed with primary diffuse breast carcinoma involving multiple lymph nodes, confirmed as strongly HER2-positive (IHC score 3+) by biopsy.(b) features a 39-year-old woman with recurrent disease and distant metastases, confirmed as weakly HER2-positive (IHC score 1+) by biopsy.

Variation in HER2 expression

HER2 expression in breast cancer demonstrated considerable variability, observed across primary tumors, metastatic sites, and different metastatic deposits within the same patient. Immunohistochemistry (IHC) and histopathology were performed on the primary tumors of all 59 enrolled breast cancer patients, identifying HER2-positive status in 43 cases (72.9%) and HER2-negative status in 16 cases (27.1%). Biopsies of metastatic sites were obtained in 35 patients (59.3%), with 28 (80.0%) showing HER2 positivity and 7 (20.0%) showing negativity. Among the 35 patients with assessable data from both primary and metastatic lesions, consistent HER2 positivity was seen in 21 patients (60.0%), consistent negativity in 6 patients (17.1%), and discordant HER2 status between primary and metastatic sites in 8 patients (22.9%). Detailed HER2 status information for these eight patients demonstrating significant discordance is presented in **Table 2**.

Table 2. Pathological HER2 expression in 8 breast cancer patients exhibiting heterogeneity between primary and metastatic sites

No.	HER2 FISH – Primary Site	HER2 IHC – Primary Site	HER2 Status – Primary Site	HER2 FISH – Metastatic Site	HER2 IHC – Metastatic Site	HER2 Status – Metastatic Site	SUVmax on HER2 PET/CT at Recurrence
1	NA	0	Negative	Positive	2+	Positive	1.8
2	NA	0	Negative	NA	3+	Positive	10.9
3	Negative	2+	Negative	Positive	2+	Positive	7.3
4	Negative	2+	Negative	NA	3+	Positive	8.7
5	NA	0	Negative	NA	3+	Positive	8.7
6	Positive	2+	Positive	NA	1+	Negative	8.5
7	Negative	1+	Negative	NA	3+	Positive	35.7
8	Negative	1+	Negative	Positive	2+	Positive	2.4

Abbreviations: HER2= human epidermal growth factor receptor 2; IHC= immunohistochemistry; FISH= fluorescence in situ hybridization; SUV= standard uptake value; NA= not available.

In the group of patients who underwent HER2-targeted PET/CT, multiple lesions were evaluated in 30 individuals. Semiquantitative assessment revealed uniform HER2 expression in 22 patients (73.3%), while 8 patients (26.7%) exhibited differing HER2 expression levels across lesions. Additionally, the SUVmax measurements of the metastatic lesions in these patients highlighted the observable heterogeneity in HER2 expression as detected by HER2-targeted PET/CT **(Figure 3)**.

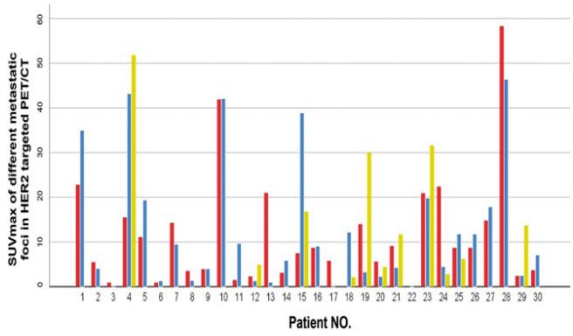


Figure 3. SUVmax measurements of various metastatic lesions on HER2-targeted PET/CT in thirty patients with advanced breast cancer.

SUVmax from HER2-targeted PET/CT and treatment response

In 9 HER2-positive breast cancer patients who underwent HER2-targeted PET/CT before neoadjuvant therapy, a pathological complete response (pCR) was achieved in 66.7% (6/9), while the remaining three patients showed a partial response (PR) at pre-surgical assessment. Although patients who attained pCR tended to have higher SUVmax values compared to those with PR, the difference was not statistically significant (P = .302; **(Figure 4a)**). Among these 9 patients, 8 (88.9%)—including all 6 pCR and 2 PR cases—continued with adjuvant trastuzumab and pertuzumab, whereas 1 patient (11.1%) with PR received adjuvant trastuzumab emtansine (T-DM1) following surgery.

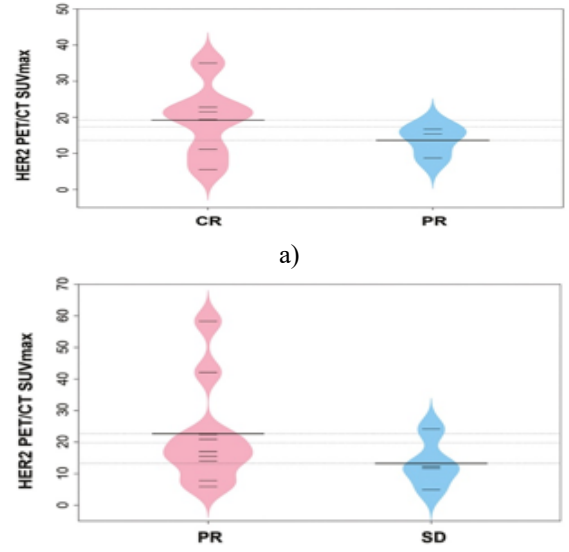


Figure 4. (a) SUVmax of lesions on HER2-targeted PET/CT in 9 HER2-positive breast cancer patients prior to neoadjuvant therapy, comparing those who achieved CR (n = 6) versus PR (n = 3); (b) SUVmax of lesions on HER2-targeted PET/CT in 13 HER2-positive patients before first-line therapy, comparing those with PR (n = 9) versus SD (n = 4).

Progression-free survival (PFS) and best overall response were further evaluated in 13 HER2-positive advanced breast cancer patients who underwent HER2-targeted PET/CT before starting first-line therapy. At the time of analysis, the median PFS was not reached; 9 patients (69.2%) achieved PR, while 4 patients (30.8%) showed SD. Although SUVmax values tended to be higher in patients with PR compared to those with SD, the difference did not reach statistical significance (P = 0.280; **(Figure 4b)**). No meaningful correlation was observed between SUVmax and PFS after first-line therapy in patients who experienced PD, with a Pearson correlation coefficient of 0.092. Following first-line treatment failure, 2 patients received second-line therapy with pyrotinib plus capecitabine, and another 2 patients were treated with T-DM1.

Figure 5a 57-year-old woman newly diagnosed with metastatic breast cancer underwent baseline lesion evaluation using Al18F-NOTA-HER2-BCH PET/CT. After 3 months of anti-HER2 therapy (docetaxel/trastuzumab/pertuzumab), follow-up imaging demonstrated complete disappearance of the primary tumor and diffuse lung metastases, indicating a clinical CR.

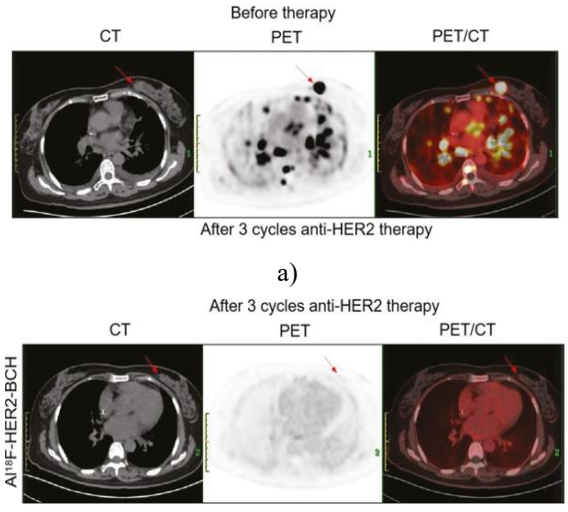


Figure 5. PET/CT imaging of the same patient with multiple metastases using 18F-FDG (a) and Al18F-

NOTA-HER2-BCH (b) before and after 3 months of anti-HER2 therapy. Arrows indicate the lesions.

Patients with advanced HER2-positive breast cancer generally have a poor prognosis and benefit most from early and continuous anti-HER2 therapy to improve survival outcomes [24]. Due to the heterogeneous expression of HER2 in breast tumors, current guidelines recommend re-biopsy of recurrent or metastatic lesions to accurately determine the cancer subtype [25–28]. Nevertheless, logistical and clinical constraints often limit the feasibility of repeated biopsies. In this context, HER2-targeted PET/CT imaging has been proposed as a non-invasive alternative, allowing assessment of HER2 expression across the whole body rather than relying on single-site biopsies [29–32].

Both preclinical and clinical studies have investigated molecular imaging strategies using HER2-targeting antibodies, such as trastuzumab and pertuzumab, labeled with isotopes including 64Cu (half-life: 12.7 hours) and 89Zr (half-life: 78.4 hours) for PET/CT imaging in breast and gastric cancer [33–36]. The ZEPHIR trial demonstrated that 89Zr-trastuzumab PET/CT, alone or combined with early FDG PET/CT, could assess HER2 heterogeneity in HER2-positive breast cancer and identify lesions and patients unlikely to benefit from T-DM1 therapy [37]. However, the prolonged circulation of antibody-based radiotracers motivates the development of smaller HER2-targeting agents. ZHER2:342, a 58–amino-acid single-chain protein forming three α-helices, binds specifically to HER2 [16], and recent efforts focus on using radionuclide-labeled ZHER2:342 derivatives for tumor imaging. In the present study, we employed Al18F-NOTA-HER2-BCH for HER2-targeted PET/CT.

Preclinical investigations have shown that HER2-affinity imaging agents preferentially accumulate in xenograft tumors with high HER2 expression [17]. These agents have been used to detect metastases and evaluate anti-HER2 therapy efficacy, as indicated by reduced tracer uptake following trastuzumab treatment [38]. Consistently, in our research, the SUVmax of HER2 IHC 3+ lesions prior to anti-HER2 therapy (n = 23) was significantly higher than that observed post-therapy (n = 16) (19.9, 95% CI: 15.7–25.3 vs 9.8, 95% CI: 5.6–14.7; P = .006). Moreover, a significant positive correlation was observed between pre-treatment SUVmax and HER2 status assessed by IHC in 27 patients (P = .034). Lesions with positive HER2 pathology showed markedly higher SUVmax compared with those that were HER2-negative (17.9 ± 13.2 vs 1.1 ± 0.3; P = .007), corroborating previous findings that tracer uptake reflects HER2 expression levels [32, 39]. These results support the potential of HER2-targeted PET/CT as a reliable, non-invasive modality for accurately evaluating HER2 status, particularly when biopsy samples are unavailable.

Our study highlights the heterogeneity of HER2 expression across both primary and metastatic sites, as well as among different metastatic lesions, by combining pathological evaluation with HER2-targeted PET/CT imaging to illustrate spatial interlesional variability. Pathological analysis revealed that 22.9% of patients (8 of 35) exhibited discrepancies in HER2 expression between primary tumors and metastatic lesions. Similarly, in HER2-targeted PET/CT imaging, 26.7% of patients (8 of 30) showed variation in HER2 expression across multiple metastatic sites based on SUVmax values. These results are consistent with prior reports indicating that up to 34 percent of breast cancer patients demonstrate heterogeneous HER2 expression [25–28]. Such phenotypic variability complicates the management of HER2-positive breast cancer, underscoring the limitations of basing systemic therapy decisions solely on the primary tumor's subtype. Consequently, repeated biopsies are necessary to capture these dynamic changes [8]. Implementing noninvasive, accurate, and reproducible methods to assess HER2 expression could address these clinical challenges.

Recent investigations have integrated 64Cu-DOTA-trastuzumab PET imaging with MRI and mathematical modeling to predict patient-specific responses to neoadjuvant chemotherapy and HER2-targeted therapy [40]. Additionally, 64Cu-DOTA-trastuzumab PET/CT has been shown to predict the effectiveness of HER2-targeted treatments by quantifying HER2 levels, supporting observations that HER2-positive lesions respond more favorably to anti-HER2 therapy than HER2-negative lesions [41]. In our previous work, 68Ga-NOTA-MAL-MZHER2 PET imaging was used to assess treatment outcomes in advanced gastric cancer, revealing that patients with high lesion uptake experienced prolonged PFS of 4–9 months versus 2–3 months for low-uptake cases [23]. In this research, we examined the relationship between HER2-targeted PET/CT SUVmax and tumor response, including therapeutic outcomes and PFS, during both neoadjuvant and first-line therapy. Our results suggested a trend toward better response among patients with higher pre-treatment SUVmax, although

statistical significance was not achieved, likely due to the limited sample size and relatively short follow-up.

Importantly, no adverse events related to HER2 PET tracer administration were observed, supporting the safety and feasibility of HER2-targeted PET/CT for evaluating HER2 expression in breast cancer. This noninvasive, whole-body imaging approach allows for repeated assessment of HER2 status, including after disease recurrence or metastasis.

Overall, our findings indicate that Al18F-NOTA-HER2-BCH PET/CT offers a promising noninvasive alternative to conventional, nonspecific radiotracers for assessing HER2 expression in breast cancer lesions. The scarcity of repeated biopsies of identical metastatic tumors has left gaps in understanding how HER2 expression evolves during therapy. Given that many metastatic breast cancer cases eventually develop treatment resistance, sequential HER2-targeted PET imaging could provide early indications of suboptimal response. Real-time, quantitative evaluation using Al18F-NOTA-HER2-BCH PET/CT allows monitoring of HER2 levels during anti-HER2 treatment, offering potential for prognostic assessment, guiding therapeutic decisions, and detecting emerging resistance.

This research had several limitations. The relatively small cohort limited the range of HER2 heterogeneity observed. Ethical and practical constraints prevented histopathological confirmation of every detected lesion, and reliance on a single biopsy per patient restricted the pathological evaluation of intra-patient heterogeneity. Further research is needed to clarify the relationship between SUVmax changes in HER2-targeted PET/CT and therapeutic response, providing deeper insights in future studies.

Conclusion

HER2-targeted PET/CT enables real-time, noninvasive, and quantitative assessment of HER2 expression across multiple lesions in breast cancer patients, addressing challenges such as biopsy limitations, tumor heterogeneity, and comprehensive evaluation of therapy effectiveness. This imaging approach facilitates pre-treatment evaluation and monitoring of HER2 expression dynamics during therapy, supporting oncologists in tailoring personalized and optimized treatment strategies for breast cancer patients.

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Conflict of Interest: None

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Ethics Statement: The study protocol was reviewed and approved by the Medical Ethics Committee of Beijing Cancer Hospital and Clinical Trial Management (Ethics Approval License No.2019KT114). Informed consent was obtained from the participants included in this study.

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