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Breast Cancer

Pretreatment ^{18}F-FDG Uptake Heterogeneity Predicts Treatment Outcome of First-Line Chemotherapy in Patients with Metastatic Triple-Negative Breast Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography • Triple-negative breast neoplasms • Metastatic breast cancer • Genetic heterogeneity • Prognosis

Abstract

Background. Intratumoral heterogeneity of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake in primary tumor has proven to be a surrogate marker for predicting treatment outcome in various tumors. However, the value of intraindividual heterogeneity in metastatic diseases remains unknown. The aim of this study was to evaluate pretreatment positron emission tomography/computed tomography (PET/CT) ^{18}F-FDG-based heterogeneity for the prediction of first-line treatment outcome in metastatic triple-negative breast cancer (mTNBC).

Materials and Methods. mTNBC patients from three clinical trials (NCT00601159, NCT01287624, and NCT02341911) with whole-body ^{18}F-FDG PET/CT scan before first-line gemcitabine/platinum were included. Heterogeneity index (HI) and the maximum of FDG uptake (MAX) across total metastatic lesions (-T) on baseline PET/CT scans were assessed. HI was measured by MAX divided by the minimum FDG uptake across metastatic lesions. Optimal cutoffs were determined by time-dependent receiver operator characteristics (ROC) analysis. Progression-free survival (PFS) and overall survival (OS) were estimated by Kaplan-Meier method and compared by log-rank test.

Results. A total of 42 mTNBC patients were included in this study. The median PFS of patients with high HI-T (>1.9) and high MAX-T (>10.5) was significantly shorter than patients with low HI-T (<1.9; p = .049) and low MAX-T (<10.5; p = .001). In terms of OS, only high MAX-T was significant for poorer outcome (p = .013). ROC curve analysis confirmed the predictive value of MAX and HI in mTNBC patients. Area under the ROC curve for MAX-T and HI-T was 0.75 and 0.65, indicating a higher predictive accuracy than conventional clinical risk factors.

Conclusion. HI and MAX measured among metastatic lesions on pretreatment ^{18}F-FDG PET/CT scans could be potential predicators for first-line treatment outcome in patients with mTNBC. ***The Oncologist*** 2018;23:1144–1152

Implications for Practice: Intratumoral heterogeneity of ^{18}F-fluorodeoxyglucose (FDG) uptake in primary tumor has proven to be a robust surrogate predictive marker. A novel positron emission tomography/computed tomography (PET/CT) parameter-heterogeneity index (HI) to quantify the heterogeneous characteristics of metastatic disease is proposed. Triple-negative breast cancer (TNBC) is a highly heterogeneous disease and remains a clinical challenge. The predictive performance of HI, along with the maximum FDG uptake (MAX), measured on pretreatment PET/CT scans in patients with metastatic TNBC was evaluated. Results indicate that HI and MAX may serve as applicable imaging predicators for treatment outcome of metastatic TNBC in clinical practice.

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Introduction

Triple-negative breast cancer (TNBC) is defined as estrogen receptor (ER) negative, progesterone receptor negative, and human epidermal growth factor receptor 2 negative disease, which accounts for 15%–20% of breast cancer [1]. Compared with other subtypes, TNBC is associated with higher rate of recurrence, shorter disease-free survival, and poorer prognosis [2–4], remaining a clinical challenge for oncologists. The median survival for metastatic triple-negative breast cancer (mTNBC) is only 1 year [5]. Platinum-based chemotherapy has demonstrated promising efficacy in the treatment of mTNBC [6–9]. However, TNBC is a highly heterogeneous disease, which has been classified into six intrinsic molecular subtypes by gene expression profiling [10,11]. Predictive markers to identify mTNBC patients who could benefit more from platinum-based treatment are highly demanded.

Intratumor heterogeneity has been demonstrated to have profound implications on malignant behaviors and treatment responses [12–15]. Functional molecular imaging offers an important noninvasive approach to biologically characterize tumor heterogeneity and predict treatment outcome. Several studies have proven the predictive value of intratumor heterogeneity of baseline ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-positron emission tomography (PET) in various primary tumors, including esophageal cancer [16], lung cancer [17], cervical cancer [18], and early breast cancer [19,20]. Common methods include textural analysis [21,22], the coefficient of variance [23], cumulative standard uptake value (SUV)-volume histograms (CSH) [24], the area under the CSH [23,25], and fractal analysis [26].

Previous texture analysis had found that TNBC exhibited more tumor heterogeneity than non-TNBC [27]. Therefore, we hypothesized that heterogeneity might also be a potential predictive and prognostic biomarker in patients with TNBC.

Despite the growing attention attached in primary tumors, limited evidence exists regarding the predictive value of ^{18}F-FDG heterogeneity in metastatic disease. Metastatic lesions could behave completely differently in terms of tumor biology and metabolism either compared with primary lesions or between each other [28,29]. Findings in primary tumors might not be applicable in metastatic disease. Besides, PET/computed tomography (CT) metrics mentioned above are too complicated to be applied in metastatic settings during clinical practice with regard to the existence of multiple metastatic lesions. Thus, a feasible parameter that could reflect the intraindividual heterogeneity across various metastatic lesions is in demand.

Herein, we proposed a novel quantitative index to represent the heterogenetic characteristics of metastatic disease. The purpose of this study was to evaluate the value of heterogeneity among metastatic lesions on pretreatment PET/CT in predicting treatment outcome of patients with mTNBC.

Materials and Methods

Patient Cohort and Treatment

Three prospective clinical trials have been conducted in Fudan University Shanghai Cancer Center (FUSCC) to investigate the efficacy of gemcitabine plus platinum (GP) as the first-line treatment for mTNBC: a phase II study (NCT00601159), a multicenter phase III study (GP arm, NCT01287624), and an ongoing clinical phase II trial (GP arm, NCT02341911). Patients enrolled in these trials who had received whole-body ^{18}F-FDG PET/CT scan within a month before initiating GP treatment were included in this observational study. All patients who met this criterion were included in subsequent analysis. Imaging data, complete medical history, tumor evaluation, and follow-ups were retrieved from a medical electronic database system.

All patients received GP regimen as their first-line treatment for mTNBC and were treated, evaluated, and followed up strictly as clinical trials' protocol suggested. No effort was made to influence the standard care of patients included in this observational study. Tumor response was assessed every two cycles until disease progression. After disease progression, information about survival status was obtained every 3 months.

The study has been approved by the institutional review board, and the need for written informed consent was waived as it's a retrospective study.

PET/CT Imaging

^{18}F-FDG was generated automatically by the cyclotron (CTI RDS Eclipse ST, Siemens, Knoxville, TN). The radiochemical purity of ^{18}F-FDG was over 95%.

All patients fasted for at least 6 hours before the ^{18} F-FDG PET/CT, and the blood glucose levels were under 10 mmol/L. The PET/CT image acquisitions were initiated on a Siemens biograph 16HR PET/CT scanner approximately 1 hour after the intravenous injection of 7.4 MBq/kg of ^{18}F-FDG. Before and after the injection, the patients were kept lying comfortably in a quiet, dimly lit room.

The PET/CT acquisition parameters were as follows: CT scanning was first performed, from the proximal thighs to head, milliseconds with 120 kV, 80–250 mA, pitch 3.6 mm, tube rotation time 0.5 milliseconds. Immediately after CT scanning, a PET emission scan that covered the identical transverse field of view was obtained. Acquisition time was 2–3 minutes per table position. PET image data sets were reconstructed iteratively by applying the CT data for attenuation correction, and coregistered images were displayed on a workstation. PET images were filtered with a Gaussian filter (Full width at half maximum, FWHM: 5.1 mm) so that small variations can be regarded as representing heterogeneity rather than noise [30].

Imaging Interpretation

A multimodality computer platform (Syngo; Siemens) was used for image review and manipulation. Two board-certified experienced nuclear medicine physicians evaluated the images independently. The reviewers reached a consensus in cases of discrepancy. Quantification of glucose metabolic activity was obtained using the SUV normalized to body weight.

The maximum SUV (SUVmax) for metastatic lesions were evaluated by manually placing an individual region of interest on coregistered and fused transaxial PET/CT images. The boundaries were drawn large enough to

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include the visceral metastasis and nonvisceral metastasis in the axial, coronal, and sagittal PET images. A connecting outline of the volume of interest was set using a cutoff value of 40% SUVmax, and the contour around the target lesion inside the boundaries was automatically produced. Considering partial volume effect and repeatability, lesions less than 10 mm in diameter were not included in further analysis. Bone lesions were only included when confirmed by CT or MRI. MAX and MIN stood for the maximum and minimum FDG uptake across all metastatic lesions. A quantitative measure of intraindividual heterogeneity in patients with metastatic disease, heterogeneity index (HI), was measured by MAX divided by MIN. MAX and HI were assessed for total metastatic lesions (-T), visceral metastatic lesions (-V), and nonvisceral metastatic lesions (-N).

Statistical Analysis

Quantitative data are presented as median (range) or number of patients (percentage). Treatment outcome was assessed by progression-free survival (PFS) and overall survival (OS). PFS was measured from the date of GP initiation to the first documented disease progression or death. OS was defined as the time between date of GP initiation and date of death or last follow-up. Disease progression was determined by RECIST version 1.1.

The optimal cutoff values for PET/CT parameters were determined by time-dependent survival receiver operating characteristic (ROC) analysis (survival ROC library in R), which took into account the duration of time until censoring or progression [31]. The optimal cutoff points were used to discriminate high- and low-value groups, as well as for plotting. The survival analyses were then estimated by Kaplan-Meier method and compared by log-rank test. All statistical analyses were conducted using SPSS version 22 (IBM, Armonk, NY). All p values were two-sided, and the significance level of statistical tests was set at $p < .05$.

Results

Patient and Tumor Characteristics

A total of 42 patients with mTNBC had underwent whole-body ^{18}F-FDG PET/CT scan in FUSCC within a month before initiating first-line GP treatment and were included in the analysis. The demographics and clinical characteristics of these patients are summarized in Table 1.

Median age was 48 years (range 35–64). A total of 42.9% of the patients had ≥3 metastatic sites. Common sites of metastases included lung (40.5%), bone (35.7%), and liver (19.0%). More than half of the patients had visceral involvement (61.9%). A total of 328 metastatic lesions were measured and analyzed.

Predictive Value of Treatment Outcome

At the time of analysis, 81.0% of the patients had documented disease progression (n = 34) and 50.0% of the patients had died (n = 21). The median PFS was 8.6 months (95% confidence interval [CI]: 7.1–10.1), and the median OS was 19.9 months (95% CI: 17.1–22.8).

Table 1. Patients and tumor characteristics

Characteristics	mTNBC, n = 42, n (%)
Age, years	
Median (range)	48 (35–64)
Menopausal status	
Postmenopausal	25 (59.5)
Premenopausal	17 (40.5)
ECOG score	
0	12 (28.6)
1	30 (71.4)
Disease-free interval, months	
<12	11 (26.2)
>12	31 (73.8)
Number of metastatic sites	
1	14 (33.3)
2	10 (23.8)
≥3	18 (42.9)
Metastatic sites	
Lung	17 (40.5)
Liver	8 (19.0)
Bone	15 (35.7)
Visceral disease	26 (61.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; mTNBC, metastatic triple-negative breast cancer.

We first examined the significance of conventional clinical risk factors. The results showed that the existence of liver metastasis (p = .008) and bone metastasis (p = .007) were significantly associated with shorter PFS. In terms of OS, patients with disease-free interval (DFI) over 12 months (p = .031), patients with fewer than three metastatic sites (p = .019) and patients without bone metastasis (p = .033) had significantly better outcome. The analysis of prognostic factors for PFS and OS are summarized in Table 2.

Univariate analyses were then performed to investigate the predictive and prognostic value of PET parameters. The optimal cutoff value for PFS was determined by time-dependent ROC analysis. The median PFS of patients with high HI-T (>1.9) was 7.8 months, significantly shorter than 10.9 months in patients with low HI-T (<1.9, p = .049; Fig. 1A). The median PFS of patients with high MAX-T (>10.5) was also significantly shorter than patients with low MAX-T (<10.5; 5.1 vs. 9.3 months, p = .001; Fig. 1B). In terms of OS, high MAX-T (>10.5) was significant for poorer outcome (15.6 vs. 27.6 months, p = .013; Fig. 1D). The median OS was also numerically shorter in patients with high HI-T, although not significantly (19.9 vs. 25.6 months, p = .597; Fig. 1C). These results demonstrated that both MAX-T and HI-T were significant predictive factors for PFS, whereas OS was only associated with MAX-T (Fig. 1).

Exploratory analysis was also performed to investigate the predictive value of HI and MAX measured in visceral and nonvisceral metastatic lesions. In patients with visceral metastasis, only HI-V was a significant predictive factor for PFS, whereas MAX-V was not significant for either PFS or

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Table 2. Analysis of risk factors associated with PFS and OS

Factors	*n*	PFS, months (95% CI)	*p* value	OS, months (95% CI)	*p* value
Clinical risk factors					
Age, years					
>48	21	8.2 (5.2–11.2)	.585	19.9 (14.8–25.1)	.514
≤48	21	8.9 (7.5–10.3)		20.4 (9.6–31.2)	
Menstruation status					
Postmenopausal	25	7.3 (4.1–10.6)	.973	27.4 (14.9–39.9)	.733
Premenopausal	17	8.9 (7.7–10.1)		15.0 (6.7–23.4)	
Disease-free interval, months					
>12	31	8.9 (8.0–9.8)	.525	27.4 (14.1–40.8)	.031[a]
<12	11	5.1 (2.9–7.3)		13.9 (10.5–17.3)	
No. of metastatic sites					
1–2	24	8.9 (8.4–9.4)	.071	31.3 (15.8–46.8)	.019[a]
≥3	18	6.7 (4.2–9.2)		15.0 (10.8–19.2)	
Visceral disease					
Yes	26	8.2 (5.6–10.8)	.916	20.4 (16.8–24.1)	.905
No	16	8.9 (5.9–11.9)		19.9 (9.7–30.1)	
Liver metastasis					
Yes	8	3.8 (1.1–6.6)	.008[a]	18.5 (4.4–32.9)	.063
No	34	8.9 (7.5–10.3)		27.4 (15.2–39.6)	
Lung metastasis					
Yes	17	9.8 (8.1–11.5)	.083	31.3 (16.3–46.3)	.181
No	25	6.0 (1.6–10.5)		18.5 (11.9–25.1)	
Bone metastasis					
Yes	15	5.6 (3.0–8.3)	.007[a]	16.5 (12.0–20.9)	.033[a]
No	27	9.1 (7.8–10.4)		31.3 (8.0–54.6)	
PET/CT parameters					
In all patients					
HI-T					
>1.9	28	7.8 (4.4–11.2)	.049[a]	19.9 (17.4–22.5)	.597
<1.9	11	10.9 (8.4–13.5)		25.6 (10.9–44.3)	
MAX-T					
>10.5	19	5.1 (4.0–6.2)	.001[a]	15.6 (8.3–22.9)	.013[a]
<10.5	23	9.3 (8.4–10.2)		27.6 (16.4–38.7)	
In patients with visceral metastatic lesions[b]					
HI-V					
>2.0	8	6.0 (3.8–8.3)	.026[a]	20.4 (not reached)	.644
<2.0	8	10.9 (4.0–17.9)		19.4 (2.6–36.2)	
MAX-V					
>7.1	9	5.1 (3.5–6.8)	.151	11.5 (9.7–13.3)	.113
<7.1	15	9.3 (7.2–11.3)		27.6 (14.5–40.6)	
In patients with nonvisceral metastatic lesions					
HI-N					
>2.4	17	8.6 (7.4–9.8)	.880	19.4 (13.9–23.1)	.968
<2.4	15	6.0 (4.1–7.9)		18.5 (9.4–29.4)	
MAX-N					
>10.5	18	5.1 (2.6–7.7)	.024[a]	15.6 (9.0–22.1)	.054
<10.5	17	8.9 (8.3–9.5)		27.6 (17.0–38.2)	

[a] $p < .05$ is considered significant.
[b] Lesions less than 10 mm in diameter were not included.
Abbreviations: CI, confidence interval; HI, heterogeneity index; HR, hazard ratio; MAX, maximum of standard uptake value across metastatic lesions; -N, nonvisceral lesions; OS, overall survival; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival; -T, total lesions; -V: visceral lesions.

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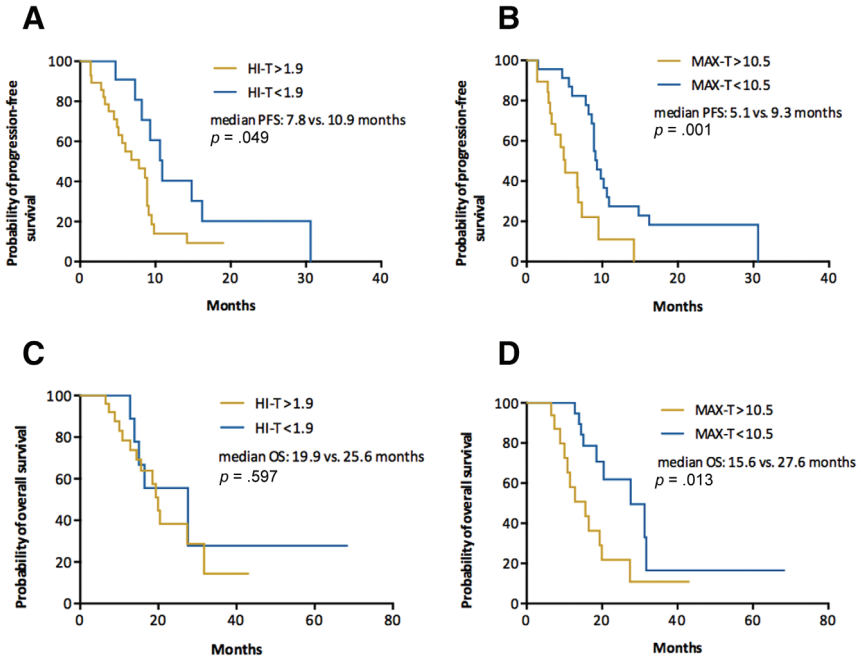

Figure 1. All patients. Kaplan-Meier curves of PFS **(A, B)** and OS **(C, D)** stratified by HI-T **(A, C)** and MAX-T **(B, D)**.
Abbreviations: HI, heterogeneity index; MAX, maximum of standard uptake value across metastatic lesions; OS, overall survival; PFS, progression-free survival; -T, total lesions.

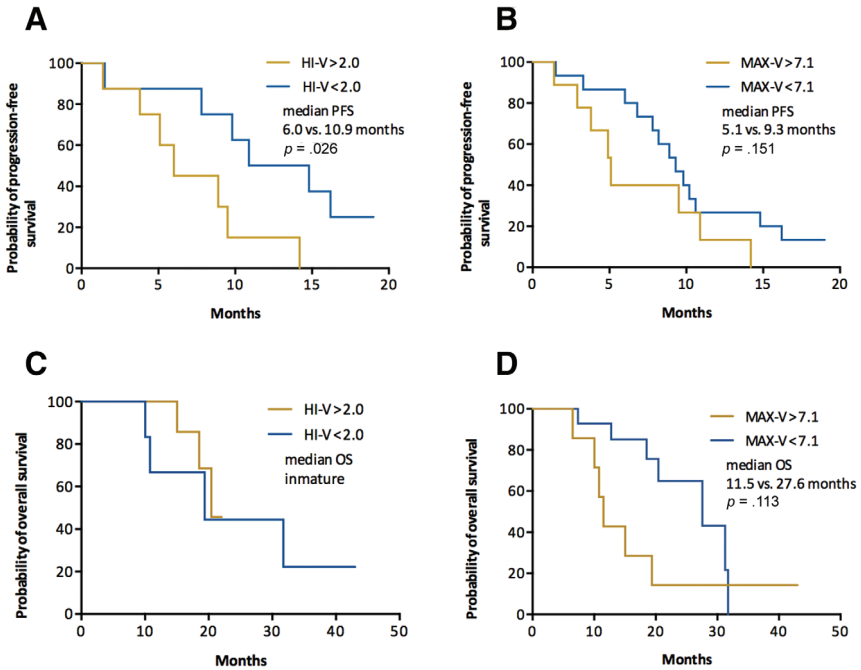

Figure 2. Patients with visceral metastasis. Kaplan-Meier curves of PFS **(A, B)** and OS **(C, D)** stratified by HI-V **(A, C)** and MAX-V **(B, D)**.
Abbreviations: HI, heterogeneity index; MAX, maximum of standard uptake value across metastatic lesions; OS, overall survival; PFS, progression-free survival; -V, visceral lesions.

OS (Fig. 2). In patients with nonvisceral metastasis, however, only MAX-N had significant predictive and borderline prognostic value (Fig. 3).

Time-Dependent ROC Analysis

To further assess and compare the predictive performance of PET/CT parameters, time-dependent ROC curves for censored and survival data and areas under the ROC curve (AUC) were investigated (Fig. 4).

MAX-T and HI-T showed an AUC of 0.75 and 0.65 in all patients, indicating higher predictive accuracy than clinical risk factor, including age, DFI, number of metastatic sites, and liver metastasis. Besides, MAX and HI have both demonstrated greater potential in predicting PFS when measured in visceral lesions with an AUC of

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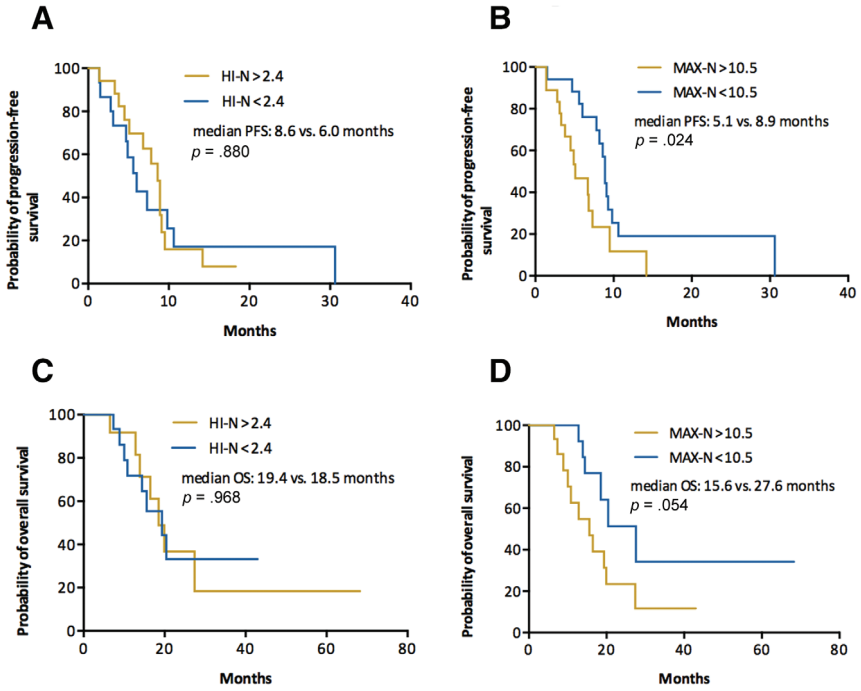

Figure 3. Patients with nonvisceral metastasis. Kaplan-Meier curves of PFS **(A, B)** and OS **(C, D)** stratified by HI-N **(A, C)** and MAX-N **(B, D)**. Abbreviations: HI, heterogeneity index; MAX, maximum of standard uptake value across metastatic lesions; -N, nonvisceral lesions; OS, overall survival; PFS, progression-free survival.

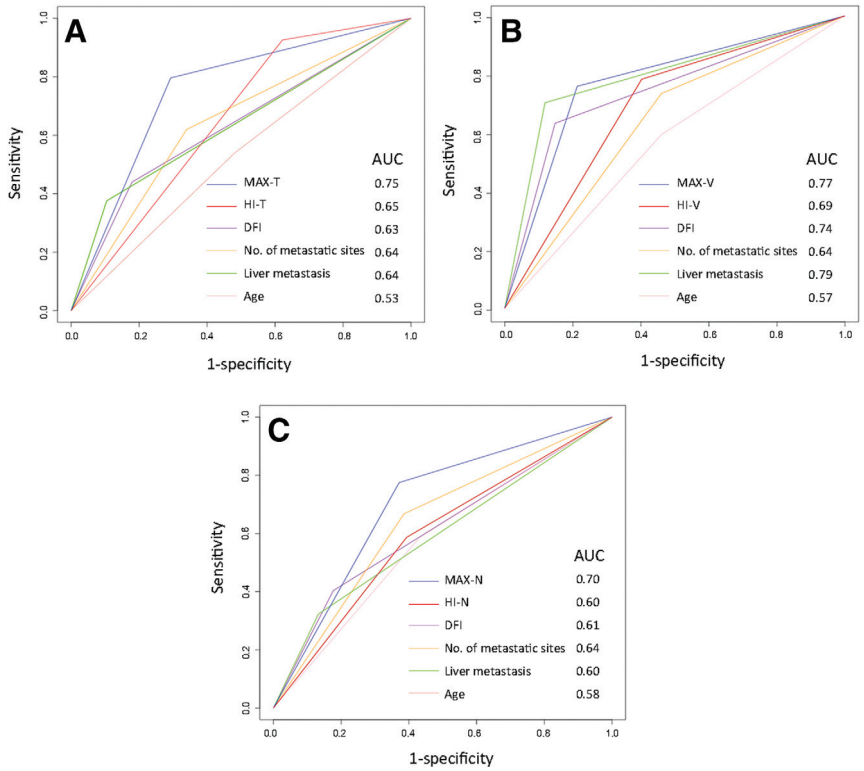

Figure 4. Time-dependent receiver operator characteristics curves for MAX, HI, and clinical predictive factors. **(A):** All patients. **(B):** Patients with visceral metastasis. **(C):** Patients with nonvisceral metastasis.
Abbreviations: AUC, area under the receiver operator characteristic curve; DFI, disease-free interval; HI, heterogeneity index; MAX, maximum of standard uptake value across metastatic lesions; -N, nonvisceral lesions; -T, total lesions; -V: visceral lesions.

0.77 and 0.69, compared with 0.70 and 0.60 when measured in nonvisceral lesions. MAX has shown steadily higher predictive value in all patient cohort (AUC 0.75), visceral metastasis cohort (AUC 0.77), and nonvisceral metastasis cohort (AUC 0.70) compared with conventional clinical factors. The performance of HI, however,

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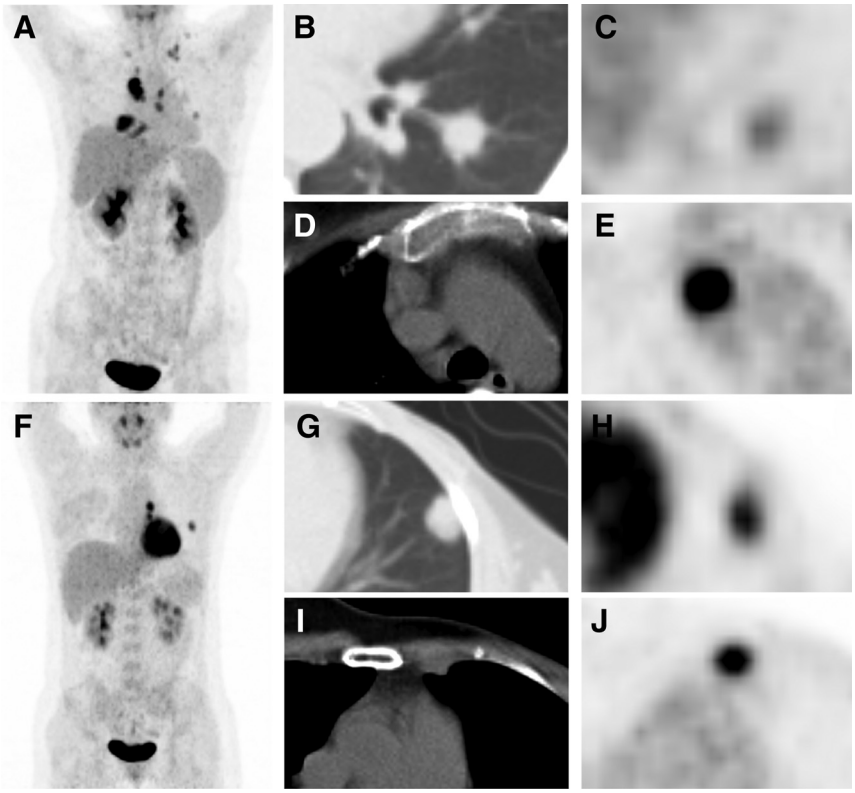

Figure 5. Representative images. **(A–E):** A 45-year-old female patient with metastatic triple-negative breast cancer (mTNBC) underwent ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) scan (**A**, maximum intensity projection [MIP] image). We detected that the left lung lesion had the lowest ^{18}F-FDG uptake in all metastatic lesions (**B**, CT image; **C**, PET image, minimum FDG uptake across all lesions [MIN]: maximum standard uptake value [SUVmax] = 2.0), whereas the mediastinal lymph node lesion had the highest uptake (**D**, CT image; **E**, PET image, maximum FDG uptake across all lesions [MAX]: SUVmax = 15.3). Therefore, heterogeneity index (HI)-total lesions (-T) of this patient was 7.7, and she had a progression-free survival (PFS) of 3.3 months and an overall survival (OS) of 7.4 months. **(F–J):** A 35-year-old female patient with mTNBC underwent ^{18}F-FDG PET/CT scan (**F**, MIP image). We detected that the left lung lesion had the lowest ^{18}F-FDG uptake in all metastatic lesions (**G**, CT image; **H**, PET image, MIN: SUVmax = 5.9), whereas the left internal mammary lymph node lesion had the highest uptake (**I**, CT image; **J**, PET, MAX: SUVmax = 8.8); Therefore, HI-T of this patient was 1.5, and she had a PFS of 10.6 months and an OS of 15.0 months.

was inferior to clinical factors in patients with nonvisceral metastasis.

Collectively, our results demonstrated that both MAX and HI, measured in metastatic lesions, were promising predictive indicators of treatment outcome and could provide additional information to conventional clinical risk factors. Images of representative tumors are shown in Figure 5.

Discussion

We proposed a novel quantitative index-HI, to represent the heterogenetic characteristics of metastatic disease. Our study indicated that baseline HI-T detected by ^{18}F-FDG PET/CT can predict treatment efficacy for patients with mTNBC. Heterogeneity of FDG uptake among metastatic lesions could be affected by many factors, such as cellular hypoxia, necrosis, vascularization, and proliferation [32]. These factors are also closely related to the physiologic mechanism of chemotherapy resistance. Thus, patients with a high extent of FDG uptake heterogeneity are likely to be less responsive to platinum-based chemotherapy and may benefit more from clinical trials of novel agents. No significant association was observed between intraindividual heterogeneity and OS, which was partially due to different treatment strategies patients received afterwards.

Although SUVmax has been widely used as a prognostic biomarker in various primary tumors [21,33–36], its role in metastatic breast cancer (MBC) has not been fully understood. Zhang et al. [37] and Cokmert et al. [38] have proven the prognostic value of SUVmax in patients with ER-positive and unselected MBC. The only study conducted in mTNBC cohort, however, showed that SUVmax was not significantly correlated with OS [39]. As admitted by the author, confounding factors existing in this study, such as different PET machines and treatment regimens, could have biased the results [39]. In order to minimize the influence of previous treatment on tumor heterogeneity and patient outcome, our study was conducted in a cohort of treatment-naive mTNBC patients with baseline PET/CT undertook in our hospital before being treated with the same regimen. Our results demonstrated that baseline MAX-T was effective for the prediction of both PFS and OS in mTNBC, which was consistent with previous findings in early TNBC [40]. Thus, conventional SUVmax could also serve as a potential surrogate marker of treatment outcome and survival in patients with mTNBC.

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The ROC curve analysis confirmed that both MAX-T and HI-T can successfully identify platinum-sensitive patients from unselected mTNBC patients, with an AUC of 0.75 and 0.65, respectively, indicating higher predictive accuracy than conventional clinical risk factors, including age, DFI, number of metastatic sites, and liver metastasis. Although the predictive performance of HI alone was moderate, these novel parameters detected in baseline PET/CT could offer additional information for patients selecting other than clinical risk factors.

Considering that the metabolic processes may differ greatly between viscera and nonviscera, we further explored the predictive value of MAX and HI measured in visceral and nonvisceral lesions respectively. Our data showed that both MAX and HI measured in visceral metastases has demonstrated greater potential in predicting PFS than these parameters measured in nonvisceral lesions. Visceral involvement has been proved to be an independent indicator of worse prognosis in patients with MBC by various studies [41–43]. So, it is possible that PET parameters measured in visceral lesions are of higher value in predicting treatment outcome, for the fact that visceral involvement has a greater impact on pharmacodynamics as well as patients' survival. However, validation from prospective studies with larger patient cohorts and predefined stratification are needed to verify this speculation. Besides, the performance of MAX was steadier across all cohorts, whereas the predictive value of HI measured in nonvisceral lesions was not satisfactory.

The underlying biological mechanisms behind these findings are still under investigation. The relation between microenvironment heterogeneity and multidrug resistance has been widely studied recently and hopefully could shed a light on this field.

We establish a novel parameter to represent the intraindividual heterogeneity among metastatic lesions, and it has proven to be applicable and effective as a predictive marker in clinical practice. To the best of our knowledge, we were also the first to investigate the predictive value of ^{18}F-FDG PET/CT heterogeneity in patients with mTNBC. Heterogeneity and MAX measurement on pretreatment PET/CT could help oncologists to identify patients that would benefit more from platinum-based chemotherapy so as to select the optimal treatment strategy for individual mTNBC patients.

There were several limitations in the present study. First of all, it should be acknowledged that this study was based on a small cohort of Asian patients, so that optimal cutoff values shown in this study might not be applicable to all patients. Validation from prospective studies with larger patient cohorts are necessary to confirm our findings. Moreover, we didn't correct the partial volume effect. But we studied lesions that were over 10 mm in diameter, so the partial volume effect might not significantly affect the results. In addition, heterogeneity measured by ^{18}F-FDG distribution could only reflect tumor heterogeneity in terms of glucose metabolism. However, the heterogeneity of a malignant tumor also manifests as its complex biological mechanism, such as oxygen consumption, cell proliferation, and apoptosis. More studies are needed to explore the application of various bioparameters to provide a multidimensional vision of intratumoral heterogeneity. Finally, the underlying biological mechanisms of interlesional heterogeneity in mTNBC need to be further investigated by translational studies.

Conclusion

This pilot study highlights the value of HI, as well as MAX, measured among metastatic lesions on pretreatment ^{18}F-FDG PET/CT scans in predicting first-line treatment outcome of mTNBC. The results of this study indicate that ^{18}F-FDG-based heterogeneity among metastatic disease, especially in visceral lesions, could help identify mTNBC patients who could benefit from platinum-based chemotherapy.

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Author Contributions

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Disclosures

The authors indicated no financial relationships.

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