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Multimodal MR functional imaging for pathological grading and monitoring trastuzumab response in HER2-positive breast cancer

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Abstract: Accurate noninvasive assessment of tumor grade and therapeutic response in HER2-positive breast cancer remains challenging. This prospective, single-center study aimed to evaluate the diagnostic value of multimodal MR functional imaging in grading malignant breast tumors and monitoring trastuzumab response. Eighty HER2-positive patients confirmed by IHC/FISH were enrolled, including 41 low-grade and 39 high-grade tumors (Nottingham grading system). Patients underwent comprehensive MR imaging, including diffusion tensor imaging, MR spectroscopy and perfusion imaging at baseline and during therapy. Tumor morphological features (size, necrosis, hemorrhage, edema, boundary clarity) and functional MR parameters (FA, tCho, MTT, TTP) were analyzed for correlation with pathological grade and treatment response. High-grade tumors showed larger size, more necrosis, hemorrhage and edema ($P<0.05$). Functional MR parameters, particularly tCho, MTT and TTP, correlated positively with tumor grade ($P<0.05$). ROC analysis demonstrated high diagnostic accuracy (sensitivity 89.2%, specificity 79.5%, AUC=0.887). Typical MR imaging patterns also reflected trastuzumab responsiveness, indicating potential for noninvasive monitoring of therapy. Multimodal MR functional imaging thus provides a sensitive and specific tool for tumor grading and evaluation of targeted therapeutic response.

Keywords: Multimodal MR functional imaging, HER2-positive breast cancer, trastuzumab, nottingham grade, therapy monitoring, MR spectroscopy, diffusion tensor imaging, perfusion imaging

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INTRODUCTION

Breast cancer is the most prevalent malignancy in the world, whereas in China, malignant breast cancers account for approximately 35-60% of total breast tumors, with an annual incidence rate of 3-8 new cases per 100,000 residents (Smolarz *et al.,* 2022). Pancreas and lung cancers are the only cancers with reduced five-year mortality rates owing to malignant breast cancers and thus it is a public health problem. Etiology and pathogenesis are multifactorial, involving exposure to carcinogens, lifestyle, genetic susceptibility, environmental exposures and possibly electromagnetic radiation (Xiong *et al.,* 2025). Clinical presentation is determined by tumor size, location, biological behavior and extension to adjacent tissues, therefore making early diagnosis and optimal treatment planning challenging (Lukasiewicz *et al.,* 2021). Accurate localization, Nottingham grading and rapid measurement of response to therapy are therefore critical to guide individual clinical management and optimize patient outcome (Swaminathan *et al.,* 2023; Obeagu and Obeagu, 2024; Solanki and Visscher, 2020).

Pathological diagnosis is the reference standard for tumor grading and diagnosis but is invasive, of limited sample volume and prone to misdiagnosis or occult lesions, particularly for heterogenous tumors (Matsumoto *et al.,* 2021). Magnetic resonance imaging (MRI) has become a noninvasive and valuable method for assessment of tumor morphology, tissue composition and microenvironmental characteristics (Prasad *et al.,* 2020). Multimodal MRI combines the different functional imaging modes-diffusion tensor imaging (DTI), diffusion-weighted imaging (DWI), arterial spin labeling (ASL), susceptibility-weighted imaging (SWI) and proton magnetic resonance spectroscopy (MRS)-to provide both structural and functional data relevant to breast tumor biology, microstructure, perfusion and metabolism. This fusion facilitates extensive tumor grade and aggressiveness evaluation beyond conventional imaging (Hoffmann *et al.,* 2024; Hsu *et al.,* 2025).

Of the malignant breast carcinomas, HER2-positive carcinomas are aggressive, more commonly recurred and have poor prognosis when not treated (Fanizzi *et al*., 2023). Trastuzumab, a humanized anti-HER2 monoclonal antibody, inhibits tumor cell proliferation and promotes antibody-dependent cellular cytotoxicity, improving survival. However, all the patients do not respond equally and early detection of responders and non-responders is required to optimize therapy, limit unnecessary exposure and tailor treatment. Clinical evaluation is now largely based on size change of the tumor or pathological evaluation, which may lag behind true biological response

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(Tang *et al.,* 2021; Perrone *et al.,* 2021; Fogazzi *et al.,* 2022; Zakaria *et al.,* 2023; Lopez-Gonzalez *et al*., 2024). Recent studies indicate that breast-specific multimodal MRI biomarkers such as fractional anisotropy (FA), total choline (tCho), mean transit time (MTT) and time to peak (TTP) could reflect tumor microstructure, perfusion and metabolism. These parameters may be used as noninvasive markers of tumor grade and trastuzumab response, allowing for real-time monitoring and personalization of treatment (Wang *et al.,* 2022; Chiu and Yen, 2023).

This prospective, single-center trial enrolled 80 hospitalized HER2-positive patients from January 2022 to December 2023. HER2 status was determined with IHC/FISH and the patients were enrolled consecutively. The primary purpose was to evaluate the diagnostic performance of multimodal MRI to grade pathology by Nottingham system. The secondary purpose was to identify the MRI parameters' suitability for trastuzumab response monitoring. We had anticipated that multimodal MRI correlates with pathological grade and is predictive of early response to trastuzumab treatment. In all, the study was designed to determine whether multimodal MRI has the potential to be a noninvasive, accurate, tumor-characterization tool for preoperative planning and guidance of individualized clinical decision-making to optimize patient outcomes in HER2-positive malignant breast cancer.

MATERIALS AND METHODS

Study cohort and eligibility criteria

From January 2022 to December 2023, 80 HER2-positive patients with pathologically confirmed malignant breast tumors were enrolled in this single-center prospective study. Histopathologically confirmed malignant breast tumor, age 30-65 years, fitness for multimodal MRI scanning, no neoadjuvant surgery, radiotherapy, chemotherapy, or targeted therapy, adequate imaging quality and normal mental status to give informed consent were the inclusion criteria. Exclusion factors were severe dysfunction of vital organs (heart, liver and kidney), history of other malignancies, mental illness, pregnancy or lactation, poor compliance, or contraindications for MRI. Consecutive patients were enrolled to minimize selection bias. There were 41 patients who had low-grade (Nottingham grade 1-2) and 39 patients who had high-grade (Nottingham grade 3) tumors. All patients underwent multimodal MRI prior to initiation of trastuzumab therapy and provided written informed consent. HER2 positivity was determined by IHC and/or FISH prior to registration.

Trastuzumab treatment

HER2-positive patients received trastuzumab according to standard clinical practice: starting intravenous loading dose of 8 mg/kg with 6 mg/kg every three weeks thereafter. Baseline and interval multimodal MRI scans during treatment were performed to evaluate treatment response. Imaging parameters were correlated with Nottingham grade and early trastuzumab responsiveness.

Multimodal MRI protocol

Conventional MRI

All MRI scans were performed on a GE Signa HD 3.0T system using an 8-channel phased-array breast coil. Conventional imaging sequences included T1-weighted imaging (T1WI; TR = 2027 ms, TE = 26.7 ms), T2-weighted imaging (T2WI; TR = 5400 ms, TE = 95 ms) and fluid-attenuated inversion recovery (FLAIR; TR = 8002 ms, TE = 146.4 ms, slice thickness = 6 mm, interslice spacing = 0.5 mm, FOV = 220 × 180 mm, matrix = 288 × 192, NEX = 2), along with sagittal T1WI. Contrast-enhanced imaging was performed following intravenous injection of 0.1 mmol/kg Gd-DTPA at 4-5 mL/s. Post-contrast sagittal and coronal images were acquired with a slice thickness of 0.9 mm and interslice spacing of 0.45 mm.

Functional MRI

Functional imaging included diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), proton magnetic resonance spectroscopy (^1H-MRS) and breast-specific perfusion imaging using dynamic contrast-enhanced MRI (DCE-MRI). DWI was acquired using an SE-EPI sequence (TR = 4880 ms, TE = 80 ms, slice thickness = 6 mm, b-values = 5 and 1000 s/mm²), while DTI used an SE-EPI sequence (TR = 8300 ms, TE = 50 ms, slice thickness = 4 mm, 32 diffusion directions, b-values = 0 and 1000 s/mm²). ^1H-MRS was performed with a PRESS sequence (TR = 1700 ms, TE = 144 ms, voxel size = 20 × 20 × 20 mm³). Perfusion imaging derived pharmacokinetic parameters including K^trans, V_e and time-to-peak (TTP). All functional datasets were processed using dedicated post-processing software.

Image processing and analysis

Two radiologists with over 10 years of experience independently analyzed all images, blinded to pathological grade, clinical information and HER2 status. Conventional MRI assessed tumor size, location, cystic necrosis, hemorrhage, enhancement, peritumoral edema, boundary clarity and internal architecture. DWI and DTI provided apparent diffusion coefficient (ADC, $\times 10^{-3}$ mm²/s) and fractional anisotropy (FA, range 0–1) values. ^1H-MRS quantified total choline (tCho) and other relevant metabolites, while perfusion MRI values (K^trans, V_e, TTP) were averaged over repeated regions of interest, excluding necrotic or vascular areas.

Observation indexes

The primary outcome was the correlation of multimodal MRI parameters with Nottingham tumor grade and the secondary outcome was the early MRI changes after trastuzumab therapy. Functional and conventional MRI

features in low-grade and high-grade tumors were compared. Diagnostic performance was evaluated by receiver operating characteristic (ROC) curve analysis with measurement of sensitivity, specificity, area under the curve (AUC) and 95% confidence intervals.

STATISTICAL ANALYSIS

Data were analyzed using SPSS 24.0. The categorial data are expressed as percentages (%) and compared using χ^2 tests. Continuous data are expressed as mean ± SD and compared using independent t-tests. ROC analysis was applied to assess predictive value of MRI parameters for tumor grading and trastuzumab response (Statistical significance was considered at $P < 0.05$).

RESULTS

Comparison of qualitative MRI features according to pathological grade and response to trastuzumab

No significant differences between patients of different Nottingham grades were seen in tumor site, involved side, enhancement pattern, or internal architecture score (ITSS) ($P > 0.05$). Differences were seen in tumor size, cystic necrosis, hemorrhage, peritumoral edema, clarity of tumor boundary and internal fiber organization between low-grade (Nottingham grade 1-2) and high-grade (Nottingham grade 3) tumors ($P < 0.05$). All (80) the patients were HER2-positive by IHC/FISH and received trastuzumab. Early changes on MRI after trastuzumab included reduction of peritumoral edema and partial recovery of boundary clarity in responding tumors (Table 1 & Fig. 1).

Quantitative MRI parameters by pathological grade and early trastuzumab response

There were no notable ADC ($\times 10^{-3}$ mm²/s) differences among tumor grades ($P > 0.05$). FA (0-1 range), tCho, MTT and TTP were higher in high-grade tumors compared with low-grade tumors ($P < 0.05$). Early trastuzumab responders had modest but detectable decreases in tCho and MTT, suggesting possible early imaging biomarkers of response (Table 2 & Fig. 2).

Correlation of imaging parameters with pathological grade and early response to trastuzumab

Spearman correlation analysis demonstrated that tumor size, cystic necrosis, hemorrhage, tumor edema, boundary definition, FA, tCho, MTT and TTP were all positively correlated with Nottingham tumor grade ($P < 0.05$). Early trastuzumab response was associated with small decreases in tCho and MTT, which can be considered as potential early biomarkers of treatment effect (Table 3).

Multimodal MRI predictive value for pathological grading and early trastuzumab response

ROC analysis showed that FA, tCho, MTT and TTP provided good diagnostic performance for Nottingham tumor grading (89.2% sensitivity, 79.5% specificity, AUC = 0.887, 95% CI 0.798–0.931). Changes in tCho and MTT also detected early responders to trastuzumab and multimodal MRI is therefore recommended for the follow-up of treatment (Table 4).

DISCUSSION

Breast cancer is a very heterogeneous tumor characterized by disordered cell proliferation, vascular and lymphatic invasion and highly aggressive infiltration into adjacent tissues (Nguyen *et al.,* 2020). All these feature high recurrence, metastasis and mortality and have a significant impact on the survival and quality of life of the patients. Nottingham criteria-based pathological grade (grade 1-3) reflects increasing malignancy and prognostic diversity (Zhang *et al.,* 2020). Low-grade tumors are also more sensitive to regular treatment, while high-grade tumors are short and sensitive in survival. Accurate and prompt grading is therefore crucial for personal treatment planning (Perrone *et al.,* 2021).

Conventional MRI provides anatomical imaging but is not sensitive in assessing tumor microstructure, perfusion and metabolism and hence its application to grading and early response monitoring is limited (Scola *et al.,* 2023). Multimodal MRI integrating ADC, DTI, DCE-derived MTT and TTP and MRS-measured total choline (tCho) provides a convergent assessment of tumor cellularity, microstructural integrity, perfusion and metabolic activity (Yan *et al.,* 2025). In this study, variations in tumor size, cystic necrosis, hemorrhage, peritumoral edema, boundary definition and internal fiber organization between low- and high-grade tumors were clearly visible with multimodal MRI. These imaging features also correlate with histopathologic grade and can guide individualized clinical management (Martucci *et al.,* 2023).

Aggressive HER2-positive tumors are treated with Trastuzumab, a targeted monoclonal antibody that inhibits HER2 signaling and elicits immune-mediated cytotoxicity. Early response determination is critical to prevent exposure to ineffective therapy. Initial MRI changes in our 80 HER2-positive patients after trastuzumab consisted of reduction of peritumoral edema, improvement in boundary definition and modulation of quantitative measures such as FA, tCho, MTT and TTP. These observations suggest multimodal MRI is an early, noninvasive indicator of response to therapy that can be detected before measurable changes in tumor size (Portnow *et al.,* 2023; Yu *et al.,* 2025).

Quantitative MRI measurements provide information regarding the mechanistic processes of tumor biology. ADC reflects water diffusion and is inversely proportional to cellularity, FA measures diffusion anisotropy, which is high in high-grade breast cancer as a consequence of dense microstructure, which is in agreement with our results.

Table 1: Qualitative MRI parameter comparison by tumor grade and early trastuzumab response

Parameter	Low-grade (n=41)	High-grade (n=39)	χ^2/t	P-value	Notes on trastuzumab response
Tumor location	–	–	0.089	0.596	No significant change post-treatment
Tumor diameter (mm)	33.9 ± 10.2	45.2 ± 11.4	5.12	0.001	Slight reduction in responders
Cystic necrosis (<25% / ≥25%)	3 / 26	20 / 19	12.46	0.003	Necrotic reduction post-trastuzumab
Hemorrhage (yes/no)	21 / 8	8 / 31	15.37	0.007	–
Peritumoral edema (mild/moderate/severe)	–	–	8.39	0.041	Early decrease in responders
Tumor boundary clarity (clear/blurred)	21 / 8	13 / 26	5.43	0.002	Improved clarity in responsive patients

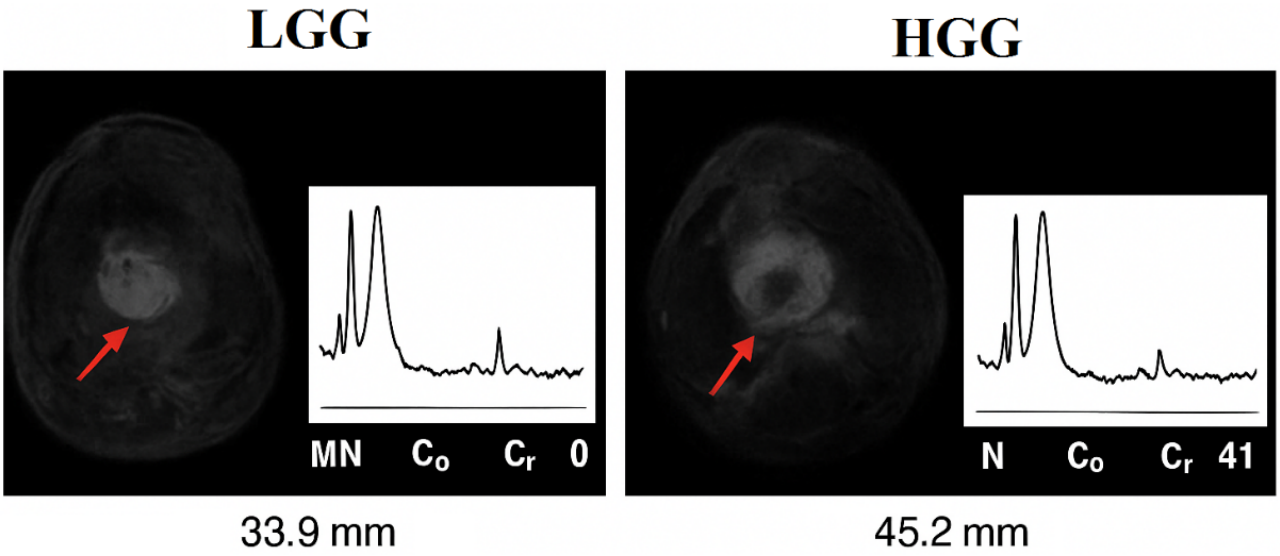

Fig. 1: Multimodal MRI scans of low-grade and high-grade malignant breast cancers with variations in tumor size, necrosis, edema, boundary definition, and total choline (tCho) peaks. Arrows indicate necrosis, edema, or hemorrhage.

Table 2: Quantitative MRI parameters by tumor grade and early trastuzumab response

Parameter	Low-grade (n=41)	High-grade (n=39)	t	P-value	Notes
ADC ($\times 10^{-3}$ mm²/s)	1.33 ± 0.30	1.31 ± 0.22	0.85	0.398	–
FA	0.29 ± 0.05	0.42 ± 0.07	8.12	<0.001	Slight decrease in responders
tCho (arbitrary units)	1.37 ± 0.23	2.69 ± 0.18	4.39	0.005	Decreased in responders
MTT (s)	0.92 ± 0.29	1.06 ± 0.18	9.03	0.001	Slight improvement in perfusion
TTP (s)	21.4 ± 3.57	23.3 ± 5.26	5.32	0.013	–

Note: Parameters tracked pre-treatment and after first trastuzumab cycle.

Table 3: MRI parameter correlation with tumor grade and early trastuzumab response

Parameter	β	S.E.	Wald χ^2	OR	P-value	95% CI	Notes
FA	0.41	0.12	8.68	1.51	0.005	1.12–2.03	Slight decrease in responders
tCho	1.43	0.24	5.38	4.18	0.001	1.53–5.24	Decreased in early responders
MTT	0.33	0.10	12.83	1.39	0.005	1.12–1.71	–
TTP	0.42	0.11	13.30	1.52	0.002	1.18–1.85	–

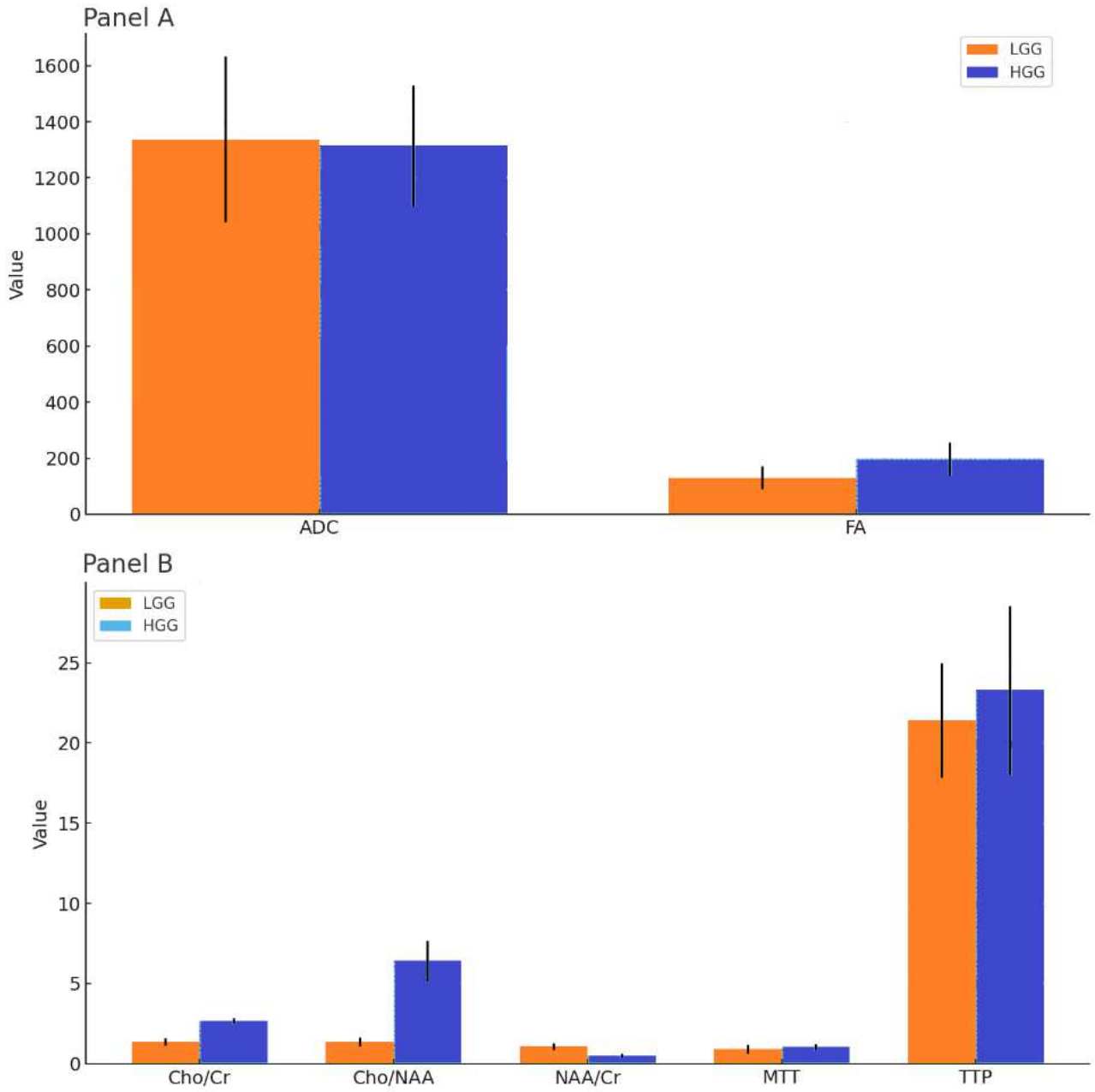

Fig. 2: Quantitative multimodal MRI parameter differences in high-grade (HGG) and low-grade (LGG) malignant breast tumors; Panel A: Diffusion and anisotropy parameters (ADC, FA). Panel B: Metabolic and perfusion parameters (Cho/Cr, Cho/NAA, NAA/Cr, MTT, TTP). HGG tumors versus LGG exhibited significantly increased FA, Cho/Cr, Cho/NAA, MTT, and TTP, and decreased NAA/Cr values ($P < 0.05$). Error bars indicate standard deviation.

Table 4: ROC analysis for tumor grading and early trastuzumab response

Parameter	Sensitivity	Specificity	Critical value	AUC	95% CI	Notes
FA	0.856	0.781	0.35	0.85	0.78-0.91	Early decrease in responders
tCho	0.823	0.705	1.4	0.97	0.82-0.99	Decrease indicates response
MTT	0.819	0.683	1.0	0.69	0.57-0.79	–
TTP	0.831	0.694	22.96	0.69	0.58-0.80	–
Combined	0.892	0.795	–	0.887	0.798-0.931	Most accurate for grading and response

MTT and TTP reflect perfusion kinetics and vascular permeability, high in highly vascular high-grade tumors. tCho amounts from MRS reflect cellular proliferation and membrane turnover. High-grade tumors in this study had elevated FA, tCho, MTT and TTP, whereas low-grade tumors showed reduced values, supporting their potential as noninvasive markers of the grade of tumor. Early response to trastuzumab was associated with decreases in tCho and moderate decreases in FA, MTT and TTP, suggesting early therapeutic effects on tumor cellularity, metabolism and perfusion.

These findings have several clinically important implications. MRI biomarkers including fractional anisotropy (FA), total choline (tCho), mean transit time (MTT) and time-to-peak (TTP) have the potential for detecting HER2-positive patients who will be responsive to trastuzumab, enabling more precise, targeted therapy. Noninvasive, early measurement of therapeutic response can decrease unnecessary exposure to ineffective treatment as well as its associated toxicity. Furthermore, longitudinal multimodal MRI offers objective, quantitative follow-up, allowing for the potentially more accurate evaluation of the effectiveness of treatment compared to size-based measurements alone (Khaniabadi *et al.,* 2020; Cronin *et al.,* 2023). Drawbacks are the small, single-center cohort, short follow-up duration and study of only early MRI markers. Large multicenter cohorts, longer follow-up and serial imaging would be incorporated in future research to cross-validate MRI parameters as predictors of long-term trastuzumab response and patient outcomes (Whitman *et al.,* 2025).

CONCLUSION

Multimodal MRI allows for both qualitative and quantitative measurements for accurate grading of malignant breast cancers (Nottingham grades 1-3) and also offers a sensitive, noninvasive means for early trastuzumab response detection in HER2-positive patients. Through imaging of tumor microstructural changes, perfusion characteristics and metabolism (FA, tCho, MTT, TTP) prior to detectable size reduction, multimodal MRI enables early response assessment of treatment and facilitates personalized treatment. The integration of new imaging with targeted treatment enables clinical decision-making, patient stratification and potential improved long-term results, which illustrates the strength of multimodal MRI in precision oncology in HER2-positive breast cancer.

Ethical approval

The study was approved by the Ethics Committee of the Department of Radiology, Beijing Jishuitan Hospital (Beijing- China) with approval No. JST-RAD-2022-014. All subjects provided written informed consent prior to registration and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Author contributions

Luo Songjiang, Liu Feng, Wang Wei, Li Siyu, and Wu Xiaoqing contributed to the study conception, data acquisition, and analysis. Luo Tenglong supervised the project, provided critical revisions, and guided the interpretation of results. All authors contributed to drafting, reviewing, and approving the final manuscript.

Conflict interests

The authors declare no conflict of interest.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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