

Early One-Cycle Post-Neoadjuvant Chemotherapy Volumetric and SER-based Changes on DCE-MRI: Timely Predictors of Response and Prognosis in Breast Cancer

Alisa Mohebbi

Tehran University of Medical Sciences

Mehrad Zare

Tehran University of Medical Sciences

Zahra Moradi

Tehran University of Medical Sciences

Afshin Mohammadi

`mohammadi.a@umsu.ac.ir`

Urmia University of Medical Sciences

Research Article

Keywords: breast neoplasms, magnetic resonance imaging, neoadjuvant therapy, recurrence

Posted Date: July 10th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9937464/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Early identification of response to neoadjuvant chemotherapy (NAC) in breast cancer is critical for optimizing treatment strategies. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) provides a non-invasive method for monitoring tumor response and prognosis. This study investigates whether early MRI-derived parameters during treatment can predict clinical response and recurrence-free survival (RFS) in breast cancer patients receiving NAC.

Methods

In this retrospective study, 47 patients with stage II–III invasive breast cancer underwent DCE-MRI at three time points: before NAC, one cycle after initiation, and after completion of anthracycline therapy. Tumor size, volume, and signal enhancement ratio (SER)-based functional tumor volume (FTV) were quantified using semi-automated post-processing techniques. A reduction of $\geq 20\%$ in any metric defined treatment response. Receiver operating characteristic (ROC) analyses assessed discriminatory ability, and RFS was compared between two groups.

Results

Early volumetric changes between baseline and one-cycle post-treatment MRI demonstrated strong predictive value for clinical response. Volume change achieved the highest discriminatory ability (AUC = 0.825; sensitivity = 72.7%, specificity = 76.9%). SER-based FTV changes showed comparable performance (AUC = 0.822; sensitivity = 72.7%, specificity = 76.9%). Early changes consistently outperformed both late changes and size-based metrics.

Conclusion

Early volumetric and SER-based functional tumor volume reductions on DCE-MRI after one cycle of neoadjuvant chemotherapy are significant predictors of clinical response and are associated with improved recurrence-free survival. These findings support the integration of early MRI biomarkers into personalized treatment planning for breast cancer patients.

Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and a leading cause of cancer-related mortality, despite significant advances in systemic therapy and imaging (1–3). Neoadjuvant chemotherapy (NAC) is now integral to the management of stage II-III disease because it downstages tumors and increases breast-conservation eligibility (4, 5). Yet clinical and

pathological responses to NAC are highly heterogeneous; a subset of patients attains pathological complete response, whereas others derive minimal benefit while enduring substantial toxicity (6). Consequently, radiologists face an urgent mandate to identify robust imaging biomarkers that can detect therapeutic efficacy early in the treatment course, thereby enabling timely modification of systemic regimens and improving long-term outcomes (7, 8).

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is widely acknowledged as an accurate modality for assessing breast tumor biology non-invasively (9). Beyond conventional unidimensional measurements codified by RECIST (Response Evaluation Criteria In Solid Tumors), multiparametric DCE-MRI offers quantitative metrics that capture both morphological and microvascular alterations elicited by cytotoxic agents (10–12). Despite increasing interest in the clinical utility of MRI biomarkers, routine use of size variation in guiding NAC remains limited (13). The size evaluation of treatment response is conducted late in the therapeutic course, often after several chemotherapy cycles or even post-surgery, leaving little opportunity to adjust ineffective treatment strategies (14, 15). However, other DCE-MRI parameters, including gross tumor volume and the signal enhancement ratio-defined functional tumoral volume (SER-defined FTV), are of particular interest; gross tumor volume is defined as the three-dimensional space occupied by the lesion. By contrast, SER-defined FTV refers to the subset of voxels within the segmented tumor that exhibit an SER above a specific threshold, reflecting viable, well-perfused tumor tissue. Gross volume provides a global measure of tumor burden, whereas FTV offers insight into the biologically active tumor fraction (16)(17). Nevertheless, the responsiveness and prognostic value of early volumetric and SER-defined FTV changes, as well as their relative performance compared to late-treatment readouts, remain incompletely defined.

Although several studies have evaluated DCE-MRI for early prediction of NAC response, most have been limited to single or dual time-point assessments and short follow-up intervals (baseline and mid-treatment or completion of therapy). However, single-point models capture only a snapshot of tumor biology and cannot delineate the temporal sequence of vascular and metabolic changes. Moreover, the short duration of clinical follow-up in these studies precludes assessment of long-term outcomes, such as recurrence-free survival (RFS). We further correlate early volumetric and SER-based changes with a median follow-up of 60 months, establishing the prognostic value of these imaging biomarkers for durable clinical benefit.

The present study addresses these knowledge gaps by hypothesizing that early changes in volumetric and SER-defined FTV after one cycle of NAC would outperform later or single time-point MRI metrics in predicting treatment response and recurrence-free survival.

Material and methods

This retrospective, single-institution imaging cohort study leveraged a prospectively acquired longitudinal DCE-MRI collection hosted by The Cancer Imaging Archive (18). All imaging and clinical data originated from the BREAST-MRI-NACT-PILOT collection. Three serial breast MRIs comprising baseline

(MRI-1), early after the first anthracycline NAC cycle (MRI-2), and late after the fourth anthracycline NAC cycle (MRI-3) were quantitatively analyzed for each eligible patient. The primary objectives were to quantify the performance of individual MRI performance as well as early (MRI-1 to MRI-2) and late (MRI-1 to MRI-3) percentage changes in tumor size, tumor volume, and SER-defined FTV for discrimination of clinical responders and RFS. The imaging study and data-sharing initiative received institutional ethics approval; written informed consent covered secondary analyses. TCIA anonymization complied with HIPAA Safe Harbor requirements. The current study follows STARD reporting standards.

Study Population:

The inclusion criteria required (1) histology showing invasive carcinoma confirmed by core needle biopsy, (2) AJCC stage II and III disease, (3) diagnostic-quality baseline DCE-MRI, (4) imaging at 6 ± 2 days after first anthracycline cycle for MRI-2, (5) end-anthracycline MRI at the fourth anthracycline cycle ± 7 days, (6) definitive breast-conserving or mastectomy surgery with pathology, and (7) no prior history of breast cancer or related treatment, ensuring an untreated baseline. A total of 68 consecutive patients were originally recruited under the parent institutional review board–approved protocol based on these inclusion criteria. Exclusion criteria (1) non-surgical management, (2) absent baseline MRI, (3) poor image quality, (4) interval metastatic progression (5) stage I or inflammatory T4d disease since these do not mirror the population most commonly receiving NAC, (6) motion artifacts or wrong orientation on baseline MRI as this was required for longitudinal quantification, (7) scan absent or greater than 10 days for early MRI since this was needed to capture biological changes before size regression, and (8) no surgery since this was needed for RFS and pathological endpoints. Four were excluded based on these criteria leading to inclusion of 64 patients. For the current analysis additional stricter criteria were also applied to preserve longitudinal completeness and evidence synthesis, yielding a final analytic sample of 47 patients. The principal reason the analytic cohort is smaller than the public dataset is omission of patients (10) missing the mandated all three MRI scans (especially, MRI-2 scan) or (11) showing technically inadequate fat suppression that precluded reliable SER mapping (see Fig. 1 for flow diagram).

NAC Regimen:

All participants received four 3-weekly cycles of doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) as first-line NAC. Some patients subsequently received weekly paclitaxel ($80 \text{ mg/m}^2 \times 12$) before surgery; these additional taxane cycles occurred after MRI-3 and therefore did not influence early imaging readouts. Growth-factor support and dose adjustments followed institutional standards. Median total NAC duration from first anthracycline infusion to definitive surgery was 19 weeks with an interquartile range of 18–20 weeks. To avoid confounding effects of targeted therapies on imaging biomarkers and long-term outcomes, none of the HER2-positive patients received anti-HER2 agents; all participants were treated uniformly with anthracycline- and taxane-based neoadjuvant chemotherapy followed by standard adjuvant chemotherapy.

Clinical Assessment and Reference Standard:

As the reference test, physical examinations were conducted by board-certified breast surgeons on identical calendar days at MRI-1 and MRI-3. Clinical response (reference test) was defined as a > 33.3% reduction in tumor size on physical examination (19). MRI-based response (index test) thresholds were determined for each volumetric and SER-based metric by constructing receiver operating characteristic (ROC) curves against the clinical reference and selecting the cut point that maximized Youden's J statistic. Across metrics, the optimal imaging threshold was approximately a 20% reduction from baseline. Thus, for all ROC and sensitivity–specificity analyses, patients with $\geq 20\%$ reduction in MRI metrics were classified as imaging responders, against clinical responders defined by > 33.3% size reduction on exam. Surgeons were blinded to interim MRI findings; radiologists were conversely blinded to physical measurement and pathologic results. RFS was also calculated from the surgical day.

Image Data Analysis:

Tumor size was measured as the longest unidimensional diameter on the axial plane of the early post-contrast series, following RECIST guidelines. Tumor volume was automatically calculated using the segmented volume of interest (VOI). Additionally, the SER-defined FTV volume was measured to capture the extent of tumor regions that exhibited high initial uptake and subsequent washout. All imaging-derived parameters were reviewed and confirmed by experienced breast radiologists to ensure accurate and consistent measurement. All imaging analysts remained blinded to clinical examination findings, chemotherapy dose modifications, pathologic response, and survival outcomes to minimize expectation bias during segmentation and post-processing. Percentage changes were calculated between time points: $\Delta\text{Metric}_{1-2} = ((\text{MRI-1 Metric} - \text{MRI-2 Metric}) / \text{MRI-1 Metric}) \times 100\%$ in any of the three metrics (size, volume, SER-defined FTV).

The FTV was defined as the volume of voxels within the manually delineated tumor region of interest (ROI) exhibiting an SER above a predefined threshold. SER for each voxel was calculated as

$$\text{SER} = \frac{S_{\text{post1}} - S_{\text{pre}}}{S_{\text{post2}} - S_{\text{pre}}}$$
, where S_{pre} is the pre-contrast signal intensity, S_{post1} is the early post-contrast (first post-contrast phase) signal intensity, and S_{post2} is the delayed post-contrast (second post-contrast phase) signal intensity. Voxels with $\text{SER} \geq 0.7$ were classified as “functional,” reflecting substantial early enhancement consistent with viable, well-perfused tumor tissue. The total FTV was computed by summing the volumes of all functional voxels (voxel volume: 1.2 mm³) within the ROI.

Segmentation of tumor lesions was performed using threshold-based segmentation combined with a controlled watershed algorithm, implemented in MATLAB (MathWorks, Natick, MA). All imaging-derived parameters were obtained through validated semi-automated algorithms requiring only initial ROI seed placement. Tumor size, gross volume, and SER-defined FTV metrics were calculated automatically without manual contouring or interpretation. Therefore, inter-observer agreement analysis and drift mitigation procedures were not applicable, as all measurements were reproducible outputs of

automated pipelines. Detailed explanations of the MRI acquisition protocol are provided in Supplementary A.

Statistical analysis:

All statistical analyses were conducted using MedCalc Statistical Software (version 23.2.7; MedCalc Software Ltd, Ostend, Belgium) and Stata 18 (StataCorp LLC, College Station, TX, USA). To assess the discrimination performance of MRI-derived parameters, we calculated the area under the curve (AUC), along with corresponding sensitivity and specificity values. These metrics were assessed at each imaging time point (MRI-1, MRI-2, and MRI-3), as well as for percentage changes between MRI-1 to MRI-2 (early change), and MRI-1 to MRI-3 (late change). Descriptive statistics presented continuous variables as mean $\pm$ SD or median with IQR and categorical variables as counts with percentages. Normality testing used Shapiro-Wilk; non-normal distributions were summarized via medians. Prior to analysis, a reduction of $\geq 20\%$ in tumor volume, SER volume, or tumor size was used to define radiologic response. Patients were classified as:

- True positive: $\geq 20\%$ reduction and clinical response
- False negative: $\geq 20\%$ reduction and clinical non-response
- True negative: $< 20\%$ reduction and clinical non-response
- False positive: $< 20\%$ reduction and clinical response

To explore the prognostic value of volumetric reductions, patients were similarly grouped according to whether they experienced a $> 20\%$ or $\leq 20\%$ decline in these parameters. RFS was then compared between groups. Correlations between MRI-derived changes and clinical outcomes were examined using the Pearson correlation coefficient. Multivariable logistic regression used to explore additive predictive power of combined MRI metrics. Survival analysis used Kaplan-Meier curves stratified by early imaging response. Comparisons of AUC values were performed using DeLong's test. Kaplan-Meier survival differences between response groups were assessed using the log-rank test. A p-value < 0.05 was considered statistically significant.

Results

Demographic and clinicopathological characteristics:

The study cohort consisted of 47 female patients with a mean age of 47.86 ± 9.5 years (range: 21–89 years). The mean tumor size decreased from 5.4 ± 2.76 cm at the time of the first MRI (MRI-1) to 3.8 ± 2.5 cm at the third MRI (MRI-3). A similar reduction was observed in mean tumor volume, which declined from 28.9 ± 34.01 cm³ at MRI-1 to 7.2 ± 19.2 cm³ at MRI-3. Based on radiologic assessment of treatment response, 26 patients demonstrated a favorable response, whereas 11 showed no significant therapeutic effect. Among the 47 patients enrolled, 10 did not have sufficient clinical data to permit response

evaluation and were excluded from responder–non-responder analyses. Additional patient demographics and clinical characteristics are summarized in Table 1.

Role of MRI Metrics for Response to NAC:

Receiver operating characteristic (ROC) analysis demonstrated that early changes in MRI-derived parameters between MRI-1 and MRI-2 yielded the highest predictive accuracy in distinguishing responders from non-responders to NAC. The corresponding AUC values and confidence intervals are summarized in Table 2, with the associated ROC curves presented in Fig. 2. In addition, Fig. 3 provides complementary waterfall plots that illustrate individual patient-level changes in MRI metrics, offering a visual representation of treatment response variability.

The change in tumor volume from MRI-1 to MRI-2 achieved the highest discriminatory ability with an AUC of 0.825 ($P < 0.001$). When applying the predefined 20% reduction threshold, this metric demonstrated a sensitivity of 72.7% and specificity of 76.9% for identifying treatment response. SER-defined FTV changes between MRI-1 and MRI-2 exhibited comparable predictive accuracy with an AUC of 0.822 ($P < 0.001$), achieving identical diagnostic performance characteristics of 72.7% sensitivity and 76.9% specificity at the same reduction threshold. These findings underscore the clinical value of both morphological and functional volumetric assessments in early treatment monitoring. Tumor size changes from MRI-1 to MRI-2, on the other hand, while demonstrating significant predictive capability with an AUC of 0.731 ($P = 0.008$), provided substantially lower performance compared to volume and SER-defined FTV changes.

Evaluation of imaging parameter changes between MRI-1 and MRI-3 timepoints yielded moderate discriminatory performance. SER-defined FTV changes from MRI-1 to MRI-3 demonstrated an AUC of 0.724 ($P = 0.011$), while tumor volume changes over the same interval achieved an AUC of 0.717 ($P = 0.015$). Both metrics showed statistically significant associations with treatment response, though their discriminatory performance remained inferior to their respective early change counterparts. Tumor size changes over this extended interval (MRI-1 to 3) achieved an AUC of 0.755 ($P = 0.001$), with a sensitivity of 63.6% and a specificity of 65.4%.

Baseline time-point MRI metrics demonstrated limited predictive power, with AUCs near chance at baseline (0.517–0.549, all $P > 0.65$) and modest improvements at the mid-treatment timepoint (AUCs 0.628–0.675, $P > 0.06$). Late single time-point assessments achieved statistical significance (AUCs 0.696–0.713, $P < 0.04$) but remained inferior to temporal change metrics.

A combined model integrating tumor volume and SER-defined FTV volume was also evaluated to determine whether multiparametric assessment could enhance predictive accuracy beyond individual metrics. This integrated approach demonstrated an AUC of 0.818 (95% CI: 0.657 to 0.925, $P < 0.001$) with a sensitivity of 72.7% and specificity of 65.4%. Despite achieving statistical significance, the combined model's performance was not superior to the early change metrics, specifically, both tumor volume

changes and SER-defined FTV volume changes. This finding indicates that combining volumetric and functional parameters did not provide added value over the individual assessment of only early tumor volume or SER-defined FTV volume changes, suggesting that these metrics may capture overlapping biological information regarding early treatment response. The odds ratio (OR) values in multivariable logistic regression were 0.887 (95% CI 0.218–3.691; $p = 0.868$) and 1.174 (95% CI 0.289–4.764; $p = 0.822$) respectively for SER-defined FTV and volumetric changes. Two clinical examples are illustrated in Figs. 4 and 5.

Assessment of MRI Metrics for Evaluating Prognosis:

The prognostic significance of early volumetric changes was assessed by stratifying the 47 study participants according to whether they achieved a reduction greater than 20% in tumor volume and SER-defined FTV between MRI-1 and MRI-2. Patients were followed for 2407.8 days (95% CI: 2067.0 to 2748.5 days). During the follow-up period, 15 patients (31.9%) experienced tumor recurrence, while 32 patients (68.1%) remained recurrence-free, providing a robust dataset for survival analysis.

When patients were classified based on SER volume reduction, 30 patients demonstrated reductions exceeding 20%, while 17 patients showed lesser reductions below this threshold. The survival analysis revealed clinically meaningful differences between these groups. Patients with greater SER volume reductions demonstrated superior RFS outcomes, with a mean survival time of 2452.8 days (95% CI: 2050.6 to 2854.9 days) compared to 2247.3 days (95% CI: 1662.3 to 2832.4 days) for those with minimal reductions (HR 1.54; 95% CI: 0.55–4.27; $p = 0.401$). Notably, the recurrence event rates differed between groups, with 8 out of 30 patients (26.7%) experiencing recurrence in the high-reduction group versus 7 out of 17 patients (41.2%) in the low-reduction group (Fig. 6A). Similar prognostic patterns and values emerged when patients were stratified by tumor volume changes (Fig. 6B) (HR 1.54; 95% CI: 0.55–4.27; $p = 0.401$). Consistent with the SER volume findings, patients achieving greater than 20% tumor volume reduction maintained longer recurrence-free intervals, with identical survival metrics reflecting the substantial overlap between these volumetric parameters. The concordance between tumor volume and SER volume stratification underscores the biological relevance of early volumetric changes as markers of treatment effectiveness.

Correlation analysis:

Based on Fig. 7, Pearson correlation analysis demonstrated strong negative correlations between early changes in MRI parameters and clinical response outcomes. Changes in tumor volume between MRI-1 and MRI-2 timepoints showed a robust inverse correlation with treatment response ($r = -0.561$, $P < 0.001$), indicating that patients achieving greater volumetric reductions were significantly more likely to respond favorably to NAC. Similarly, early changes in SER-defined FTV exhibited nearly identical correlation strength with clinical response ($r = -0.562$, $P < 0.001$), reinforcing the biological relevance of both morphological and functional volumetric assessments in predicting therapeutic efficacy. The conventional radiological tumor size changes between MRI-1 and MRI-2 also demonstrated a significant

negative correlation with response ($r = -0.563$, $P < 0.001$). However, the discriminatory performance of this parameter was inferior to that of volumetric measures, as established through ROC analysis.

When examining correlations between MRI-1 and MRI-3 changes, the strength of associations with clinical response showed modest attenuation compared to early changes. Late volumetric changes maintained statistically significant but slightly weaker correlations with response ($r = -0.454$, $P = 0.005$ for tumor volume; $r = -0.455$, $P = 0.005$ for SER volume). Similarly, radiological size changes over the extended MRI-1 to MRI-3 interval demonstrated a significant inverse correlation ($r = -0.555$, $P < 0.001$). However, these findings consistently supported the superior predictive value of early imaging changes over later assessments.

Discussion

DCE-MRI has emerged as a pivotal tool for monitoring treatment response in breast cancer patients undergoing NAC, offering insights into both morphological and functional tumor characteristics. Our study demonstrates that early volumetric changes in tumor and SER-defined FTV measured between baseline and one cycle post-treatment provide superior predictive value for clinical response compared to single-time-point assessments or late-interval changes as well as size-related parameters. The temporal dynamics of these metrics, particularly the distinction between early and late treatment changes, provide important insights into the biological mechanisms underlying treatment response and the optimal timing for imaging-based assessment.

The observed superior performance of early changes compared to late-interval measurements reflects the fundamental biological principle that functional alterations precede morphological changes during effective chemotherapy (20, 21). Studies have consistently demonstrated that therapy-induced tumor functional changes, including alterations in vascular permeability and cellular density, manifest within days to weeks of treatment initiation, well before substantial size reduction becomes apparent (22). The early changes in tumor volume and SER-defined FTV observed in our study likely reflect these initial biological responses, including increased tumor cell apoptosis, reduced cellular density, and compromised tumor vasculature integrity (23, 24). Studies have consistently shown that changes in tumor physiology, including altered perfusion and increased apoptosis, are detectable on functional MRI parameters such as the apparent diffusion coefficient and dynamic contrast-enhanced metrics within the first treatment cycle (25, 26). These early changes represent a "window of opportunity" for response assessment, as they occur before the development of secondary effects such as fibrosis and inflammation that can confound later evaluations (27, 28). This temporal relationship explains why tumor volume changes and SER-defined FTV volume changes performed better compared to the more modest discriminatory performance of late-interval changes.

The utility of SER-defined FTV as a predictive biomarker also reflects its sensitivity to the heterogeneous vascular characteristics within breast tumors (29, 30). SER measurements capture both early enhancement patterns, reflecting tissue perfusion and capillary permeability, and late washout

characteristics, which correlate with the degree of tumor angiogenesis and vessel maturity. The biological basis for SER measurements lies in their ability to quantify the heterogeneous enhancement patterns that characterize malignant tissue (31, 32). Tumor regions with rapid early enhancement and subsequent washout typically correspond to areas of high microvessel density and immature, leaky vasculature characteristic of aggressive malignancies. The reduction in SER-defined FTV following effective chemotherapy reflects the normalization or destruction of this abnormal vasculature, providing a functional readout of treatment efficacy that precedes morphological changes (33, 34).

In the present study, the AUC for our SER-based metric in predicting pathological complete response was 0.83. This performance is comparable to previous reports: FTV measured at 1 minute post-contrast achieved an AUC of 0.85 in triple-negative breast cancer after neoadjuvant chemotherapy (16). Lesion-to-background SER ≤ 1.6 on early-phase MRI yielded an AUC ranging from 0.71 to 0.77 (35). Together, these data indicate that our proposed metric offers diagnostic accuracy on par with established MRI-derived measures.

Our findings corroborate the results of the landmark ACRIN 6657/I-SPY trial, which established functional tumor volume changes as strong predictors of treatment response and recurrence-free survival (36, 37). In their study, Hylton and colleagues demonstrated that early changes in MRI tumor volume and SER between baseline and early treatment time points outperformed clinical examination and later imaging assessments in predicting pathologic complete response. In addition, this study uniquely demonstrates that volumetric and SER-defined FTV changes after just one cycle of anthracycline-based neoadjuvant chemotherapy outperform both later imaging time points and prior single-mid-treatment assessments. Furthermore our study extends these observations by explicitly examining the 20% reduction threshold and demonstrating its clinical utility across both volumetric and functional imaging parameters. The biological significance of the 20% reduction threshold used in our analysis finds support in multiple previous investigations. Recent studies have validated reduction thresholds ranging from 20% to 50% as clinically meaningful indicators of treatment response (38, 39). Our choice of 20% reduction represents a pragmatic balance between sensitivity and specificity, enabling identification of responding patients while minimizing false-positive classifications that could lead to inappropriate treatment modifications.

Furthermore, the findings consistently demonstrated that volumetric parameters (either tumor volume or SER volume) outperformed traditional unidimensional tumor size in predicting treatment response. This aligns with the understanding that tumor shrinkage may not always occur uniformly in all directions. In fact, volume and enhancement patterns provide a more comprehensive representation of tumor burden and vascularity (40). In addition, a combined model that incorporates both tumor volume and SER-defined FTV volume was tested to see if assessing multiple parameters together could improve prediction accuracy compared to using each parameter separately. The findings indicated that combining these measurements did not enhance predictive performance beyond what each metric could achieve alone.

As for clinical applications, early prediction of treatment response to NAC demonstrates clear superiority over late assessment strategies through fundamental clinical advantages that significantly impact patient outcomes. Clinically, early identification of non-responders enables prompt treatment modification, preventing prolonged exposure to ineffective and potentially toxic regimens while maximizing opportunities for alternative therapeutic interventions (41, 42). This approach facilitates adaptive treatment algorithms that can escalate therapy for poor responders or potentially de-escalate for excellent responders, aligning with precision medicine principles (43). Furthermore, early detection prevents the confounding effects of secondary processes such as fibrosis and inflammation that can obscure the relationship between imaging findings and true therapeutic efficacy at later timepoints (33). The temporal advantage of early assessment also optimizes resource utilization, reduces healthcare costs, and supports patient preferences for personalized treatment decisions that minimize unnecessary morbidity while maximizing therapeutic benefit (44, 45). Ultimately, this strategy enhances clinical decision-making by providing actionable information when treatment modifications can still meaningfully impact patient outcomes and prognosis (46).

In the prognosis analysis, our findings highlight the importance of early volumetric changes in tumor and SER volume as predictors of long-term outcomes. Despite similar recurrence rates between the two groups, patients with reductions greater than 20% in these volumes showed a more favorable RFS. This suggests that larger early reductions reflect more profound biological changes, such as increased necrosis or altered vascularity, which are more predictive of successful treatment and better prognosis than traditional tumor size (47, 48).

While this study offers valuable insights into the response assessment and prognosis evaluation in breast cancer patients, several limitations should be considered. First, the retrospective nature of the study introduces the potential for selection bias and limits the ability to establish causality. Second limitation of our study is the modest sample size of 47 patients, which reflects our application of stringent inclusion criteria—stage II–III invasive breast cancer, three standardized DCE-MRI time points, a uniform chemotherapy regimen, and a median follow-up of 60 months. While this yields a homogeneous cohort and precise AUC estimates for early imaging biomarkers, it constrains generalizability. Future multicenter studies with broader eligibility are warranted to validate these findings in larger and more diverse populations.. Additionally, a formal reproducibility analysis, including Intraclass Correlation Coefficients with Bland–Altman limits of agreement for continuous metrics and Cohen’s Kappa for categorical response classifications was not performed in this retrospective cohort. Future prospective studies should incorporate these assessments to confirm measurement robustness and facilitate clinical translation. Furthermore, this study focused on only three MRI parameters, which may not capture the full complexity of tumor characteristics. Future studies should consider incorporating additional imaging metrics, such as diffusion-weighted imaging (DWI), to provide a more comprehensive evaluation of treatment response and prognosis. These factors highlight the need for larger, prospective studies with more advanced imaging techniques to further validate and refine the findings of this study.

Conclusion

In summary, early volumetric and functional MRI metrics provide robust predictive value for assessing response to NAC and prognostic determination in breast cancer, outperforming late or size-based imaging assessments. Standardization and validation efforts remain essential for broader clinical application. Ultimately, early MRI-based response assessment holds promise for enhancing precision oncology and optimizing patient care.

Declarations

Conflict of Interest

The authors declare that they have no competing interests.

Consent to Participate

Written informed consent was obtained from all participants included in the study. The study protocol and consent procedures were reviewed and approved by the University of California, San Francisco Institutional Review Board and the Committee of Human Research under the University of California, San Francisco Human Research Protection Program (approval period: 1995–2002). All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments.

Declaration of AI-assisted technologies in the manuscript preparation process

We acknowledge the use of AI-based tools for grammar checking during the final stage of manuscript preparation.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contribution

Author Contributions: A.M.: conceptualization, methodology, formal analysis, visualization, validation, writing—review and editing. M.Z.: conceptualization, methodology, writing—original draft, writing—review and editing. Z.M.: writing—original draft, writing—review and editing. Af.Mo: supervision, validation, writing—review and editing.

Acknowledgement

The authors would like to acknowledge all investigators and institutions involved in the acquisition and curation of the dataset used in this study.

Data Availability

The data supporting the findings of this study are publicly available in The Cancer Imaging Archive (TCIA) at: <https://www.cancerimagingarchive.net/collection/breast-mri-nact-pilot/>

References

1. Terry MB, Colditz GA. Epidemiology and Risk Factors for Breast Cancer: 21st Century Advances, Gaps to Address through Interdisciplinary Science. *Cold Spring Harbor Perspect Med.* 2023;13(9).
2. El Masri J, Phadke S. Breast Cancer Epidemiology and Contemporary Breast Cancer Care: A Review of the Literature and Clinical Applications. *Clin Obstet Gynecol.* 2022;65(3):461–81.
3. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229–63.
4. Kazerouni AS, Peterson LM, Jenkins I, Novakova-Jiresova A, Linden HM, Gralow JR, et al. Multimodal prediction of neoadjuvant treatment outcome by serial FDG PET and MRI in women with locally advanced breast cancer. *Breast Cancer Res.* 2023;25(1):138.
5. Yang W, Yang Y, Zhang C, Yin Q, Zhang N. A clinicopathological-imaging nomogram for the prediction of pathological complete response in breast cancer cases administered neoadjuvant therapy. *Magn Reson Imaging.* 2024;111:120–30.
6. Romeo V, Accardo G, Perillo T, Basso L, Garbino N, Nicolai E, et al. Assessment and Prediction of Response to Neoadjuvant Chemotherapy in Breast Cancer: A Comparison of Imaging Modalities and Future Perspectives. *Cancers (Basel).* 2021;13:14.
7. Kim S-Y, Cho N, Choi Y, Lee SH, Ha SM, Kim ES, et al. Factors Affecting Pathologic Complete Response Following Neoadjuvant Chemotherapy in Breast Cancer: Development and Validation of a Predictive Nomogram. *Radiology.* 2021;299(2):290–300.
8. Panthi B, Adrada BE, Candelaria RP, Guirguis MS, Yam C, Boge M et al. Assessment of Response to Neoadjuvant Systemic Treatment in Triple-Negative Breast Cancer Using Functional Tumor Volumes from Longitudinal Dynamic Contrast-Enhanced MRI. *Cancers (Basel).* 2023;15(4).
9. Galati F, Rizzo V, Trimboli RM, Kripa E, Maroncelli R, Pediconi F. MRI as a biomarker for breast cancer diagnosis and prognosis. *BJR Open.* 2022;4(1):20220002.
10. Kim JH, Park VY, Shin HJ, Kim MJ, Yoon JH. Ultrafast dynamic contrast-enhanced breast MRI: association with pathologic complete response in neoadjuvant treatment of breast cancer. *Eur*

Radiol. 2022;32(7):4823–33.

11. Zeng Q, Ke M, Zhong L, Zhou Y, Zhu X, He C, et al. Radiomics Based on Dynamic Contrast-Enhanced MRI to Early Predict Pathologic Complete Response in Breast Cancer Patients Treated with Neoadjuvant Therapy. *Acad Radiol*. 2023;30(8):1638–47.
12. Panthi B, Mohamed RM, Adrada BE, Boge M, Candelaria RP, Chen H, et al. Longitudinal dynamic contrast-enhanced MRI radiomic models for early prediction of response to neoadjuvant systemic therapy in triple-negative breast cancer. *Front Oncol*. 2023;13:1264259.
13. Wang M, Du S, Gao S, Zhao R, Liu S, Jiang W, et al. MRI-based tumor shrinkage patterns after early neoadjuvant therapy in breast cancer: correlation with molecular subtypes and pathological response after therapy. *Breast Cancer Res*. 2024;26(1):26.
14. Reig B, Lewin AA, Du L, Heacock L, Toth HK, Heller SL, et al. Breast MRI for Evaluation of Response to Neoadjuvant Therapy. *Radiographics*. 2021;41(3):665–79.
15. Panico C, Ferrara F, Woitek R, D'Angelo A, Di Paola V, Bufi E et al. Staging Breast Cancer with MRI, the T. A Key Role in the Neoadjuvant Setting. *Cancers (Basel)*. 2022;14(23).
16. Musall BC, Abdelhafez AH, Adrada BE, Candelaria RP, Mohamed RMM, Boge M, et al. Functional Tumor Volume by Fast Dynamic Contrast-Enhanced MRI for Predicting Neoadjuvant Systemic Therapy Response in Triple-Negative Breast Cancer. *J Magn Reson imaging: JMRI*. 2021;54(1):251–60.
17. Xiao J, Rahbar H, Hippe DS, Rendi MH, Parker EU, Shekar N, et al. Dynamic contrast-enhanced breast MRI features correlate with invasive breast cancer angiogenesis. *NPJ Breast Cancer*. 2021;7(1):42.
18. Newitt D, Hylton N. Single site breast DCE-MRI data and segmentations from patients undergoing neoadjuvant chemotherapy Version 2 ed. The Cancer Imaging Archive. 2016.
19. Partridge SC, Gibbs JE, Lu Y, Esserman LJ, Tripathy D, Wolverton DS, et al. MRI measurements of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence-free survival. *AJR Am J Roentgenol*. 2005;184(6):1774–81.
20. Li W, Onishi N, Gibbs JE, Wilmes LJ, Le NN, Metanat P et al. MRI-Based Model for Personalizing Neoadjuvant Treatment in Breast Cancer. *Tomography*. 2025;11(3).
21. Xu L, Zhou F, Su L, Wang L. Quantitative dynamic contrast-enhanced MRI parameters effectively predict treatment efficacy of neoadjuvant chemotherapy in breast cancer. *Am J Transl Res*. 2025;17(2):1039–48.
22. Moloney B, Li X, Hirano M, Saad Eddin A, Lim JY, Biswas D, et al. Initial experience in implementing quantitative DCE-MRI to predict breast cancer therapy response in a multi-center and multi-vendor platform setting. *Front Oncol*. 2024;14:1395502.
23. Yao M, Ye D, Wang Y, Shen T, Yan J, Zou D, et al. Application of DCE-MRI radiomics and heterogeneity analysis in predicting luminal and non-luminal subtypes of breast cancer. *Front Oncol*. 2025;15:1523507.
24. Zhang X, Chen X, Fu Y, Zhou H, Lin Y. Study on heterogeneity of vascularity and cellularity via multiparametric MRI habitat imaging in breast cancer. *BMC Med Imaging*. 2025;25(1):159.

25. Tudorica A, Oh KY, Chui SY, Roy N, Troxell ML, Naik A, et al. Early Prediction and Evaluation of Breast Cancer Response to Neoadjuvant Chemotherapy Using Quantitative DCE-MRI. *Transl Oncol.* 2016;9(1):8–17.
26. O'Flynn EA, DeSouza NM. Functional magnetic resonance: biomarkers of response in breast cancer. *Breast Cancer Res.* 2011;13(1):204.
27. Sharma A, Sharma S, Sood S, Seam RK, Sharma M, Fotedar V. DCE-MRI and parametric imaging in monitoring response to neoadjuvant chemotherapy in breast carcinoma: a preliminary report. *Pol J Radiol.* 2018;83:e220–8.
28. Mouawad M, Biernaski H, Brackstone M, Lock M, Yaremko B, Shmuilovich O, et al. DCE-MRI assessment of response to neoadjuvant SABR in early stage breast cancer: Comparisons of single versus three fraction schemes and two different imaging time delays post-SABR. *Clin Transl Radiat Oncol.* 2020;21:25–31.
29. Li W, Arasu V, Newitt DC, Jones EF, Wilmes L, Gibbs J, et al. Effect of MR Imaging Contrast Thresholds on Prediction of Neoadjuvant Chemotherapy Response in Breast Cancer Subtypes: A Subgroup Analysis of the ACRIN 6657/I-SPY 1 TRIAL. *Tomography.* 2016;2(4):378–87.
30. Newitt DC, Aliu SO, Witcomb N, Sela G, Kornak J, Esserman L, et al. Real-Time Measurement of Functional Tumor Volume by MRI to Assess Treatment Response in Breast Cancer Neoadjuvant Clinical Trials: Validation of the Aegis SER Software Platform. *Transl Oncol.* 2014;7(1):94–100.
31. Ma W, Yang L, Zhang Y, Gao Y, Jie H, Huang C. Heterogeneity Assessment of Breast Cancer Tumor Microenvironment: Multiparametric Quantitative Analysis with DCE-MRI and Discovery of Radiomics Biomarkers. *Breast Cancer* (Dove Med Press). 2025;17:573–81.
32. Ashraf A, Gaonkar B, Mies C, DeMichele A, Rosen M, Davatzikos C, et al. Breast DCE-MRI Kinetic Heterogeneity Tumor Markers: Preliminary Associations With Neoadjuvant Chemotherapy Response. *Transl Oncol.* 2015;8(3):154–62.
33. Rauch GM, Adrada BE, Kuerer HM, van la Parra RF, Leung JW, Yang WT. Multimodality Imaging for Evaluating Response to Neoadjuvant Chemotherapy in Breast Cancer. *AJR Am J Roentgenol.* 2017;208(2):290–9.
34. Li X, Arlinghaus LR, Ayers GD, Chakravarthy AB, Abramson RG, Abramson VG, et al. DCE-MRI analysis methods for predicting the response of breast cancer to neoadjuvant chemotherapy: pilot study findings. *Magn Reson Med.* 2014;71(4):1592–602.
35. Kim SY, Cho N, Shin SU, Lee HB, Han W, Park IA, et al. Contrast-enhanced MRI after neoadjuvant chemotherapy of breast cancer: lesion-to-background parenchymal signal enhancement ratio for discriminating pathological complete response from minimal residual tumour. *Eur Radiol.* 2018;28(7):2986–95.
36. Hylton NM, Gatsonis CA, Rosen MA, Lehman CD, Newitt DC, Partridge SC, et al. Neoadjuvant Chemotherapy for Breast Cancer: Functional Tumor Volume by MR Imaging Predicts Recurrence-free Survival-Results from the ACRIN 6657/CALGB 150007 I-SPY 1 TRIAL. *Radiology.* 2016;279(1):44–55.

37. Jafri NF, Newitt DC, Kornak J, Esserman LJ, Joe BN, Hylton NM. Optimized breast MRI functional tumor volume as a biomarker of recurrence-free survival following neoadjuvant chemotherapy. *J Magn Reson Imaging*. 2014;40(2):476–82.

38. Giani M, Renda I, Vallario A, Tavella K, Villanucci A, Nori J, et al. Long-term Results After Neoadjuvant Chemotherapy for Breast Cancer: A Single-center Experience. *Anticancer Res*. 2020;40(2):1079–85.

39. Yao L, Liu X, Wang M, Yu K, Xu S, Qiu P, et al. Predicting Pathological Complete Response in Breast Cancer After Two Cycles of Neoadjuvant Chemotherapy by Tumor Reduction Rate: A Retrospective Case-Control Study. *J Breast Cancer*. 2023;26(2):136–51.

40. Choi WJ, Kim WK, Shin HJ, Cha JH, Chae EY, Kim HH. Evaluation of the Tumor Response After Neoadjuvant Chemotherapy in Breast Cancer Patients: Correlation Between Dynamic Contrast-enhanced Magnetic Resonance Imaging and Pathologic Tumor Cellularity. *Clin Breast Cancer*. 2018;18(1):e115–21.

41. Tan W, Yang M, Yang H, Zhou F, Shen W. Predicting the response to neoadjuvant therapy for early-stage breast cancer: tumor-, blood-, and imaging-related biomarkers. *Cancer Manag Res*. 2018;10:4333–47.

42. Howard FM, He G, Peterson JR, Pfeiffer JR, Earnest T, Pearson AT, et al. Highly accurate response prediction in high-risk early breast cancer patients using a biophysical simulation platform. *Breast Cancer Res Treat*. 2022;196(1):57–66.

43. Janssen LM, den Dekker BM, Gilhuijs KGA, van Diest PJ, van der Wall E, Elias SG. MRI to assess response after neoadjuvant chemotherapy in breast cancer subtypes: a systematic review and meta-analysis. *NPJ Breast Cancer*. 2022;8(1):107.

44. Onishi N, Li W, Gibbs J, Wilmes LJ, Nguyen A, Jones EF, et al. Impact of MRI Protocol Adherence on Prediction of Pathological Complete Response in the I-SPY 2 Neoadjuvant Breast Cancer Trial. *Tomography*. 2020;6(2):77–85.

45. Aguiar-Ibáñez R, Mbous YPV, Sharma S, Chawla E. Assessing the clinical, humanistic, and economic impact of early cancer diagnosis: a systematic literature review. *Front Oncol*. 2025;15:1546447.

46. Álvarez-Benito M. Imaging evaluation of neoadjuvant breast cancer treatment: where do we stand? *Eur Radiol*. 2024;34(10):6271–2.

47. Tyler R, Davies E, Tan D, Hodson J, Taniere P, Thway K, et al. Tumor necrosis is significantly associated with reduced recurrence-free survival after curative resection of gastrointestinal stromal tumors. *J Surg Oncol*. 2021;123(2):432–8.

48. Zhang XK, Zhang ZL, Yang P, Cai MY, Hu WM, Yun JP, et al. Tumor necrosis predicts poor clinical outcomes in patients with node-negative upper urinary tract urothelial carcinoma. *Jpn J Clin Oncol*. 2015;45(11):1069–75.

Tables

Table 1. Patient demographics and clinical characteristics

Characteristic	Value
Age (years)	47.86 ± 9.49
Pre-treatment tumor clinical size (cm)	5.64 ± 3.52
Post-treatment tumor clinical size (cm)	2.75 ± 2.79
Breast involvement laterality	
Left-sided	24 (51%)
Right-sided	23 (49%)
Estrogen receptor status	22 (59%)
Negative	15 (41%)
Positive	
Progesterone receptor status	18 (49%)
Positive	19 (51%)
Negative	
Human epidermal growth factor 2 receptor status	13 (38%)
Positive	21 (62%)
Negative	
Clinical response to NAC	8 (21.6%)
Complete response	18 (48.6%)
Partial response	9 (24.3%)
Minimal response	2 (5.4%)
No response	
Histopathological Subtype	32 (68%)
Invasive ductal carcinoma	8 (17%)
Invasive lobular carcinoma	3 (6.4%)
Adenocarcinoma	1 (2.1%)
Inflammatory breast cancer	3 (6.4%)

Table 2. Diagnostic Performance of MRI Metrics for Predicting Treatment Response Across Different Timepoints

MRI metrics	AUC (95% CI)	P-Value
Pre-treatment MRI (MRI-1)		
Volume	0.517 (0.348 to 0.684)	0.87
SER volume	0.517 (0.348 to 0.684)	0.87
Size	0.549 (0.377 to 0.713)	0.659
Early treatment MRI (MRI-2)		
Volume	0.675 (0.501 to 0.819)	0.063
SER volume	0.675 (0.501 to 0.819)	0.063
Size	0.628 (0.454 to 0.780)	0.226
Post-treatment MRI (MRI-3)		
Volume	0.713 (0.541 to 0.850)	0.035
SER volume	0.710 (0.538 to 0.847)	0.039
Size	0.696 (0.523 to 0.836)	0.03
Early MRI changes (MRI-1 to MRI-2)		
Volume	0.825 (0.665 to 0.930)	<0.001
SER volume	0.822 (0.661 to 0.928)	<0.001
Size	0.731 (0.560 to 0.863)	0.008
Late MRI changes (MRI-1 to MRI-3)		
Volume	0.717 (0.545 to 0.852)	0.015
SER volume	0.724 (0.552 to 0.858)	0.011
Size	0.755 (0.586 to 0.881)	0.001

CI: Confidence Interval, SER: Signal enhancement ratio

Figures

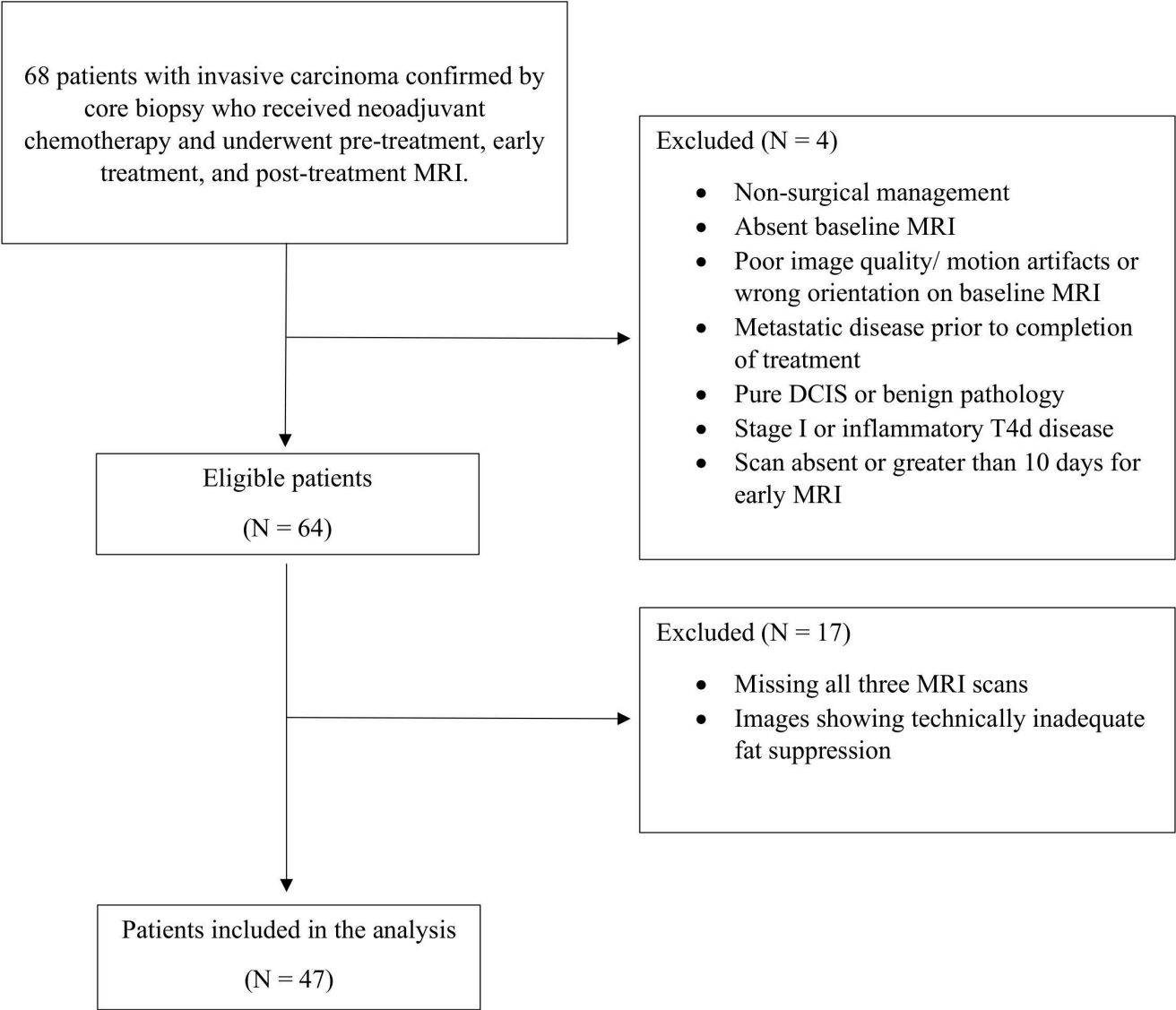
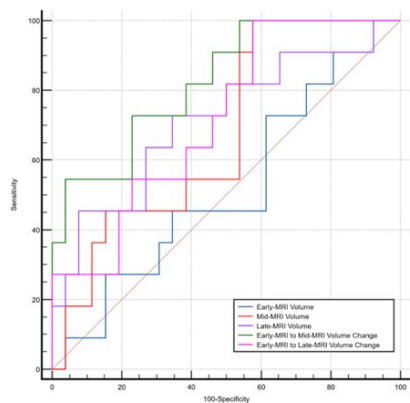


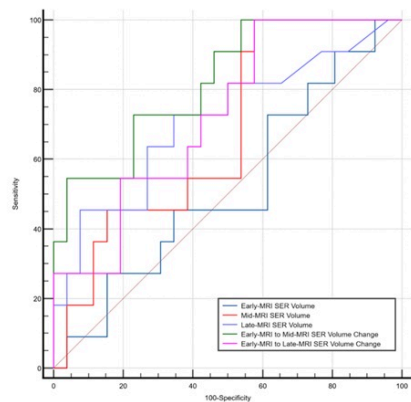
Figure 1

Flowchart illustrating the patient selection process and study inclusion criteria.

A)



B)



C)

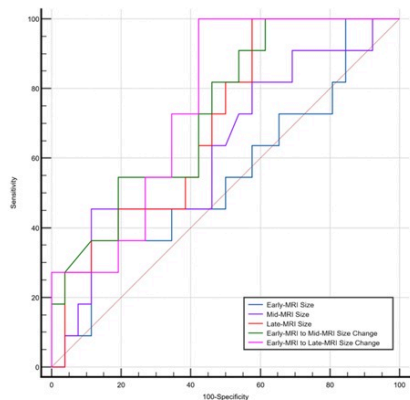
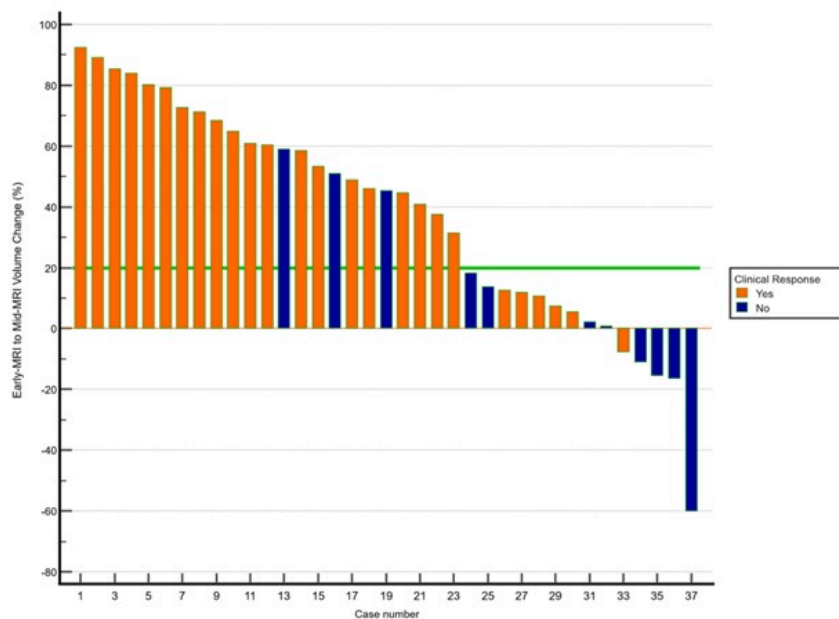


Figure 2

A) Receiver operating characteristic (ROC) curve evaluating the predictive value of tumor volume changes for response to neoadjuvant chemotherapy (NAC). B) ROC curve illustrating the accuracy of Signal Enhancement Ratio (SER) changes in predicting tumor response to NAC. C) ROC curve assessing the performance of tumor size changes in determining response to NAC.

A)



B)

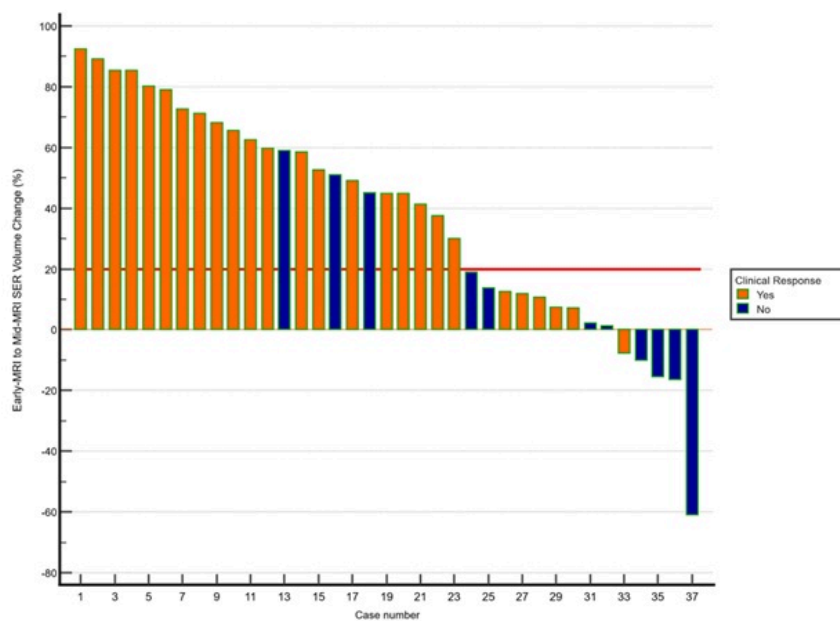


Figure 3

Waterfall plots showing distribution of percent change (%) in MRI-derived metrics following one cycle of neoadjuvant chemotherapy. The y-axis represents percent change from baseline for (A) tumor volume and (B) SER-based functional tumor volume.

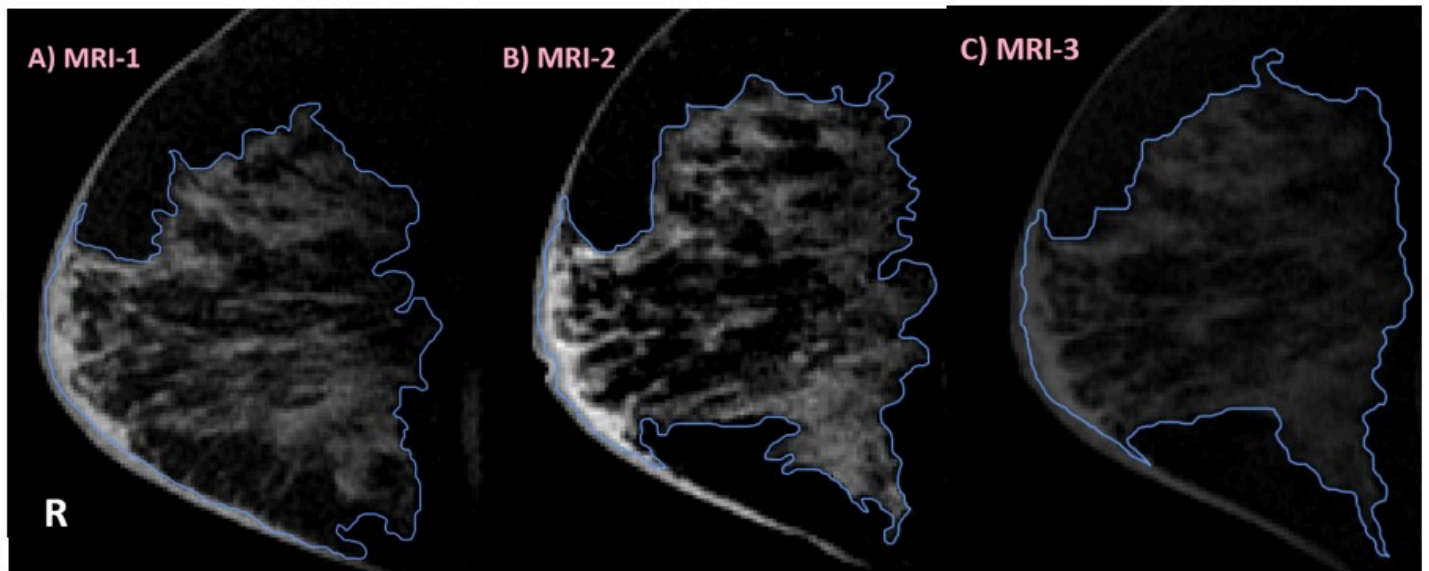


Figure 4

Serial MRI evaluation of a patient with right-sided breast cancer who achieved a complete response following NAC. (A) Pre-treatment axial breast MRI demonstrates a tumor size of 3.44 cm, tumor volume of 3.4 cm³, and SER volume of 3.4 cm³. (B) Early post-treatment MRI, acquired after the first cycle of NAC, shows a marked reduction in tumor size to 2.4 cm, tumor volume to 0.54 cm³, and SER volume to 0.5 cm³. (C) At the completion of the NAC course, the tumor size further decreased to 1.45 cm, with a tumor volume of 0.64 cm³ and SER volume of 0.6 cm³. Notably, the substantial early reduction in volumetric and functional imaging parameters anticipated the final treatment outcome more accurately than late changes in size alone.

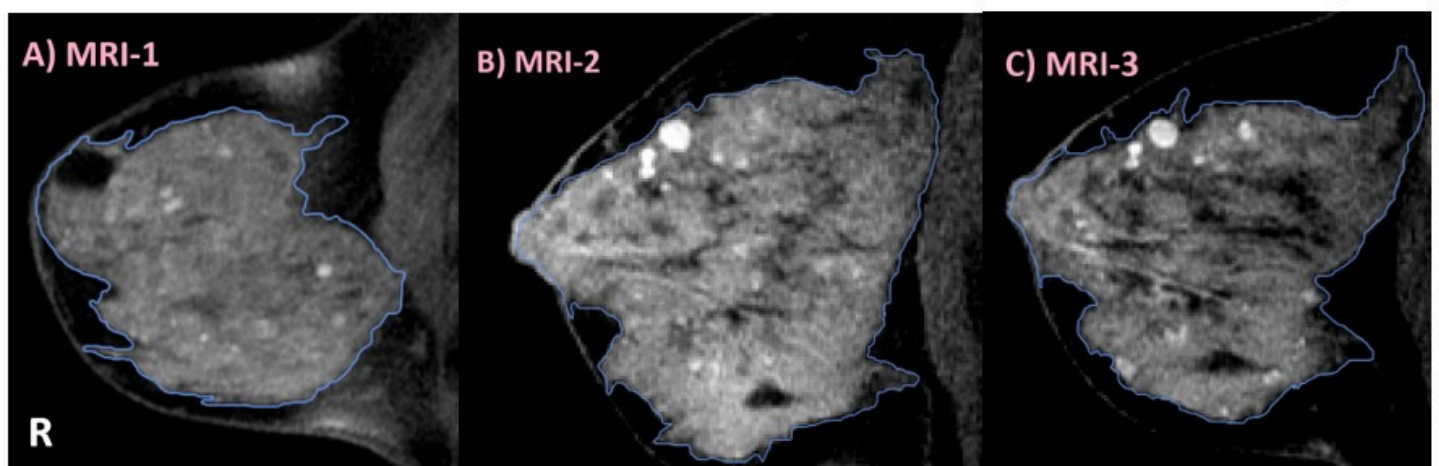


Figure 5

Longitudinal MRI assessment of a patient with right-sided breast cancer demonstrating poor response to NAC. (A) Initial pre-treatment MRI (MRI-1) revealed a large tumor measuring 8.0 cm in diameter, with a

tumor volume and SER volume of 41.9 cm³. (B) Minimal change was observed after the first NAC cycle, with tumor size measuring 7.5 cm, tumor volume 40.9 cm³, and SER volume 41.0 cm³, indicating a negligible early treatment effect in MRI-2. (C) At the end of the NAC regimen (MRI-3), the tumor size decreased to 5.4 cm; however, the delayed volumetric response (tumor and SER volumes reduced to 7.1 cm³) did not correspond to early imaging trends.

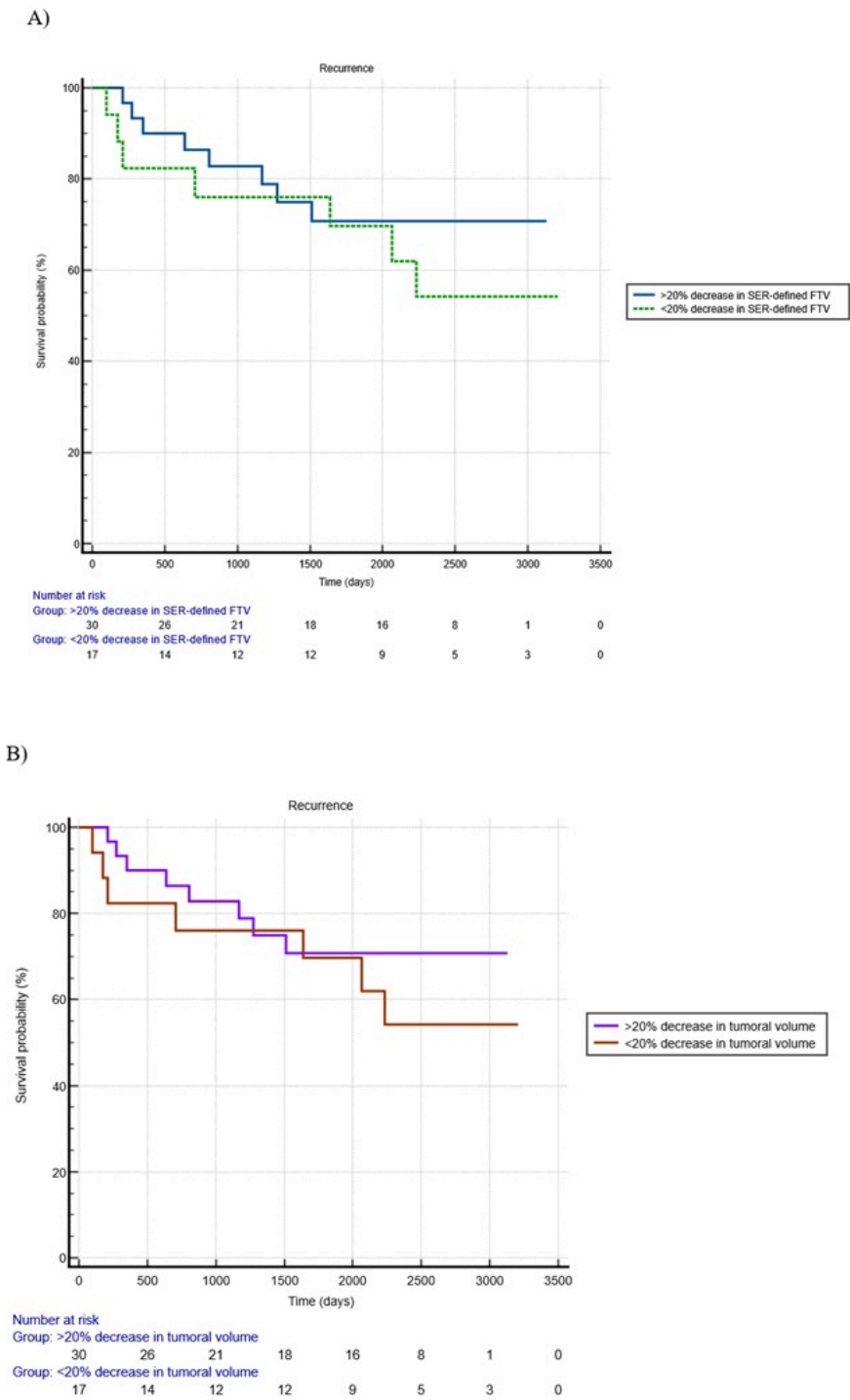


Figure 6

A) Kaplan-Meier curve of recurrence-free survival (RFS) stratified by SER-based FTV volume change. B) Kaplan-Meier curve of RFS stratified by volume change.

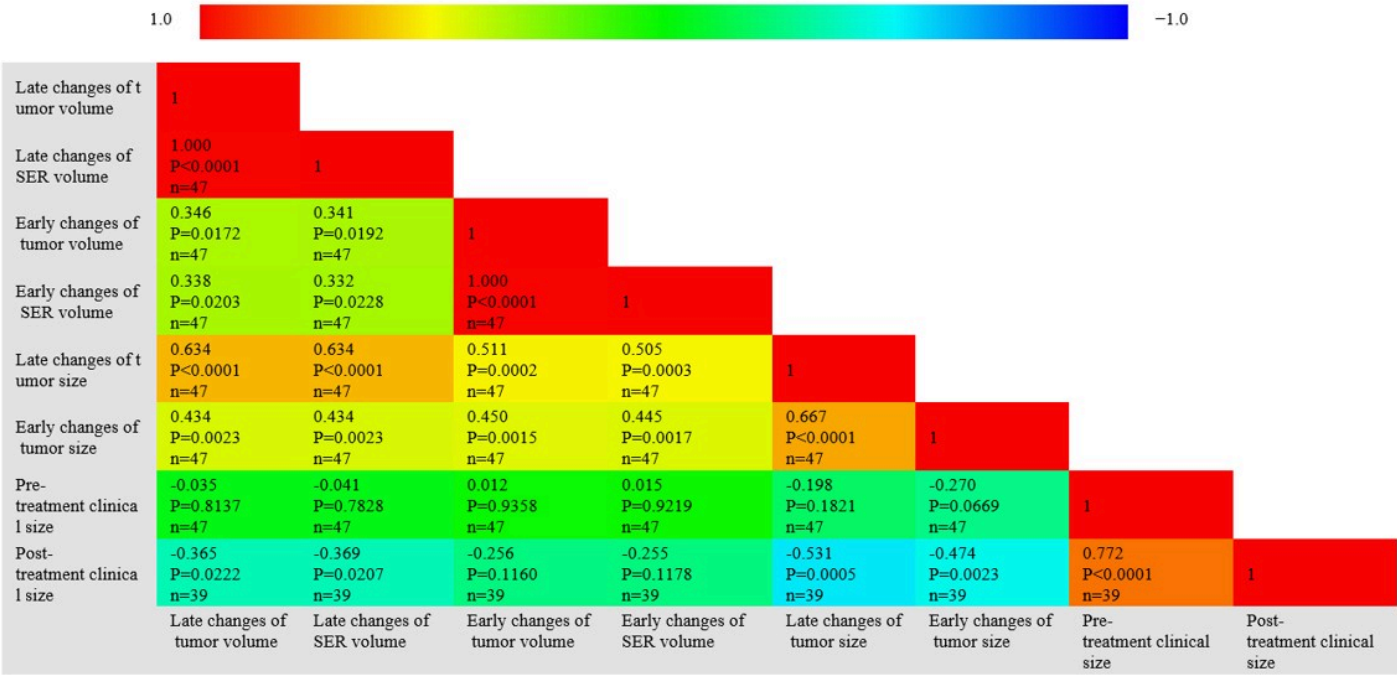


Figure 7

Pearson correlation matrix of MRI-derived parameters and clinical size measurements. The strongest positive correlations are between late changes of tumor volume and late changes of SER volume ($r = 1.000$, $P < 0.0001$) and between early changes of tumor volume and early changes of SER volume ($r = 1.000$, $P < 0.0001$). A moderate positive correlation exists between late and early changes of tumor size ($r = 0.667$, $P < 0.0001$). Pre-treatment and post-treatment clinical size measurements also correlate strongly ($r = 0.772$, $P < 0.0001$). Negative correlations are observed between clinical size measurements and imaging metrics (e.g., post-treatment clinical size vs. late changes of tumor volume: $r = -0.474$, $P = 0.0023$). All values are Pearson r coefficients with associated P -values and sample sizes (n).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryA.docx](#)