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Predicting Pathological Complete Response and 3-Year Invasive Disease-Free Survival in HER2-Positive Early Breast Cancer: An Unplanned Exploratory Analysis Comparing [18F]FDG–PET and Breast MRI in the PHERGain Trial☆

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Abstract

The PHERGain study showed that a response-adapted approach guided by [18F]FDG-PET imaging, focused on achieving pathological complete response (pCR), allowed safe omission of chemotherapy in select individuals with HER2-positive early-stage breast cancer treated with neoadjuvant dual HER2-targeted therapy (trastuzumab plus pertuzumab, or HP). Given the restricted access to [18F]FDG-PET in many centers, this investigation explored the potential of breast MRI as a substitute modality for monitoring early therapeutic response. In cohort B (n=285), participants started with two cycles of HP alone, with chemotherapy added only for those lacking response on [18F]FDG-PET. Imaging with both [18F]FDG-PET and MRI was performed at baseline (prior to treatment assignment) and after the initial two cycles (early evaluation). A follow-up MRI was also obtained prior to operative intervention (late evaluation). The analysis examined agreement between [18F]FDG-PET findings, MRI-measured tumor diminution, and RECIST 1.1 criteria on MRI, as well as their predictive value for pCR and 3-year invasive disease-free survival (iDFS).

Early assessments revealed strong agreement (78.2% accuracy) between [18F]FDG-PET response and any degree of tumor shrinkage on breast MRI, though concordance was lower when using strict RECIST 1.1 definitions (at least 30% reduction in target lesion diameters). Patients responding on [18F]FDG-PET who also demonstrated early MRI shrinkage or RECIST response had elevated pCR rates (39.0% vs. 29.6% without shrinkage; 44.0% vs. 30.4% without RECIST response). Conversely, [18F]FDG-PET non-responders lacking MRI shrinkage exhibited the poorest outcomes, with pCR of only 21.7% and 3-year iDFS of 75.3%, even after chemotherapy escalation. In [18F]FDG-PET responders continuing HP without chemotherapy, prolongation of therapy boosted late MRI complete responses (from 9.3% to 31.7%) and overall response rates (from 55.1% to 70.0%). Late MRI complete response was more reliable for forecasting pCR in hormone receptor-negative disease (positive predictive value 85.5%) compared to hormone receptor-positive cases (61.5%). While [18F]FDG-PET remains the preferred tool for directing adaptive treatment decisions in the PHERGain framework for HER2-positive early breast cancer, this exploratory analysis indicates that measurable tumor reduction via breast MRI may serve as an effective substitute in environments lacking PET access.

Keywords: [18F]FDG–PET, Magnetic resonance imaging, Trastuzumab, Pertuzumab, HER2-positive early breast cancer, Pathological complete response

Introduction

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HER2-positive breast cancer represents a diverse subtype, both clinically and molecularly, defined by overexpression of the HER2 protein and/or amplification of the ERBB2 gene [1]. This category comprises approximately 15%-20% of invasive breast cancers and carries important implications for prognosis and treatment selection[2]. The advent of targeted anti-HER2 agents has markedly enhanced survival rates in patients with early-stage and metastatic disease [3]. In the early breast cancer setting, these therapies have opened the door to de-escalation strategies, including the potential omission of chemotherapy in certain patient subsets [4]. Furthermore, attainment of pathological complete response (pCR) following neoadjuvant therapy has emerged as a robust predictor of favorable long-term prognosis, especially in HER2-positive and triple-negative subtypes[5], making it a key surrogate endpoint in trials exploring treatment reduction.

The PHERGain trial (NCT03161353) established the viability of a response-guided, pCR-oriented approach relying on [18F]FDG-PET to safely eliminate chemotherapy in individuals with HER2-positive early breast cancer undergoing neoadjuvant dual HER2 inhibition with trastuzumab and pertuzumab (HP)[6]. In the adaptive arm (group B), the study achieved its initial primary objective, with 37.9% of [18F]FDG-PET responders completing a chemotherapy-free regimen of eight HP cycles and subsequently demonstrating pCR at surgery[6]. The trial also met its second primary goal, reporting a 3-year invasive disease-free survival (iDFS) of 94.8% across all patients in this adaptive cohort [7]. Although additional validation and longer-term data are needed, these results position this PET-directed strategy as a promising chemotherapy-sparing option for discussion in routine practice with appropriately selected HER2-positive early breast cancer patients.

Breast magnetic resonance imaging (MRI) is broadly available and routinely employed for evaluating local disease extent, tracking neoadjuvant treatment effects, and informing operative decisions. In contrast, while [18F]FDG-PET is valuable for staging and response monitoring, its higher cost and restricted accessibility limit widespread use. Consequently, exploring breast MRI as a substitute for early response evaluation in the context of the PHERGain protocol is clinically relevant [8].

This report details a post-hoc exploratory evaluation of group B participants from the PHERGain study, investigating whether breast MRI could serve as an alternative to [18F]FDG-PET for assessing response to chemotherapy-free neoadjuvant HP and informing decisions regarding chemotherapy escalation. The main aims were:

- To investigate the agreement between early [18F]FDG-PET and breast MRI findings for response evaluation after two cycles of HP in HER2-positive early breast cancer (group B).
- To evaluate the predictive performance of early [18F]FDG-PET versus breast MRI for pCR and 3-year iDFS within the PHERGain adaptive framework (group B).
- To examine MRI-based responses using RECIST version 1.1 criteria at early (post-two cycles) and late (post-eight cycles) time points, and their correlation with pCR, among patients treated solely with HP (early [18F]FDG-PET responders in group B).

Materials and Methods

Study population and trial overview

This retrospective, unplanned analysis focused on individuals enrolled in group B of the PHERGain trial, a multicenter phase II randomized study that included 356 women with previously untreated, operable, stage I-IIIA HER2-positive early breast cancer featuring tumors ≥1.5 cm and at least one [18F]FDG-PET-avid lesion. The trial's primary endpoints were pCR rate in group B [18F]FDG-PET responders completing chemotherapy-free therapy and 3-year iDFS for the entire group B cohort. Full trial details have been published elsewhere [7].

In summary, group B (n=285) followed the response-adapted protocol, starting with two cycles of HP (with endocrine therapy added for hormone receptor-positive cases). Afterward, response was assessed via [18F]FDG-PET (initial adaptation point) and breast MRI. Patients classified as [18F]FDG-PET responders proceeded with six further cycles of HP alone prior to surgery, whereas non-responders switched to six cycles of docetaxel plus carboplatin alongside continued HP. Critically, the choice to introduce chemotherapy was determined exclusively by [18F]FDG-PET results. Post-surgery pathological assessment guided further adaptation: [18F]FDG-PET responders with pCR continued HP to a total of 18 cycles; those without pCR received adjuvant chemotherapy (six cycles of docetaxel/carboplatin with HP) followed by additional HP. In the non-responder group, HP was maintained up to 18 cycles total **(Figure 1)** [6, 7].

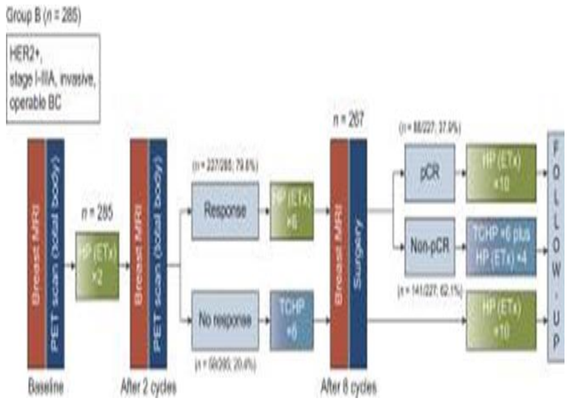

Figure 1. Adaptive study design (Group B). The PHERGain study evaluated whether metabolic imaging could select patients suitable for chemotherapy de-escalation in individuals with HER2-positive, stage I–IIIA, invasive, operable breast cancer featuring at least one breast lesion assessable by [18F]FDG–PET.
Abbreviations: [18F]FDG–PET= [18F]2-fluoro-2-deoxy-d-glucose–positron emission tomography/computed tomography, BC= breast cancer, Etx= endocrine therapy (letrozole for postmenopausal women; tamoxifen for premenopausal women), H: trastuzumab, HER2= human epidermal growth factor receptor 2, MRI: magnetic resonance imaging, non-pCR: non-pathological complete response, P= pertuzumab, pCR= pathological complete response, TCHP= docetaxel, carboplatin, trastuzumab, and pertuzumab

[18F]FDG–PET assessment: definition of [18F]FDG–PET responders

Whole-body [18F]FDG–PET scans were performed at baseline and after two cycles of neoadjuvant treatment, following protocols from the European Association of Nuclear Medicine (EANM) via its EANM Research Limited (EARL) program. Centralized image analysis and quality control were conducted according to European Organisation for Research and Treatment of Cancer (EORTC) standards by two independent, blinded reviewers at two imaging centers (reviewers unaware of patient details, treatment assignment, or clinical outcomes). Patients showing target lesions with at least a 40% reduction in maximum standardized uptake value (SUVmax) from baseline were classified as [18F]FDG–PET responders.

Breast MRI assessments: definition of MRI reduction and MRI response (RECIST v1.1)

Breast MRI was performed at baseline, after two cycles of neoadjuvant therapy (early MRI), and after eight cycles just prior to surgery (late MRI) **(Figure 1)**. Evaluations were done locally. MRI response was classified as partial response (PR) or complete response (CR) based on RECIST version 1.1 criteria:

- CR: complete disappearance of all target lesions
- PR: ≥30% reduction in the sum of diameters of target lesions relative to baseline

An ad hoc definition of MRI reduction was applied for any decrease in target lesion diameter compared to baseline. These radiological assessments excluded new lesions or progression in non-target lesions, though disease progression on MRI was recorded when detected.

Definitions and assessments of outcomes: pCR and 3-year iDFS

Pathological complete response (pCR) was defined as absence of invasive cancer in the breast and axilla (ypT0/is ypN0), assessed by local pathologists post-surgery according to guidelines from the Breast International Group–North American Breast Cancer Group (BIG-NABCG) [9].
Three-year invasive disease-free survival (iDFS) was calculated as the proportion of patients alive without ipsilateral invasive breast tumor recurrence, locoregional invasive recurrence, distant recurrence, contralateral invasive breast cancer, second primary non-breast malignancy, or death from any cause, measured at 3 years post-surgery.

Analysis strategy

To evaluate concordance in response assessment between [18F]FDG–PET and breast MRI, agreement was assessed between [18F]FDG–PET response/non-response and breast MRI reduction/non-reduction or RECIST v1.1 response/non-response after two cycles of trastuzumab plus pertuzumab (HP) in group B patients.
Early predictive accuracy of [18F]FDG–PET and breast MRI for pCR and 3-year iDFS was compared by examining pCR and iDFS rates among [18F]FDG–PET responders and non-responders, stratified by MRI radiological response (reduction or RECIST response) in group B.
Early and late MRI responses were analyzed by first determining RECIST v1.1 response rates after two and eight cycles of HP in [18F]FDG–PET responders (group

B). Then, the predictive value of early and late MRI PR/CR for pCR was evaluated by hormone receptor (HR) status, using positive predictive value (PPV) in relevant subgroups.

Statistical analysis

Accuracy of [18F]FDG–PET response versus MRI reduction was computed as the proportion of concordant cases [true positives (TP: MRI reduction + PET response) + true negatives (TN: no MRI reduction + PET non-response)] among all patients assessed by both modalities (TP + TN + false positives + false negatives), with 95% confidence intervals (CIs) via the Clopper–Pearson method. Accuracy versus MRI response (RECIST) was similarly calculated.

The F1-index was derived to adjust for imbalance in responder/non-responder numbers {F1 = TP / [TP + 0.5 × (FP + FN)]}. Positive predictive values [PPV = TP / (TP + FP)] and negative predictive values [NPV = TN / (TN + FN)] were also provided.

pCR and 3-year iDFS rates were reported for [18F]FDG–PET and MRI responders/non-responders, as well as patients with/without MRI reduction. pCR rates among MRI complete or partial responders after cycle 2 or 8 of HP were calculated (restricted to patients without neoadjuvant chemotherapy), with PPV described by HR-negative versus HR-positive subgroups. pCR rate estimates included Clopper–Pearson 95% CIs.

Three-year iDFS was estimated using the Kaplan–Meier method, with 95% CIs via the log–log approach. The statistical plan for pCR was previously outlined [7]. For further details on statistical methods, see prior reports [6, 7].

Results and Discussion

Demographics of enrolled patients

Enrollment included 71 individuals in group A and 285 in group B, drawn from 45 sites in seven countries across Europe. Recruitment spanned from June 26, 2017, to April 24, 2019. The two groups exhibited comparable baseline features. Hormone receptor positivity was noted in 236 cases (66.0%), nodal disease in 172 (48.0%), and stage II tumors in 269 (76.0%). Detailed patient profiles are available in an earlier report [7].

Concordance between early [18F]FDG–PET and breast MRI evaluations following two cycles of neoadjuvant trastuzumab-pertuzumab (HP)

In group B, after two cycles of dual HER2-targeted therapy with trastuzumab and pertuzumab, metabolic response on [18F]FDG–PET was observed in 79.6% (227 out of 285) of cases. Tumor shrinkage on breast MRI occurred in 82.5% (235 out of 285), while formal response per RECIST 1.1 criteria (partial or complete) was seen in 47.0% (134 out of 285).

The strongest agreement with [18F]FDG–PET findings emerged when MRI was assessed simply for any dimensional reduction rather than strict RECIST response. Specifically, 88.1% (200/227) of metabolic responders demonstrated MRI shrinkage (PPV), and 39.7% (23/58) of metabolic non-responders showed no shrinkage (NPV). This translated to an overall accuracy of 78.2% (95% CI: 73.0–82.9%) and an F1 score of 86.6% (95% CI: 83.4–89.6%).

By contrast, when using RECIST-defined MRI response, only 55.1% (125/227) of [18F]FDG–PET responders met response criteria on MRI (PPV), whereas 84.5% (49/58) of non-responders failed to do so (NPV). Corresponding metrics were lower: accuracy 61.1% (95% CI: 55.1–66.7%) and F1 score 69.3% (95% CI: 63.5–75.0%).

Prognostic utility of early [18F]FDG–PET and breast MRI for pathological complete response and 3-year invasive disease-free survival

Rates of pathological complete response (pCR) tended to be greater among patients exhibiting either MRI tumor reduction or RECIST response, regardless of [18F]FDG–PET status **(Figure 2)**. The peak pCR rate of 44.0% was achieved in metabolic responders who also displayed RECIST response on MRI. Conversely, the nadir of 21.7% occurred in metabolic non-responders lacking any MRI-detectable shrinkage.

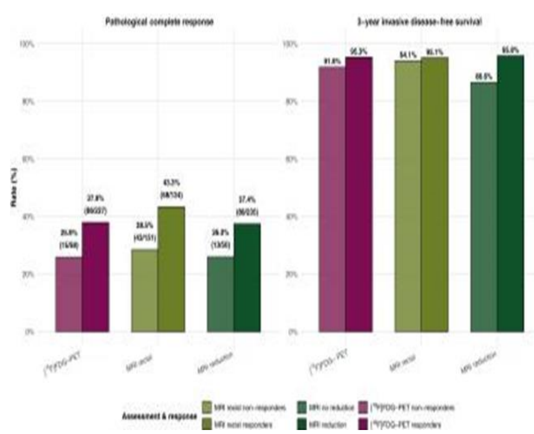

Figure 2. Evaluation of predictive value of early [18F]FDG–PET versus MRI-based measurements in

neoadjuvant therapy. Three imaging strategies were assessed for their ability to anticipate pathological complete response (pCR) and 3-year invasive disease-free survival (iDFS) after two treatment cycles: metabolic activity changes detected by [18F]FDG–PET, the numerical decrease in total lesion diameters on MRI, and response categorized by MRI RECIST v1.1 (partial or complete). [18F]FDG–PET, [18F]2-fluoro-2-deoxy-d-glucose–positron emission tomography/computed tomography; MRI, magnetic resonance imaging. Patients showing an early metabolic response on [18F]FDG–PET had very favorable 3-year iDFS (>94.8%), regardless of whether MRI indicated lesion shrinkage or RECIST-defined response, underscoring the value of early PET assessment as a predictive marker. In contrast, those who did not respond on [18F]FDG–PET and also showed no MRI lesion reduction had the lowest 3-year iDFS, at 75.3 percent **(Tables 1 and 2)**.

Table 1. Rates of [18F]FDG–PET response and breast MRI lesion reduction after two cycles of dual anti-HER2 therapy, with corresponding pCR and 3-year iDFS outcomes

Cohort	Neoadjuvant therapy (2 cycles)	[18F]FDG–PET response, n (%)	MRI reduction, n (%)	Neoadjuvant therapy (6 cycles)	pCR, %	3-year iDFS, %
Group B (n = 285)	HP ×2 (ETx)	**Yes:** 227/285 (79.6)	**Yes:** 200/227 (88.1)	HP ×6 (ETx)	39.0 (32.2–46.1) (n = 78/200)	95.1 (92.0–98.3)
			No: 27/227 (11.9)		29.6 (13.8–50.2) (n = 8/27)	96.3 (89.4–100)
		No: 58/285 (20.3)	**Yes:** 35/58 (60.3)	TCHP ×6	28.0 (14.6–46.3) (n = 10/35)	100 (100–100)
			No: 23/58 (39.6)		21.7 (7.5–43.7) (n = 5/23)	75.3 (56.9–99.6)

Abbreviations: [18F]FDG–PET= [18F]2-fluoro-2-deoxy-D-glucose–positron emission tomography/computed tomography; ETx= endocrine therapy (letrozole for postmenopausal, tamoxifen for premenopausal); H= trastuzumab subcutaneous; iDFS= invasive disease-free survival; MRI=magnetic resonance imaging; P= pertuzumab; pCR= pathological complete response; TCHP= docetaxel, carboplatin, trastuzumab, and pertuzumab.

Table 2. Rates of [18F]FDG–PET response and breast MRI response according to RECIST v1.1 after two cycles of dual anti-HER2 therapy, with corresponding pCR and 3-year iDFS outcomes

Cohort	Neoadjuvant therapy (2 cycles)	[18F]FDG–PET response, n (%)	MRI RECIST v1.1 response, n (%)	Neoadjuvant therapy (6 cycles)	pCR, %	3-year iDFS, %
Group B (n = 285)	HP ×2 (ETx)	**Yes:** 227/285 (79.6)	**Yes:** 125/227 (55.1)	HP ×6 (ETx)	44.0 (35.1–53.2) (n = 55/125)	94.8 (90.8–98.9)
			No: 102/227 (44.9)		30.4 (21.7–40.3) (n = 31/102)	95.8 (91.9–99.9)
		No: 58/285 (20.4)	**Yes:** 9/58 (15.5)	TCHP ×6	33.3 (7.5–70.1) (n = 3/9)	100 (100–100)
			No: 49/58 (84.4)		24.5 (13.3–38.9) (n = 12/49)	90.3 (81.7–99.8)

Abbreviations: [18F]FDG–PET= [18F]2-fluoro-2-deoxy-d-glucose–positron emission tomography/computed tomography; ETx= endocrine therapy (letrozole for postmenopausal, tamoxifen for premenopausal); H= trastuzumab subcutaneous; iDFS= invasive disease-free survival; MRI= magnetic resonance imaging; P= pertuzumab; pCR= pathological complete response; TCHP= docetaxel, carboplatin, trastuzumab, and pertuzumab.

Predictive value of early and late breast MRI partial and complete responses for pCR in patients receiving neoadjuvant HP ([18F]FDG–PET responders)

The occurrence of partial (PR) and complete responses (CR) on breast MRI was assessed after 2 (early) and 8 (late) cycles of therapy, and their association with pathological complete response (pCR) was analyzed. Among patients receiving only dual anti-HER2 therapy (n = 227), 9.3 percent (21/227) showed an early CR, while 45.8% (104/227) exhibited an early PR. After eight cycles, the rates of CR and PR were 31.7% (72/227) and 38.3% (87/227), respectively. Consequently, the objective response rate (ORR) increased from 55.1% following two HP cycles to 70.0 percent after 8 cycles **(Table 3)**.

Table 3. Late and early breast MRI responses by RECIST v1.1 in group B [18F]FDG–PET responders (n = 227)

RECIST v1.1 category	Late assessment (after 8 cycles), n (%)	Early assessment (after 2 cycles), n (%)
CR (complete response)	72 (31.7)	21 (9.3)
PR (partial response)	87 (38.3)	104 (45.8)
SD (stable disease)	48 (21.1)	92 (40.5)
PD (progressive disease)	8 (3.5)	0 (0)
NE (not evaluable)	12 (5.3)	10 (4.4)
ORR (CR + PR)	159 (70.0)	125 (55.1)

Abbreviations: CR= complete radiological response; PR= partial radiological response; SD= stable disease; PD, progressive disease; NE= not evaluable; ORR= objective response rate.

The predictive performance of [18F]FDG–PET for pCR varied according to hormone receptor (HR) status, with positive predictive values (PPV) differing between HR subtypes. Among HR-negative tumors, [18F]FDG–PET responders had a lower PPV for pCR at 75.0%, whereas in HR-positive tumors, the PPV was numerically higher at 82.0%.

The predictive capacity of early and late breast MRI responses for pCR based on HR status was also examined **(Figure 3)**. In HR-negative patients, 11.4% (8/70) achieved an early complete response (CR) after two HP cycles, rising 2.5-fold to 28.6 percent (20/70) after 8 cycles. Early MRI CR demonstrated a PPV of 87.5 percent (7/8; 95 percent CI, 47.3–99.7%) for pCR following eight HP cycles, closely matching the PPV of 85.0 percent (17/20; 95 percent CI, 62.1–96.8%) observed for late MRI CR. Partial responses (PR) on early MRI had a PPV of 38.9 percent (14/36; 95 percent CI, 23.1–56.5%) for achieving pCR, slightly higher than the 28.0 percent (7/25; 95 percent CI, 12.1–49.4%) PPV seen with late MRI PR.

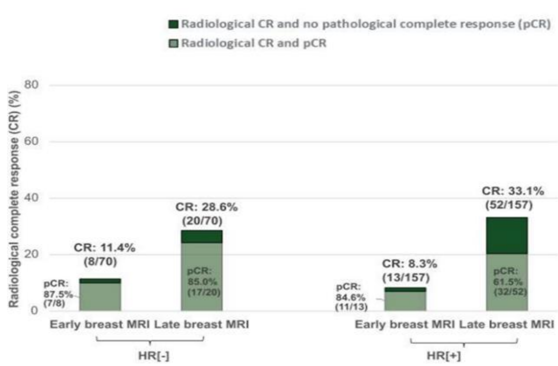

Figure 3. Predictive value of early and late breast MRI Complete Response for Pathological Complete Response (pCR) in patients receiving neoadjuvant dual HER2 blockade alone (n = 227)

Radiological complete response (CR) on MRI, assessed using RECIST criteria after two and eight cycles, and its association with pCR in PET responders from group B (n = 227) of the PHERGain trial, stratified by hormone receptor (HR) status (positive vs. negative). pCR was defined as no residual invasive cancer in the breast or axilla, regardless of ductal carcinoma in situ. Abbreviations: CR= complete response; H= trastuzumab; HR= hormone receptor; MRI= magnetic resonance imaging; non-pCR= non-pathological complete response; P= pertuzumab; pCR= pathological complete response; PET= positron emission tomography.

Among patients with HR-positive tumors, only 8.3% (13/157) exhibited early breast MRI CR after two cycles of neoadjuvant trastuzumab and pertuzumab (HP), rising substantially to 33.1 percent (52/157) after eight cycles (late MRI CR). The positive predictive value (PPV) of early MRI CR for pCR following eight cycles of HP was 84.6 percent (11/13; 95 percent CI 54.6–98.1%), surpassing the PPV of late MRI CR at 61.5 percent (32/52; 95 percent CI 47.0–74.7%). Early partial response (PR) on MRI demonstrated a PPV of 33.8 percent (23/68; 95 percent CI 22.8–46.3%) for pCR, exceeding the 26.3% PPV (10/38; 95% CI 13.4–43.1%) associated with late MRI CR.

This exploratory analysis examined breast MRI as a potential substitute for [18F]FDG-PET in assessing early response to neoadjuvant chemotherapy-free dual anti-HER2 therapy with trastuzumab and pertuzumab (HP) in HER2-positive early breast cancer (EBC) patients from group B of the PHERGain trial.

First, a strong correlation was observed between [18F]FDG-PET response and breast MRI tumor shrinkage after two cycles of HP, achieving an accuracy of 78.2 percent (95 percent CI 73.0–82.9%) and an F1-score of 86.6% (95% CI 83.4–89.6%). This robust agreement was evident particularly when MRI was interpreted using "reduction" criteria—defined as any decrease in target lesion diameter from baseline—rather than strict RECIST v.1.1 response. Such concordance indicates that breast MRI, evaluated via simple size reduction, may represent a practical substitute for early response monitoring in settings lacking access to [18F]FDG-PET.

Second, comparing early [18F]FDG-PET and breast MRI in forecasting pCR and 3-year invasive disease-free survival (iDFS) highlighted their potential synergistic utility in detecting patients with unfavorable prognosis. Consistent with recent findings [10], PET response predicted better pCR and 3-year iDFS independently of MRI status. However, patients lacking response on both modalities exhibited markedly inferior pCR (21.7%) and 3-year iDFS (75.3%) rates, even after escalation to standard chemotherapy plus dual HER2 blockade. These observations imply that dual non-response identifies high-risk individuals who might require intensified or novel therapies.

Finally, in PET responders managed solely with HP, breast MRI responses provided key observations. Early MRI CR after 2 cycles was uncommon (9.3%), but prolonged chemotherapy-free HP up to 8 cycles increased MRI CR rates to 31.7% and overall response rates from 55.1 percent (after 2 cycles) to 70.0 percent (after 8 cycles). The predictive accuracy of MRI for pCR differed by HR status: late MRI CR yielded a high PPV of 85.0% in HR-negative tumors but only 61.5% in HR-positive tumors. Thus, breast MRI appears particularly useful for tracking response during chemotherapy-free regimens in HR-negative, HER2-positive EBC [10], potentially informing treatment duration and de-escalation decisions. These results align with prior evidence of diminished MRI performance in HR-positive versus HR-negative disease [11].

[18F]FDG-PET offers clear benefits for predicting pCR in neoadjuvant breast cancer therapy and detecting occult metastases at diagnosis [12, 13], yet its clinical adoption is hindered by expense, limited availability, and interpretive expertise requirements [14]. Given these barriers, our data position breast MRI as an accessible, non-invasive, cost-effective dynamic biomarker for response evaluation during chemotherapy-free dual HER2 blockade in HER2-positive EBC where PET is unavailable. Nevertheless, pending broader comparative evidence, [18F]FDG-PET remains the standard for the PHERGain approach in routine practice. Future prospective trials validating breast MRI for early response assessment are warranted [15] to expand personalized, response-guided strategies in HER2-positive EBC.

This unplanned exploratory analysis carries important caveats. Its post-hoc design risks bias, as treatment decisions relied on PET rather than MRI, precluding direct head-to-head predictive comparisons. Local MRI assessments introduced potential variability from differing protocols and interpretations across sites. The non-standard "reduction" definition for MRI may have added subjectivity. Subgroup analyses by HR status were constrained by modest sample sizes, limiting generalizability. Moreover, MRI's prognostic impact on long-term outcomes like 3-year iDFS awaits confirmation in larger prospective cohorts. Advanced MRI metrics, such as functional tumor volume, have shown promise for pCR prediction [15, 16] and merit further exploration beyond basic diameter changes.

Conclusion

In summary, while [18F]FDG-PET is currently preferred for early response-guided strategies in HER2-positive EBC per the PHERGain protocol, this exploratory evaluation indicates that breast MRI-detected tumor shrinkage could serve as an effective alternative for directing chemotherapy-free neoadjuvant HP after initial cycles in dynamic, imaging-driven, pCR-adapted approaches when PET is inaccessible. Prospective validation is essential prior to integrating MRI-based reduction as a core biomarker. The strong PET-MRI concordance, combined predictive power for pCR and 3-year iDFS, and superior pCR prediction by MRI CR (especially in HR-negative cases) underscore MRI's supportive role in therapeutic decision-making. Study design complexities and limitations emphasize the call for additional investigations to confirm and implement these insights clinically. The adaptive PHERGain framework has delivered strong outcomes by individualizing therapy based on patient response, yet remains non-standard. Integrating multimodal imaging biomarkers with other prognostic factors promises further advances in tailored breast cancer care and better patient results.

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