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Diagnostic accuracy of modern imaging following neoadjuvant therapy for breast cancer: a comparative analysis of ultrasound versus [18F] FDG PET/MRI in breast response assessment

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Introduction: Accurately predicting pathological complete response (pCR) after primary systemic therapy (PST) in breast cancer remains a clinical challenge. This study compares the diagnostic performance of ultrasound (US) and Fluorodeoxyglucose positron emission tomography/magnetic resonance imaging ([18F]FDG PET/MRI) in predicting breast-pCR following PST.

Methods: This multicenter analysis included 143 patients: 54 node-positive patients from San Raffaele Hospital, who underwent an additional [18F]FDG PET/MRI within a prospective trial (ClinicalTrials.gov ID: NCT04826211) and 89 cases retrospectively retrieved from the database of Heidelberg Hospital, irrespectively of nodal status at diagnosis. In US, breast clinical complete response (breast cCR) was defined as a tumor size of 0 mm or no sign of tumor in the breast; in [18F]FDG PET/MRI, as the absence of significant [18F]FDG uptake on PET images and contrast-enhancement on MRI. Diagnostic accuracy was assessed across PET only, MRI only, combined PET/MRI (PET or MRI positive), and concordant PET/MRI (both positive). Subgroup analyses explored associations of breast cCR with tumor molecular subtypes.

Results: [18F]FDG PET/MRI showed a sensitivity of 62% (95% CI 42%-81%) and a specificity of 67% (95% CI 46%-83%), whereas ultrasound showed a sensitivity of

59% (95% CI 44%-73%) and a specificity of 62% (95% CI 46%-77%) in detecting breast response to PST. No significant difference was observed between [18F]FDG PET/MRI and US in terms of sensitivity (62.9%vs59.1%, p=0.93) and specificity (66.6%vs62.2%, p=0.94) in detecting response to PST. Exploratory subgroup analysis suggested variation in sensitivity: US showed a sensitivity of 73% (95% CI 0.45-0.92) in triple-negative tumors and 50% (95% CI 16%-84%) in HER2-positive tumors, while [18F]FDG PET/MRI demonstrated a sensitivity of 77% (95% CI 46%-95%) in Luminal B cancers.

Conclusion: [18F]FDG PET/MRI and US showed comparable performance in diagnostic accuracy of breast pCR following PST, with varying effectiveness across tumor subtypes. Further research should focus on multimodal imaging strategies integrated with clinical and molecular data.

KEYWORDS

breast cancer, pathological complete response (pCR), PET/MRI, primary systemic therapy, ultrasound

Introduction

Breast cancer remains the most common tumor and the leading cause of cancer death among females worldwide, underscoring the need for improved treatment strategies (1–3). Primary systemic therapy (PST) plays a key role in reducing tumor burden, enabling less invasive surgery and informing subsequent treatments (4). Furthermore, achieving pathological complete response (pCR) after PST is associated with improved overall survival and disease-free survival (5, 6). Modern trials showed that pCR rate could be higher than 70% in patients with triple negative (TN) and human epidermal growth factor receptor 2 positive (HER2+) breast cancers (7–11). Conversely, non-responders may receive additional adjuvant systemic treatments, such as capecitabine for TN and T-DM1 for HER2-positive patients with residual disease, which can improve survival outcomes and reduce recurrence risk while enabling less invasive surgical options (12, 13).

Surgical management following PST is guided by both the initial staging and the re-staging performed after chemotherapy. The primary objectives of preoperative imaging are to evaluate the therapeutic response and to estimate the extent of residual tumor tissue. Despite notable advancements in imaging modalities, accurately predicting pCR remains a persistent challenge (14, 15).

Ultrasound (US), on one hand, remains a commonly utilized modality for the detection and diagnosis of breast cancer, mainly due to low cost and large availability (16). Although it is well-tolerated by patients, its diagnostic accuracy is inherently operator-dependent, which may limit the reproducibility and consistency of residual tumor measurements. On the other hand, novel imaging technologies—such as hybrid positron emission tomography/magnetic resonance imaging with Fluorine-18 fluorodeoxyglucose ([^{18}F]FDG PET/MRI)—are emerging as promising tools to improve the detection of residual disease and to enhance the prediction of treatment response (17). [^{18}F]FDG PET/MRI integrates metabolic and morphologic data in a single session, offering superior diagnostic accuracy compared to conventional imaging. This hybrid whole-body imaging system allows for a comprehensive assessment of both local and distant disease, thereby optimizing staging and response evaluation in a single, non-invasive procedure (18, 19).

The increasing effectiveness of PST in breast cancer management has opened the door to clinical trials exploring the feasibility of omitting surgery in patients who achieve a complete response (20–23). However, no imaging modality to date has demonstrated sufficient accuracy to reliably replace surgery in confirming pCR, underscoring the urgent need for more precise preoperative assessment tools. This study aims to evaluate and compare the diagnostic performance of combined [^{18}F]FDG PET/MRI and conventional US in predicting breast pCR in patients with breast cancer treated with PST. The evaluation of axillary response will be object of a separate analysis and will not be included in this manuscript.

Patients and methods

We conducted a comparative analysis of breast cancer patients who underwent PST utilizing two distinct cohorts from separate cancer centers (Figure 1).

The first cohort (San Raffaele Cohort) included 54 patients with node-positive breast cancer of any size, recruited prospectively at IRCCS Ospedale San Raffaele in Milan, Italy, between November 2019 and August 2023. All patients were nodal-positive at diagnosis and were enrolled in a clinical research trial investigating [^{18}F]FDG PET/MRI in staging and treatment response assessment. These patients underwent [^{18}F]FDG PET/MRI imaging within a research trial with prospective data collection. This trial is registered as *SNB vs PET/MRI 1* on ClinicalTrials.gov (ID: NCT04826211). This study was approved by the Institutional Ethics Committee of IRCCS San Raffaele (Registration Nb 115/INT/2019, approved on September 12th, 2019), and all patients gave written informed consent to participate in the study. This was an unplanned additional analysis carried out within the study. This study was reported following the Standards for Reporting of Diagnostic Accuracy (STARD) reporting guidelines (24).

The second cohort (Heidelberg Cohort) consisted of a retrospective consecutive series of 88 breast cancer patients treated at

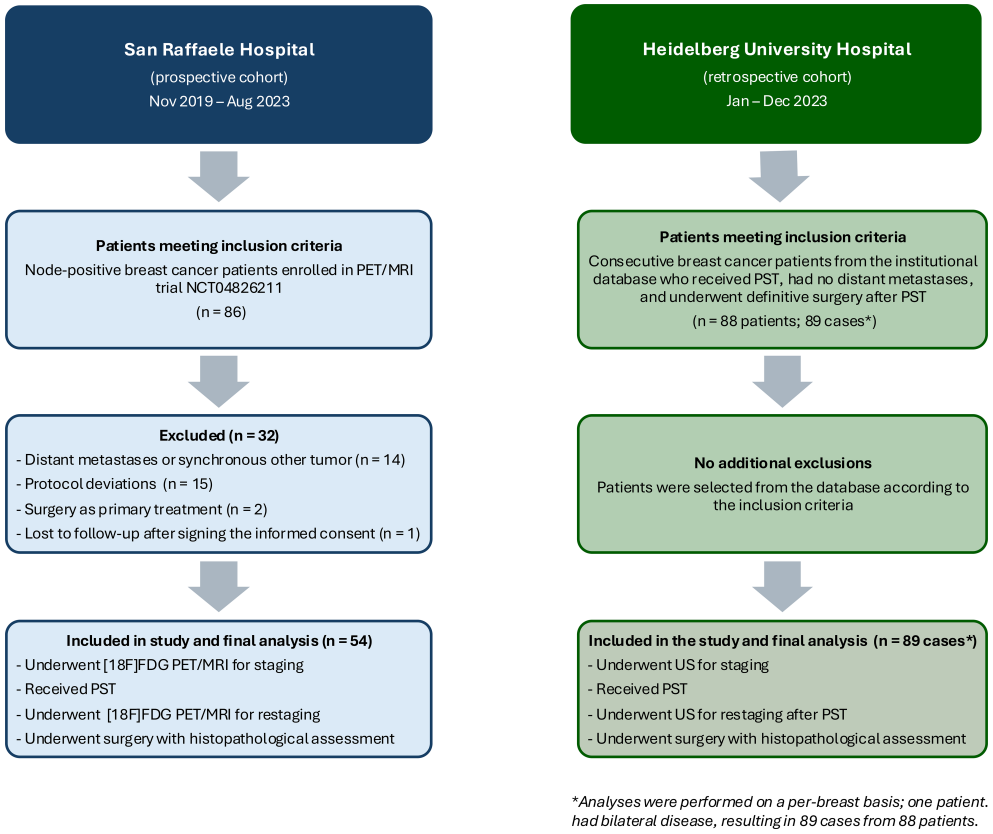

FIGURE 1
Side-byside flowchart comparing patient selection for two breast cancer study cohorts: San Raffaele Hospital (prospective) and Heidelberg University Hospital (retrospective) with inclusion criteria, exclusions, and final numbers analyzed listed for each group. *Analyses were performed on a per-breast basis; one patient had bilateral disease, resulting in 89 cases from 88 patients.

Heidelberg University Hospital in Germany, who underwent oncologic breast surgery between January and December 2023. Data from this cohort were retrospectively extracted from the institutional breast cancer database. One patient in this cohort presented with bilateral disease; thus, the analysis includes 89 cases. Overall, 62.9% of these were clinically node negative at diagnosis. All patients underwent US evaluation both prior to and following PST, before surgery. Institutional Review Board approval was obtained, and informed consent waived for this retrospective use for research purposes (Table 1).

It should be noted that the comparison between US and [^{18}F]FDG PET/MRI was not performed on paired examinations within the same patient population. Rather, diagnostic performance was evaluated in two independent cohorts derived from separate studies, and therefore the analysis should be considered an indirect comparison.

Inclusion criteria for both cohorts were: age over 18 years, histologically confirmed breast cancer diagnosis, completion of PST, and provision of informed consent. Exclusion criteria included the presence of distant metastases and failure to undergo definitive surgery following PST. For the San Raffaele cohort, additional exclusion criteria included contraindications to [^{18}F]FDG PET or MRI, contrast agent allergy, and severe renal impairment.

The primary endpoint of the study was to compare the diagnostic accuracy of [^{18}F]FDG PET/MRI versus US in predicting breast pCR, using final histopathological assessment as the reference standard. Sensitivity and specificity were calculated for each modality.

The secondary endpoint was to explore potential associations between imaging results and tumor molecular subtypes.

Patient registration

For the *San Raffaele cohort*, the process began during the patients' surgical consultation. Following the diagnosis of breast cancer with lymph node involvement, eligible patients were identified and informed about the study's objectives and procedures. After providing written informed consent, patients underwent [^{18}F]FDG PET/MRI for baseline staging. Subsequently, they received PST according to standard clinical guidelines. Upon completion of PST, patients underwent a second [^{18}F]FDG PET/MRI for re-staging. As part of the routine preoperative assessment, breast and axillary US and mammography were also performed both before and after therapy, and a clip was positioned as marker in the primary tumor at diagnosis.

For the *Heidelberg Cohort*, data were retrospectively extracted from the institutional patient database of the breast department, specifically identifying patients who had undergone PST. Patients presenting with distant metastases at diagnosis were excluded from the analysis. Breast cancer patients were managed by specialists in Obstetrics and Gynecology throughout the diagnostic, treatment, and surgical phases. At diagnosis, patients underwent clinical breast examination, mammography, and US to establish disease extent. Following the administration of PST, preoperative re-staging was performed using mammography and US to assess treatment response and guide surgical planning.

TABLE 1 Comparison of demographic and clinical characteristics between the two cohorts.

Characteristic	Heidelberg	San Raffaele	*p*-value
Mean age (SD)	49.2 (13.2)	50.7 (16.6)	0.576
cT status - no. (%)			0.601
– cTis	1 (1.1)	0 (0.0)	
– cT1	31 (34.8)	13 (24.1)	
– cT2	44 (49.4)	32 (59.3)	
– cT3	11 (12.4)	7 (13.0)	
– cT4	2 (2.2)	2 (3.8)	
cN status - no. (%)			<0.001
– cN0	56 (62.9)	0 (0.0)	
– cN1	21 (23.6)	45 (83.3)	
– cN2	5 (5.6)	2 (3.7)	
– cN3	7 (7.9)	7 (1.3)	
Grade - no. (%)			0.033
– 1	0 (0.0)	0 (0.0)	
– 2	33 (37.1)	19 (35.2)	
– 3	56 (62.9)	31 (57.4)	
– NA	0 (0.0)	4 (7.4)	
Tumor biology - no. (%)			0.012
– NST	76 (85.4)	47 (87.0)	
– NST + DCIS	10 (11.2)	0 (0.0)	
– ILC	2 (2.2)	3 (5.6)	
– Other	1 (1.1)	4 (7.4)	
Tumor Molecular Subtype - no. (%)			0.182
– Luminal A	3 (3.4)	3 (5.6)	
– Luminal B	35 (39.3)	15 (27.8)	
– Her2-positive	19 (21.3)	21 (38.8)	
– Triple negative	32 (36.0)	15 (27.8)	
ycT status - no. (%)			0.009
– ycTis	1 (1.1)	0 (0.0)	
– ycT0	43 (48.3)	17 (32.1)	
– ycT1	33 (37.1)	21 (39.6)	
– ycT2	8 (9.0)	6 (11.3)	
– ycT3	3 (3.4)	1 (1.9)	
– ycT4	1 (1.1)	0 (0.0)	
– NA	0 (0.0)	8 (15.1)	
ycN status - no. (%)			<0.001
– ycN0	79 (88.8)	25 (47.2)	
– ycN1	5 (5.6)	14 (26.4)	
– ycN2+	5 (5.6)	0 (0.0)	
– NA	0 (0.0)	14 (26.4)	
Further descriptive variables			
Breast Surgery - no. (%)			0.075
– Breast conserving surgery	52 (58.4)	33 (61.1)	
– Mastectomy	10 (11.2)	5 (9.3)	
– Nipple-Sparing Mastectomy	18 (20.2)	16 (29.6)	
– Skin-Sparing Mastectomy	9 (10.1)	0 (0.0)	
ypT status—no. (%)			0.037
– ypTis	8 (9.0)	10 (18.5)	
– ypT0	32 (36.0)	17 (31.5)	
– ypT1	32 (36.0)	12 (22.2)	
– ypT2	8 (9.0)	13 (24.1)	
– ypT3	8 (9.0)	2 (3.7)	
– ypT4	1 (1.1)	0 (0.0)	
ypN status—no. (%)			0.398
– ypN0	59 (66.3)	30 (55.6)	
– ypN1	20 (22.5)	16 (29.6)	
– ypN2+	9 (10.1)	8 (14.8)	
– NA	1 (1.1)	0 (0.0)	

(Continued)

TABLE 1 Continued

NA values were not found in the source documentation of the trial and were not included in this study analysis.

Imaging

San Raffaele Cohort: All participants underwent whole-body and breast-dedicated [^{18}F]FDG PET/MRI imaging using a fully integrated 3.0 T SIGNA^{TM} PET/MRI (General Electric HealthCare, Waukesha, WI, USA). Imaging acquisition was performed 60 minutes after intravenous administration of [^{18}F]-FDG. PET data were acquired simultaneously with MRI over a total examination time of approximately 2 hours. The MRI protocol included both non-contrast and contrast-enhanced sequences following intravenous injection of a gadolinium-based contrast agent. Standard clinical pulse sequences were acquired, including T1-weighted and T2-weighted images, diffusion-weighted imaging (DWI), and multiphase 3D sequences. Full technical details on PET/MRI protocol were previously published (25).

Image Analysis (Figures 2–4): Image interpretation was independently conducted by a radiologist and a nuclear medicine physician. Each specialist assigned separate scores for [^{18}F]FDG PET and MRI findings using a 4-point scale: 1 = negative, 2 = equivocal, 3 = suspicious, and 4 = positive (25–28). For the purpose of statistical analysis, scores of 1 and 2 were classified as negative, whereas scores of 3 and 4 were classified as positive. Diagnostic performance was assessed across three principal subsets: (a) [^{18}F]FDG PET scores alone, (b) MRI scores alone, and (c/d) combined [^{18}F]FDG PET/MRI scores.

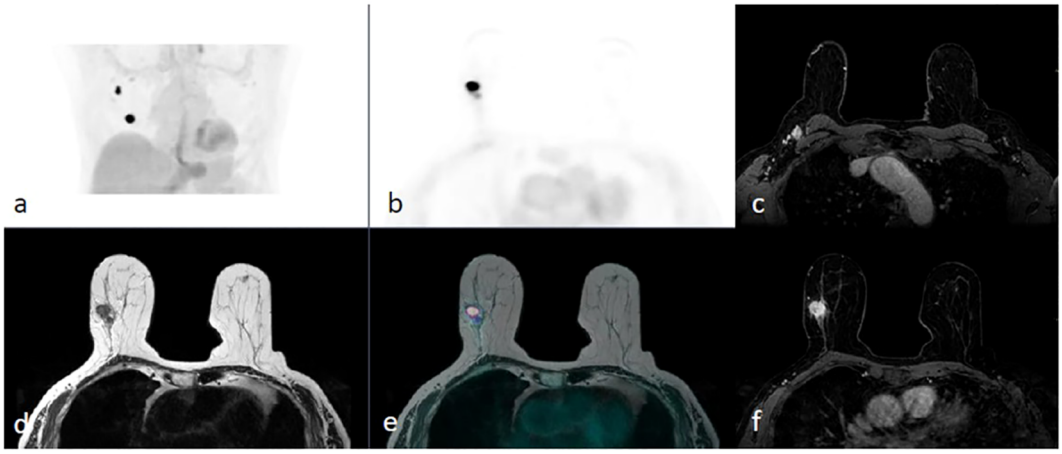

FIGURE 2
Hybrid PET/MRI images of a patient with right breast cancer and axillary lymph node involvement before treatment. **(a–e)** [^18F]FDG PET and fused PET/MRI images reveal intense tracer uptake in both the primary tumor and the metastatic axillary lymph node, confirming metabolic activity. **(c)** Dynamic contrast-enhanced MRI with gadolinium shows right axillary lymphadenopathy with pathological enhancement. **(f)** Dynamic gadolinium-enhanced MRI demonstrates an enhancing right breast lesion consistent with malignancy.

Heidelberg cohort: Key variables such as tumor size, tumor borders, and echogenicity were evaluated in the routine US performed by gynecologists. To facilitate tumor localization, a clip was positioned in the primary lesion prior to PST.

Both [^{18}F]FDG PET/MRI and US were followed by surgery within 30 days. Radiologists and nuclear medicine physicians were blinded to the reference standard, defined as the final histopathological assessment obtained after surgery.

Surgery

Surgical procedures followed guidelines and were guided by both the initial and the post-treatment staging. For localisation of non-palpable breast lesions, patients at San Raffaele underwent Radioguided Occult Lesion Localization (ROLL), whereas at Heidelberg were managed using US-guided wire localisation.

Treatment response and staging

Treatment response assessment was conducted preoperatively using [^{18}F]FDG PET/MRI in the San Raffaele cohort, and US in the Heidelberg cohort. For the purposes of this study, only the response of the primary breast tumor was considered.

Breast Clinical complete response (breast cCR) was defined as the absence of clinically detectable residual disease in the breast following PST, based on physical examination and available breast imaging, with no evidence of a residual breast mass or other findings suggestive of invasive cancer. For the purpose of this study, it was based on the

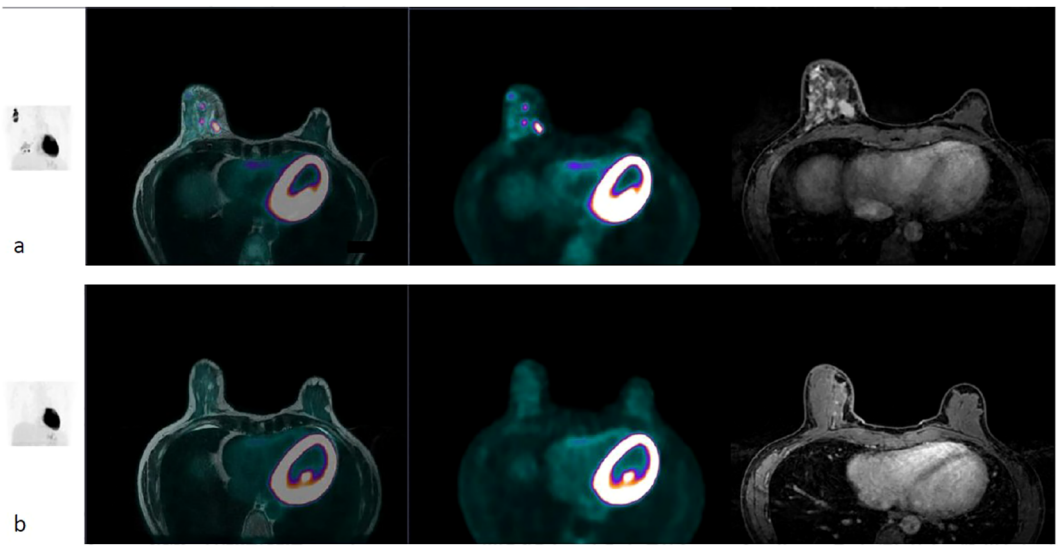

FIGURE 3
Hybrid PET/MRI images of a patient with right breast cancer before and after neoadjuvant chemotherapy. **(a)** Baseline imaging shows intense [18F]FDG uptake in the right breast lesion with corresponding enhancement and morphological abnormalities on dynamic contrast-enhanced MRI with gadolinium. **(b)** Post-treatment imaging demonstrates complete metabolic and morphological response with no residual [18F]FDG uptake and absence of pathological enhancement on gadolinium-enhanced dynamic MRI.

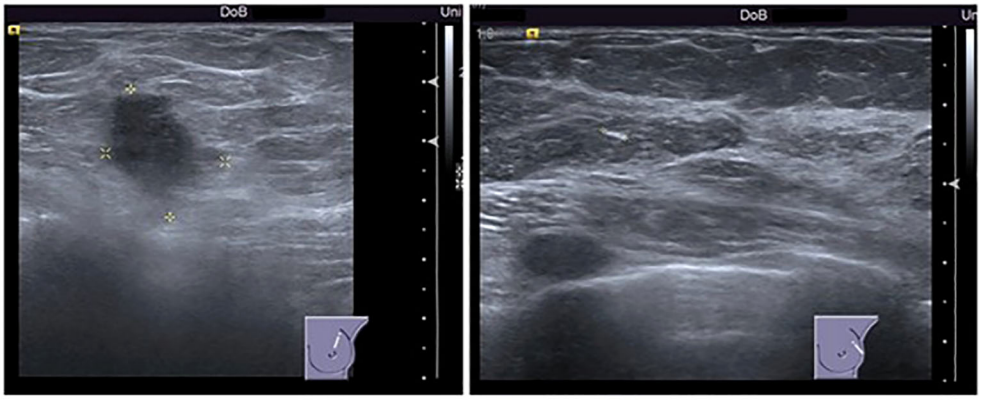

FIGURE 4
US images of breast cancer before (left) and after (right, clip only) the PST, illustrating treatment response.

ycT stage on imaging following PST, and the number and percentage of patients in each cohort demonstrating no residual tumor in the breast on imaging were reported. According to RECIST and PERCIST criteria, the breast cCR was determined by the disappearance of breast lesions on US and MRI and the complete resolution of FDG uptake to background levels on PET imaging (29, 30). In detail, US examinations were performed preoperatively by an experienced operator following a standardized institutional breast US protocol. The operator was not blinded to prior imaging (i.e. mammography), but was unaware of final histopathological outcomes at the time of image acquisition and interpretation.

Breast *pCR* was defined as the absence of residual invasive carcinoma in the breast specimen following neoadjuvant systemic therapy, irrespective of the presence of residual ductal carcinoma *in situ* (DCIS) (ypT0/is). For the purpose of this study, both ypT0 and ypTis were considered indicative of breast pCR.

Diagnostic performance calculations

To assess the diagnostic accuracy of both imaging modalities, a tumor size of 0 mm or no sign of tumor in the breast on US and a score of 1 or 2 on [^{18}F]FDG PET/MRI were defined as indicative of breast cCR.

Given that PET and MRI scores were assigned independently for each examination, diagnostic performance calculations were conducted across four scenarios:

- (a) PET alone, considering [^{18}F]FDG PET scores only;
- (b) MRI alone, considering MRI scores only;
- (c) combined PET/MRI: a positive result was defined as a score ≥3 on either [^{18}F]FDG PET or MRI, including cases where both were positive; all cases with both scores of 1 or 2 were considered negative;
- (d) concordant PET/MRI: a more stringent definition where the result was considered positive only if both [^{18}F]FDG PET and MRI yielded a score ≥3.

As exploratory analysis, these performance assessments were further stratified according to molecular subtypes, including TN, HER2-positive, and Luminal B tumors. Luminal A tumors were excluded from this analysis due to the limited numbers (three in each group) and the low metabolic activity that could impact on PET/MRI performance.

Patient data were extracted from the electronic medical records at San Raffaele and Heidelberg Hospitals, anonymized to ensure confidentiality, and compiled into Microsoft Excel spreadsheets for analysis. Statistical analyses were performed using R software, with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) calculated for each imaging modality. Comparisons between cohorts and subgroups were conducted using appropriate statistical tests, including t-tests for continuous variables, and Fisher's exact test or chi-square test for categorical variables.

TABLE 2 **Overall diagnostic performance of different imaging methods in assessing breast response after primary systemic therapy.**

	US	PET	MRI	PET/MRI concordant	PET/MRI
Sensitivity (%)	59 (95% CI 44-73)	48 (95% CI 29-68)	52 (95% CI 32-71)	37 (95% CI 19-58)	62 (95% CI 42-81)
Specificity (%)	62 (95% CI 46-77)	70 (95% CI 50-86)	81 (95% CI 62-94)	85 (95% CI 66-96)	67 (95% CI 46-83)
PPV (%)	66 (95% CI 50-80)	62 (95% CI 38-82)	74 (95% CI 49-91)	71 (95% CI 42-92)	65 (95% CI 44-83)
NPV(%)	55 (95% CI 40-70)	58 (95% CI 39-75)	63 (95% CI 45-79)	58 (95% CI 41-73)	64 (95% CI 44-81)

TABLE 3 Performance of all different imaging modalities (p values).

	Sensitivity	Specificity	PPV	NPV
US vs PET	0.69	0.49	1	0.97
US vs MRI	0.16	0.70	0.67	0.75
US vs PET/MRI	0.93	0.94	0.62	1
PET vs MRI	0.52	1	0.84	0.65
PET vs PET/MRI	1	0.41	0.79	1
MRI vs PET/MRI	0.35	0.58	1	0.79

Results

A total of 143 patients were included in this analysis: 89 from Heidelberg and 54 from San Raffaele. Demographic and clinical characteristics of both cohorts are summarized in Table 1. The mean age was 49.2 ± 13.2 years in the Heidelberg cohort and 50.7 ± 16.6 years in the San Raffaele cohort, with no statistically significant difference between the groups (p = 0.576).

At the time of diagnosis, the majority of patients in both cohorts were with early-stage tumors. Following PST, 43 patients (48.3%) in the Heidelberg cohort were downstaged to ycT0 compared to 17 patients (32.1%) in the San Raffaele cohort (Table 1).

Postoperative histopathological analysis revealed ypT0 in 32 patients (36.0%) and ypTis in 8 patients (9.0%) in the Heidelberg cohort. In the San Raffaele cohort, 17 patients (31.5%) achieved ypT0, and 10 patients (18.5%) had ypTis. This difference in the breast pCR was not statistically significant (p = 0.6).

Overall, the clinical and demographic characteristics of the two cohorts were broadly comparable exception for the nodal status at diagnosis (Table 1).

The breast cCR was achieved in 44 patients (49.4%) in the Heidelberg cohort and in 17 patients (31.5%) in the San Raffaele cohort (p = 0.038).

Diagnostic performance

Breast tumor response to PST was evaluated under different diagnostic scenarios, as detailed in Table 2. Additionally, the concordant PET/MRI scenario – where both [^{18}F]FDG PET and MRI results were positive– was also assessed.

No statistically significant difference was observed when comparing all imaging modalities (Table 3):

Subgroup analysis

All recruited patients were stratified into three molecular subtypes: TN, HER2+ tumors, and Luminal B tumors. The detailed diagnostic performance results for each subgroup are presented in Tables 4–6.

Furthermore, Figure 5 presents a visual comparison of sensitivity, specificity, PPV, and NPV across the molecular subgroups.

Discussion

In this multicenter comparative study, we assessed the diagnostic accuracy of US and [^{18}F]FDG PET/MRI in predicting breast pCR following PST. Despite the limitations associated with the inclusion of retrospectively and prospectively recruited cohorts from two different institutions, differences in nodal status at diagnosis, and a relatively small sample size with limited statistical power, our findings indicate that both imaging modalities yield comparable overall performance in detecting residual disease in the breast.

In the Heidelberg cohort, 49.4% of patients showed breast cCR on US, while the San Raffaele cohort reported a lower breast cCR rate of 31.5% on [^{18}F]FDG PET/MRI. This discrepancy may be attributed to the high sensitivity yet relatively low specificity of [^{18}F]FDG PET/MRI, leading to a higher false positive rate (31).

Overall, imaging performance did not change significantly across different imaging modalities and in particular, no significant difference was observed between [^{18}F]FDG PET/MRI and US in breast response assessment. In detail, [^{18}F]FDG PET/MRI demonstrated a sensitivity of 62% (95% CI 42%-81%), aligning with prior evidence showing high sensitivity but moderate specificity of MRI alone after PST (31, 32). Prior research reported MRI specificity ranging from 60% to 89%, while one study cited a specificity of only 53% for MRI alone, increasing to 97% when combined with [^{18}F]FDG PET (15, 33). Recent studies on hybrid PET/MRI systems have highlighted the added value of metabolic information provided by PET in enhancing overall staging and response assessment (34). However, de Mooij et al. already demonstrated that the combined use of [^{18}F]FDG PET and MRI does not improve the diagnostic accuracy of qualitative assessment of primary tumor response following neoadjuvant chemotherapy. Moreover, they reported comparable diagnostic performances for [^{18}F]FDG PET and MRI

TABLE 4 Diagnostic performances of different imaging methods in assessing breast response in triple negative breast cancer patients.

	US	PET	MRI	PET/MRI concordant	PET/MRI
Sensitivity (%)	73 (95% CI 45-92)	60 (95% CI 15-95)	40 (95% CI 5-85)	40 (95% CI 5- 85)	60 (95% CI 15-95)
Specificity (%)	65 (95% CI 38-86)	70 (95% CI 35-93)	80 (95% CI 44-97)	80 (95% CI 44-97)	70 (95% CI 35-93)
PPV (%)	65 (95% CI 38-86)	50 (95% CI 12-88)	50 (95% CI 7-93)	50 (95% CI 7-93)	50 (95% CI 12-88)
NPV (%)	73 (95% CI 45-92)	78 (95% CI 40-97)	73 (95% CI 39-94)	73 (95% CI 39-94)	78 (95% CI 40-97)

TABLE 5 Diagnostic performances of different imaging methods in assessing breast response in luminal B breast cancer patients.

	US	PET	MRI	PET/MRI concordant	PET/MRI
Sensitivity (%)	57 (95% CI 34-77)	46 (95% CI 19-75)	77 (95% CI 46-95)	46 (95% CI 19-75)	77 (95% CI 46-95)
Specificity (%)	58 (95% CI 28-85)	0 (95% CI 0-84)	0 (95% CI 0-84)	0 (95% CI 0-84)	0 (95% CI 0-84)
PPV (%)	72 (95% CI 47-90)	75 (95% CI 35-97)	83 (95% CI 52-98)	75 (95% CI 35-97)	83 (95% CI 52-98)
NPV (%)	41 (95% CI 18-67)	0 (95% CI 0- 41)	0 (95% CI 0-71)	0 (95% CI 0-41)	0 (95% CI 0-71)

TABLE 6 Diagnostic performances of different imaging methods in assessing breast response in HER2+ -positive breast cancer patients.

	US	PET	MRI	PET/MRI concordant	PET/MRI
Sensitivity (%)	50(95% CI 16-84)	33 (95% CI 4-78)	17 (95% CI 0-64)	17 (95% CI 0-64)	33 (95% CI 4-78)
Specificity (%)	64(95% CI 31-89)	80 (95% CI 52-96)	93 (95% CI 68-99)	100 (95% CI 79-100)	73 (95% CI 45-92)
PPV (%)	50(95% CI 16 -84)	40 (95 CI 5-85)	50 (95% CI 1-99)	100 (95% CI 3-100)	33 (95% CI 4-78)
NPV (%)	64 (95% CI 66-90)	75 (95% CI 48-93)	74 (95% CI 49-91)	75 (95% CI 51-91)	73 (95% CI 45-92)

when used as standalone modalities (17). Our results are consistent with this evidence, as we did not observe any significant advantage over routine US in the evaluation of breast tumor response. Likewise, no significant difference in diagnostic performance between US and [18F]FDG PET/MRI was observed, even when ypTis/DCIS cases were conservatively classified as non-breast pCR, suggesting that outcome definitions did not influence the results (unpublished results). Notably, findings from the overall trial in San Raffaele Hospital (SNB vs PET/MRI 1) corroborate these observations, extending the lack of added value of [^{18}F]FDG PET/MRI to the assessment of axillary response.

From a biological perspective, several factors may explain the absence of superiority of [^{18}F]FDG PET/MRI. First, residual disease after neoadjuvant chemotherapy—particularly in luminal subtypes—is often characterized by low cellular density and reduced metabolic activity, limiting the sensitivity of [^{18}F]FDG uptake (35, 36). Second, MRI may overestimate residual disease due to treatment-related fibrosis, edema, or scattered residual tumor cells, thereby reducing specificity (37). When combined, these modality-specific limitations are not necessarily complementary and may instead compound interpretative uncertainty in qualitative assessments. However, alternative methodological approaches may yield different results. In particular, quantitative assessment and earlier imaging during neoadjuvant chemotherapy have been shown to improve the predictive performance of PET and MRI (17, 37). Therefore, the lack of superiority observed in our study may be partly attributable to the use of a qualitative, end-of-treatment evaluation approach.

Even the NPV, although numerically higher in the PET/MRI group 64% (95% CI 44%-81%), does not reach statistical significance when compared with US. This finding contrasts with recently published data from the same institution, which reported improved performance of [^{18}F]FDG PET/MRI in assessing the axillary

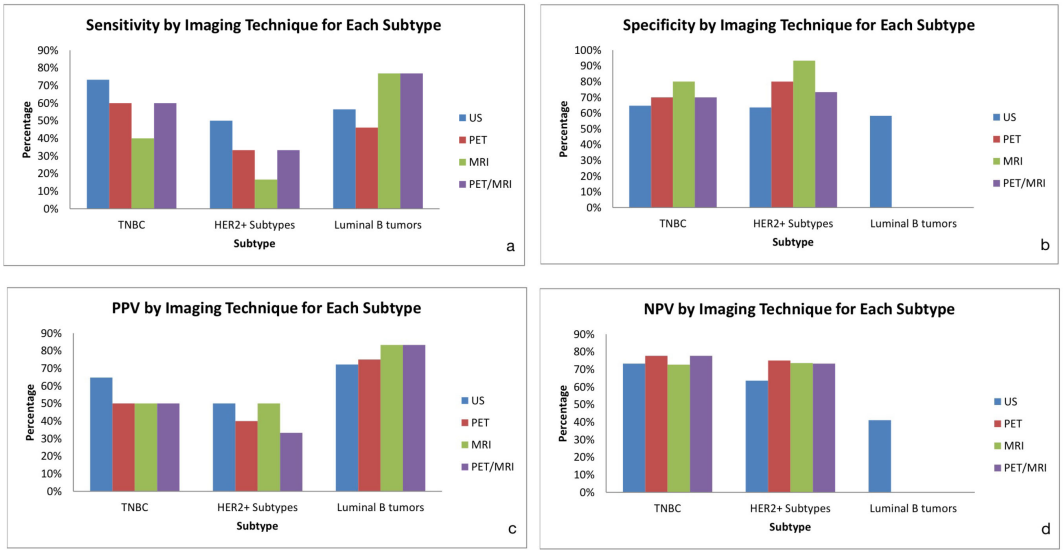

FIGURE 5
Sensitivity **(a)**, specificity **(b)**, positive predictive value [PPV, **(c)**], negative predictive value [NPV, **(d)**] analysis of TN, HER2+, and luminal B subgroups.

response in the upfront surgery setting (25), but aligns with previously reported trials in the neoadjuvant scenario (17).

In our exploratory analysis, imaging performance appeared to vary according to tumor subtype, suggesting that imaging strategies may benefit from a more individualized approach. These differences might be related to underlying biological variations in tumor response to treatment. For instance, in TN and non-luminal HER2+ breast cancers, treatment often results in rapid tumor shrinkage or collapse, leading to minimal histological evidence when pCR is achieved. In contrast, luminal breast cancers tend to regress more diffusely and heterogeneously, leaving scattered residual tumor cells without a significant reduction in tumor volume (38). As a result, the relatively higher sensitivity for US in TN tumors might reflect the typically well-demarcated and hypoechoic features, which may enhance detectability. Conversely, the trend towards better performance of [^{18}F]FDG PET/MRI in Luminal B tumors suggests a potential role for hybrid imaging in capturing the more subtle and heterogeneous response patterns associated with hormone receptor-positive cancers. However, these considerations are constrained by the relatively small sample size, which increases the risk of overinterpreting subgroup trends and therefore warrants cautious interpretation. They are intended to generate hypotheses for future research, aligning with previous studies that have reported subtype-related variability in imaging accuracy (34, 39–41).

Altogether, US demonstrated a good performance in evaluating breast response following PST, corroborated by its established role as a widely accessible and cost-effective tool for assessing residual disease. Yet, its lower sensitivity, especially in non-TN subtypes, highlights its limitations in detecting minimal residual disease or heterogeneous response patterns (41–43). In contrast, [^{18}F]FDG PET/MRI, as an emerging imaging technology, might achieve greater diagnostic accuracy with increased clinical experience and protocol optimization, and also use of rapidly developing novel radiotracers.

Accurately predicting pCR is essential for guiding individualized treatment. Thus, precise imaging is crucial not only for de-escalation strategies but also for timely therapeutic intensification (4). The variability in performance among imaging modalities, particularly [^{18}F]FDG PET/MRI, underscores the need for further research, including also the use of quantitative analysis, different timing of execution of re-staging exams, and artificial intelligence-driven strategies (22, 44).

A major strength of this study lies in its multi-institutional design, combining prospective data from San Raffaele with retrospective data from Heidelberg Hospital. This approach provides broader insights into imaging performance across different clinical environments. Additional strengths include the comparison of a widely used imaging modality (US) with an emerging hybrid technique ([^{18}F]FDG PET/MRI), offering valuable data to inform clinical decision-making. The stratification of results by molecular subtype adds clinical depth by highlighting imaging performance across biologically distinct breast cancer subtypes; however, given the limited statistical strength, these findings should be considered exploratory and hypothesis-generating, to be confirmed in larger prospective cohorts. The use of diagnostic performance metrics allows for a comprehensive evaluation of each modality's diagnostic utility.

Nonetheless, several limitations must be acknowledged. First, both cohorts had limited sample size in the full population as well as in tumor subgroups and differed in patient selection and imaging protocols, which may introduce heterogeneity and limit the statistical power. Second, US assessments are operator-dependent and potentially subject to variability. Third, although [^{18}F]FDG PET/MRI provides rich diagnostic information, the technology remains resource-intensive and not widely available, limiting its current applicability. These factors may influence the generalizability and clinical applicability of the findings. Furthermore, another limitation of this study is the non-head-to-head nature of the comparison. US and PET/MRI were evaluated in separate cohorts, and differences in patient characteristics, baseline nodal burden, imaging protocols, and institutional practices may have influenced the observed diagnostic performance, limiting direct comparability between the two modalities.

To conclude, despite the cutting-edge multiparametric imaging offered by [^{18}F]FDG PET/MRI, US remains a simple, valuable and widely accessible tool in the context of PST. Our findings suggest that tailoring imaging modalities to tumor biology may enhance the accuracy of breast pCR prediction and support more personalized, effective treatment strategies.

Conclusions

This study evaluated the diagnostic performance of US and [^{18}F]FDG PET/MRI following PST in breast cancer patients. US showed performance broadly comparable to the more complex and resource-intensive PET/MRI. While these findings suggest that PET/MRI did not demonstrate a clear incremental diagnostic advantage over US in this setting, they should be interpreted cautiously and cannot be taken as definitive evidence against its clinical utility.

Neither imaging modality demonstrated sufficient diagnostic accuracy to support omission of surgery or replacement of histopathologic assessment. These results highlight the persistent need to integrate imaging findings with clinical and molecular data, rather than relying on imaging alone for therapeutic decision-making.

Future studies should be designed as prospective, ideally head-to-head evaluations within the same patient cohort, ideally incorporating multimodal and standardized imaging protocols, to more robustly define the added value of PET/MRI over conventional US. In addition, integrated imaging approaches, including radiomic analyses and artificial intelligence–based models, may further enhance the prediction of treatment response.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitato Etico Ospedale San Raffaele. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

RD: Methodology, Conceptualization, Writing – review & editing, Data curation, Writing – original draft. SS: Writing – review & editing, Formal analysis, Methodology, Writing – original draft, Data curation. AP: Supervision, Writing – review & editing, Writing – original draft, Formal analysis, Methodology, Data curation, Validation. CC: Investigation, Data curation, Writing – review & editing, Writing – original draft, Methodology. FG: Writing – original draft, Writing – review & editing, Formal analysis, Data curation. LA: Data curation, Writing – review & editing, Writing – original draft. FGe: Writing – review & editing, Writing – original draft, Data curation. PS: Data curation, Writing – review & editing, Writing – original draft. IN: Writing – original draft, Writing – review & editing, Data curation. CL: Writing – original draft, Data curation, Writing – review & editing. EV: Writing – original draft, Writing – review & editing, Data curation. GD: Data curation, Writing – original draft, Writing – review & editing. GF: Writing – review & editing, Writing – original draft, Data curation. NR: Writing – original draft, Writing – review & editing, Validation, Data curation, Methodology. VZ: Writing – review & editing, Data curation, Writing – original draft. SB: Data curation, Writing – review & editing, Writing – original draft. GC: Writing – review & editing, Data curation, Writing – original draft. SC: Data curation, Writing – review & editing, Writing – original draft. FC: Writing – review & editing, Writing – original draft, Data curation. MR: Writing – original draft, Data curation, Writing – review & editing. LL: Writing – review & editing, Writing – original draft, Supervision. GV: Supervision, Writing – original draft, Writing – review & editing. SZ: Supervision, Writing – review & editing, Writing – original draft. IS: Supervision, Writing – original draft, Writing – review & editing. GB: Supervision, Writing – original draft, Writing – review & editing. PP: Writing – review & editing, Writing – original draft, Supervision. AC: Writing – original draft, Supervision, Writing – review & editing. JH: Writing – original draft, Writing – review & editing, Supervision. OG: Supervision, Writing – review & editing, Methodology, Writing – original draft, Funding acquisition, Validation.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declared that generative AI was not used in the creation of this manuscript.

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