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[^{18}F]FDG PET/MRI for axillary staging in node positive breast cancer patients receiving primary systemic therapy. A prospective single arm trial

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ABSTRACT

Background: Management of axillary nodes in breast cancer (BC) remains controversial. Increasingly, node-positive patients receive primary systemic therapy (PST), achieving axillary downstaging in up to 70% of cases. However, current imaging methods, despite being pivotal in the choice for PST, show limited accuracy in assessing treatment response. This study evaluated the diagnostic performance of hybrid [^{18}F]FDG PET/MRI as non-invasive, single-step tool for post-PST nodal assessment.

Methods: This prospective, single-arm, monocentric interventional trial (SNBvsPET/MRI1, ClinicalTrials.gov NCT04826211) was conducted at San Raffaele Scientific Institute, Milan. Patients with node-positive BC eligible for PST were enrolled between September 2019 and December 2024. In addition to routine imaging, including axillary ultrasound (A-US), [^{18}F]FDG PET/MRI was performed before and after PST. Scans were independently reviewed by two radiologists and two nuclear medicine physicians. Final pathology served as the reference standard.

Findings: Of 109 screened patients, 68 were included in the final analysis Mean(SD) age was 52.3(11.0) years. Residual axillary disease was pathologically confirmed in 30(44.2%) patients. [^{18}F]FDG PET/MRI correctly identified 16 cases (sensitivity 53.3%, specificity 68.4%, PPV 57.1%, NPV 65.0%). Diagnostic accuracy varied by BC subtype with higher PPV in luminal (85.7%) and greater NPV in HER2+ and triple-negative tumors (83.3%). Overall, the performance of [^{18}F]FDG PET/MRI and A-US were not significantly different ($p > 0.05$).

Interpretations: [^{18}F]FDG PET/MRI accuracy for axillary staging in node-positive BC patients following PST is limited. Our findings are hypothesis-generating to design future trials and suggest that tailoring imaging to molecular subtype may optimize axillary evaluation and better inform surgical decision-making after PST.

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1. Introduction

The management of axillary lymph nodes in breast cancer remains one of the most debated and rapidly evolving areas in the field. A growing proportion of patients with initially node-positive disease now receive primary systemic therapy (PST) prior to surgery, achieving axillary downstaging in up to 70% of cases [1–3]. Recent advances in response-adapted treatment pathways underscore the importance of reliable non-invasive tools capable of accurately predicting nodal status and thereby reducing the need for extensive axillary surgery. Currently, patients with node-positive breast cancer who convert to node-negative status after PST are candidates for sentinel node biopsy (SLNB) or targeted axillary dissection, thereby avoiding axillary dissection (ALND). Ongoing trials are investigating whether node-negative patients who are exceptional responders could even omit surgical axillary staging altogether [4]. This paradigm shift has created new challenges for clinicians, as reliable assessment of nodal response after PST is crucial to tailor surgical strategies and avoid both under- and overtreatment. Conventional diagnostic approaches, including axillary ultrasound (A-US), have limited accuracy in predicting residual nodal disease and often require invasive confirmation. A-US is currently the most widely used preoperative imaging modality; however, preliminary results from the large, prospective AXSANA trial confirmed its limited accuracy after PST [5].

In this context, there is a pressing need for more reliable, non-invasive imaging approaches. Hybrid [^{18}F]FDG PET/MRI has emerged as a promising imaging modality, combining superior soft tissue characterization with functional metabolic information in a single step. This dual approach allows for a more comprehensive evaluation of both primary tumor and axillary nodes, potentially improving preoperative decision-making and guiding surgical strategies [6,7]. The present trial was designed to investigate whether [^{18}F]FDG PET/MRI could provide a more accurate and non-invasive evaluation of axillary nodal status after PST, and to compare its diagnostic performance with that of standard preoperative A-US.

2. Patients and methods

2.1. Study design

This was a prospective interventional monocentric single-arm trial conducted at the San Raffaele Scientific Institute in Milan. The study received approval from the San Raffaele Ethical Committee on 12th September 2019. Patients were assessed for eligibility and recruited between September 2019 and December 2024. The trial was unintentionally registered late on ClinicalTrials.gov (NCT04826211) on May 25th, 2020, after the enrolment of 15 patients, due to a procedural oversight rather than any intention to conceal study details. No interim analyses were conducted, and no data were reviewed before trial registration. The study protocol was published in 2021, and the trial was monitored by the San Raffaele Clinical Trial Center. Reporting followed the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines for diagnostic accuracy studies [8,9]. Data were analyzed between January and June 2025.

Eligible participants were women aged >18 years with a proven diagnosis of early-stage breast cancer of any size who were candidates for primary systemic therapy and had histologically or cytologically confirmed axillary lymph node involvement at diagnosis. Patients with clear clinical and radiological evidence of overt nodal disease could also be included without fine-needle aspiration or core biopsy confirmation. Axillary lymph nodes were considered overtly metastatic when clinically evident—defined as palpable and firm on physical examination—or when A-US demonstrated one or more of the following suspicious features: cortical thickening >3 mm, focal or diffuse eccentric cortical hypertrophy, loss or displacement of the fatty hilum, round or irregular nodal morphology, non-hilar cortical blood flow on color Doppler imaging, or indistinct margins suggestive of extranodal extension. Lymph nodes meeting these criteria were classified as metastatic [10]. All participants were required to provide written informed consent.

Patients were excluded if they had inflammatory breast cancer, were pregnant, had distant metastatic disease, did not undergo surgery after completion of primary systemic therapy, or had contraindications to PET or MRI, including claustrophobia or allergy to the MRI contrast agent.

Eligible patients were screened by the breast surgical oncologist or the medical oncologist at the first consultation. After routine diagnostic exams, including A-US, enrolled patients also underwent [^{18}F]-FDG PET/MRI done as a staging imaging tool before and after PST. [^{18}F]-FDG PET/MRI protocol in our institution was previously reported [11].

After the initial enrolment, all women with pN + or cN + disease at diagnosis began PST and underwent a mid-treatment reassessment consisting of a clinical examination, unilateral mammography, and breast and A-US. Upon completion of PST, each patient attended a surgical consultation during which the second [^{18}F]-FDG PET/MRI and routine imaging (mammography, breast, and A-US) were scheduled.

2.2. Neoadjuvant chemotherapy regimens

PST typically comprised four cycles of doxorubicin/epirubicin and cyclophosphamide (either every 3 weeks or dose dense anthracyclines), followed by 12 weekly paclitaxel (or 4 cycles of docetaxel every 3 weeks). For HER2-positive tumors, HER2-targeted agents (trastuzumab with or without pertuzumab) were incorporated into the neoadjuvant regimen and usually an anthracyclines spare regimen as TCHP (Taxotere, carboplatin, pertuzumab and trastuzumab) was preferred [12]. Triple negative tumors were treated, according to year of diagnosis with sequential chemotherapy comprising anthracyclines and taxanes (± carboplatin) or chemo-immunotherapy with addition of pembrolizumab to standard chemotherapy [13].

2.3. Surgery

Surgery was subsequently performed according to the response observed on post-PST imaging, consisting of either breast-conserving surgery or mastectomy for the breast, and SLNB or ALND for the axilla according to our institutional standard practice. SLNB was performed using a subdermal injection of a single radiotracer, technetium-99m (^{99m}Tc)-labelled colloid. In case of residual positive axillary lymph nodes on standard preoperative imaging or micro-/macro-metastases of the sentinel node on intraoperative pathologic evaluation, ALND was performed. No targeted axillary dissection was performed, neither marking of initially positive axillary lymph node.

2.4. Pathological analysis

Core needle biopsies of the primary tumour obtained before treatment were used to determine histological subtype and grade. ER and PR status were considered positive when ≥10% of tumour cell nuclei showed immunoreactivity. HER2 positivity was defined as either an IHC score of 3+ or confirmed gene amplification by fluorescence in situ hybridisation (FISH). Tumour grading followed the modified Bloom–Richardson (Nottingham) system. The sentinel node was analyzed according to the protocol described by Viale et al. [14,15]. Pathology report on tumour and sentinel nodes follows WHO Classification of Tumors of the Breast, and TNM Classification, 8th edition, 2017.

Post-treatment breast and axillary surgical specimens were evaluated to assess pathological response. Residual tumour size was recorded macroscopically and verified microscopically. Breast pathological complete response (pCR) was defined as the absence of residual invasive carcinoma (ypT0/is). Axillary pCR was defined as the absence of metastatic tumour cells or the presence of isolated tumour cells only

(≤0.2 mm or <200 cells). Residual axillary disease was defined as the presence of micrometastases (>0.2–2.0 mm) and/or macrometastases (>2.0 mm).

2.5. PET/MRI acquisition and image interpretation

PET/MRI acquisitions were performed using a fully hybrid 3.0 T SIGNA™ PET/MRI (General Electric HealthCare, Waukesha, WI, USA) scanner prior and after PST, including whole-body, dedicated breast and axillary scans. The acquisition protocol is described in our previous paper [11]. All patents feasted for around 6 h prior the exam and were scanned about an hour after intravenous injection of [^{18}F]FDG, after the glucose blood level control.

Images were acquired and reconstructed as described previously and evaluated by two experienced radiologists and two nuclear medicine physicians, all of whom were blinded to clinical data. Evaluations were performed first separately and then, in cases of discordance between the two PET or MRI readers, consensus was made after discussion. Qualitative scores were given to both PET and MRI images and in case of discordance, a major score was given as the final result.

2.6. Criteria for definition of positive nodes on PET after PST

The criteria used for nodal qualitative assessment on PET after PST were as follows:

1 no significant residual FDG uptake in the axilla;
2 weak uptake in the axilla lymph nodes suggestive for benign findings;
3 moderate FDG uptake suspicious for persistence of pathological nodal involvement;
4 intense FDG uptake indicating residual metabolically active disease in axillar lymph nodes.

Specifically, scores 1 and 2 were considered indicative of either no axillary involvement or a response to PST. In contrast, scores 3 and 4 indicated axillary involvement or residual/progressive metastatic disease after PST.

2.7. Criteria for definition of positive nodes on MRI after PST

Axillary lymph nodes were assessed using a combination of morphological and functional MRI features, adapted from Baltzer et al. and subsequent publications [16–18].

1. Morphological features:

Nodes were considered suspicious when one or more of the following characteristics were present:

- Irregular margins: Lymph nodes with lobulated, angular or spiculated borders were regarded as suspicious, as these contour abnormalities are typically associated with infiltrative tumour growth.
- Cortical thickening: Focal or diffuse cortical enlargement >3 mm, particularly when accompanied by distortion of the normal nodal architecture.
- Loss of fatty hilum: Disappearance of the central fatty hilum was considered a major sign of metastatic involvement.
- Perinodal oedema: Hyperintense signal of the surrounding soft tissues on T2-weighted images suggestive of perinodal inflammatory or infiltrative changes.

2. Functional features
   - Contrast enhancement pattern: On DCE-MRI, nodes showing early, intense and heterogeneous enhancement, often followed by washout kinetics, were classified as suspicious for metastatic disease.

Interpretation and scoring: based on the combination of these morphological and functional criteria, axillary lymph nodes were assigned to a four-tier scale: 1 = negative, 2 = doubtful/probably negative, 3 = suspicious/probably positive, 4 = pathological/definitely positive.

For the purposes of analysis, scores 1–2 were considered negative and scores 3–4 positive.

Patients were classified as responders when both [^{18}F]-FDG PET and MRI indicated a response. Conversely, if either modality showed residual or progressive disease, the patient was classified as a non-responder.

A quantitative analysis of [^{18}F]-FDG PET/MRI parameters was also performed; however, no significant findings were observed regarding axillary lymph node evaluation. These results will be reported in a separate publication.

2.8. Post-PST A-US evaluation

All patients generally underwent A-US before the second [^{18}F]-FDG PET/MRI. Given the operator dependency of ultrasound assessment, A-US images were not re-reviewed by experienced radiologists; instead, all reports were classified by a dedicated breast surgeon (R.D.M.) who was blinded to the PET/MRI findings and pathological results. This surgeon has more than ten year experience in the routine interpretation of ultrasound findings in clinical practice to guide surgical decision-making regarding axillary management. Classification was performed using a 1–4 scoring system analogous to that previously described.

According to this scoring system: score 1 indicated a negative lymph node; score 2 corresponded to a doubtful or probably negative lymph node, with minimal alterations still compatible with reactive or inflammatory changes; score 3 indicated a suspicious or probably positive lymph node, characterized by several alterations of normal morphology; and score 4 corresponded to a pathological or definitely positive lymph node with completely altered morphology.

2.9. Endpoints of the trial

- The *primary endpoint* of this study was to evaluate the ability of post-PST hybrid [^{18}F]-FDG PET/MRI to identify macro-metastatic (>2 mm) axillary lymph nodes.
- The *secondary endpoint* was to analyse the staging power of [^{18}F]-FDG PET/MRI compared with preoperative A-US.

Additional explorative analyses were performed to evaluate specific patient subgroups in which the sensitivity of hybrid [^{18}F]-FDG PET/MRI was comparatively higher, with the aim of identifying patients this is imaging approach may offer potential benefit.

2.10. Statistics and power calculations

We included women with positive axillary lymph nodes before PST. We anticipated that 40% would achieve a negative lymph nodal status (i.e., ypN0) after PST. The study population was therefore divided into two groups: women with persistent positive axillary lymph nodes after PST (Group 1, representing 60% of the cohort) and women with negative axillary lymph nodes after PST (Group 2, representing 40%). We aimed to demonstrate that PET/MRI could correctly identify axillary metastasis in over 70% of cases in Group 1 ($P > 0.70$). We assumed a sensitivity of 85% in this group. A total of 110 women were required to ensure adequate power for both analyses: Group 1 ($n = 66$; >90% power; one-sided $\alpha = 0.05$) and Group 2 ($n = 44$; >80% power; one-sided $\alpha = 0.05$). Considering that approximately 25% of patients with node-positive BC are metastatic at diagnosis [19]. We planned to screen 150 patients to enrol 110 eligible participants.

To describe the population characteristics, we reported frequencies, percentages, means, and standard deviations (SD). We calculated sensitivity, specificity, and predictive values, presenting the 95% Wald

confidence interval (CI) when the sample size was ≥30 and the 95% exact CI when the sample size was <30. We used the exact McNemar test to compare sensitivities between imaging tests in patients with axillary metastasis at surgery [20], and the same test to compare specificities in patients without axillary metastasis. We compared positive and negative predictive values (PPV, NPV) between imaging tests using the method proposed by Moskowitz and Pepe [21]. Statistical significance was defined as a two-sided p-value <0.05. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), specifically the pv.rpv function from the DTComPair package.

3. Results

3.1. Patient characteristics

Between September 2019 and December 2024, 109 patients were assessed for eligibility during the study period (Table 1). A total of 87 patients with node-positive breast cancer underwent PST and [^{18}F]-FDG PET/MRI scan before and after therapy. Forty-one patients were excluded after their scans (Fig. 1).

The mean (SD) age of the 68 patients included in the final analysis was 52.3(11.0) years at diagnosis. No patient had a bilateral tumour.

Table 1
Characteristics of the study population.

Characteristic	Category	N (%)
Total		68 (100.0)
Age (years)	<50	30 (44.1)
	50-64	28 (41.2)
	≥65	10 (14.7)
	Mean (SD)	*52.3 (11.0)*
Breast side	Right	31 (45.6)
	Left	37 (54.4)
Histology at biopsy	Ductal	60 (88.2)
	Lobular	3 (4.4)
	Other	5 (7.4)
cT	1	19 (27.9)
	2	40 (58.8)
	3	7 (10.3)
	4	2 (2.9)
cN	1	59 (86.8)
	2	2 (2.9)
	3	7 (10.3)
Molecular subtype at biopsy	Luminal A	4 (5.9)
	Luminal B HER2-	20 (29.4)
	Luminal B HER2+	18 (26.5)
	HER2	9 (13.2)
	Triple negative	17 (25.0)
Neoadjuvant chemotherapy	Anthracyclines	1 (1.5)
	Taxane	12 (17.6)
	Combination	55 (80.9)
Anti-HER2 therapy	No	41 (60.3)
	Yes	27 (39.7)
pT	0	22 (32.4)
	In situ	11 (16.2)
	1a	4 (5.9)
	1b	5 (7.4)
	1c	8 (11.8)
	2	16 (23.5)
	3	2 (2.9)
pN	0	36 (52.9)
	0 (isolated)	1 (1.5)
	1 (micro)	1 (1.5)
	1	20 (29.4)
	2	6 (8.8)
	3	4 (5.9)
Number of LNs with macro metastasis	0	38 (55.9)
	1	9 (13.2)
	2	9 (13.2)
	3	2 (2.9)
	4+	10 (14.7)

The mean (SD) tumor size on imaging was 31.5 (16.7) mm at diagnosis and 10.9 (15.8) mm before surgery.

Baseline A-US assessment revealed definitive evidence of positive axillary lymph nodes in all patients. All patients presented positive axillary lymph nodes on [^{18}F]-FDG PET/MRI before PST.

All patients received taxane-based chemotherapy; 56 patients (82.4%) also received anthracyclines and 16 (23.5%) carboplatin. All 27 patients with HER2-positive breast cancer were treated with trastuzumab; among them, 22 (81.5%) also received pertuzumab, and 1 (3.7%) also received trastuzumab deruxtecan. Among the 17 patients with triple-negative breast cancer, 8 (47.1%) received pembrolizumab and 3 (17.6%) received atezolizumab.

Most patients (55 of 68, 80.9%) underwent preoperative A-US prior to the second [^{18}F]FDG PET/MRI, which was performed in all recruited patients before surgery.

Overall, 82.4%(56/68) of our patients underwent SLNB as first treatment, of these 42.8% (24/56) required ALND and 17.4%(12/68) underwent upfront ALND.

On final pathology, a total of 30 of 68 axillae (44.1%) had at least one macro-metastatic axillary lymph node. Ten out of 68 axillae (14.7%) had more than four macro-metastatic lymph nodes.

Axillary pathologically complete response (pCR) was achieved in in 38 patients (55.9%). Furthermore, 33 (48.5%) women had a pCR in the breast only, and 31 patients (45.6%) obtained pCR in both breast and axilla. As a result, 7 (10.3%) patients achieved an axillary pCR only.

After PST [^{18}F]-FDG PET/MRI had a positive score (3 or 4) in 28 patients (41.2%). 6 out of 28 patients (21.4%) presented more than four macro-metastatic lymph nodes upon histological examination. None of these patients achieved breast pCR.

After PST [^{18}F]-FDG PET/MRI had a negative score (1 or 2) in 40 patients (58.2%). In 14 out of 40 patients (35%) the presence of macro-metastatic axillary nodes was discovered after surgery. Of these, 3 patients (7.5%, 3/40) had residual N2 and one patient (2.5%) N3 disease. Of note, the patient with more than 10 positive lymph nodes presented a primary tumor with mixed lobular histotype. One of these patient with high axillary tumor burden achieved breast pCR.

3.2. Primary outcome

[^{18}F]-FDG PET/MRI was able to identify macro metastatic axillary lymph nodes in 16 cases out of 30 patients being nodal positive at final pathology (53.3%, 90% CI 35.5%-71.2%), demonstrating that the sensitivity of [^{18}F]-FDG PET/MRI after PST was higher than 50%. [^{18}F]-FDG PET/MRI correctly classified as negative 26 out of 38, showing a specificity of 68.4% (90% CI 53.6%-83.2%) women with pathologically confirmed lymph node negativity. However, [^{18}F]-FDG PET/MRI yielded a negative finding in 40 patients, of whom only 26 were true negatives upon pathological examination, showing a negative predictive value (NPV) of 65.0% (90% CI 50.2%-79.8%). Similarly, the imaging modality indicated lymph node positivity in 28 cases, whereas pathological analysis confirmed positivity in only 16 (57.1%) of these, reaching a positive predictive value (PPV) of 57.1% (90% CI 37.2%-75.5%). When compared with [^{18}F]-FDG PET alone, [^{18}F]-FDG PET/MRI demonstrated no significant differences in overall diagnostic performance. In contrast, when MRI was compared with the hybrid modality, MRI showed higher specificity (86.8% vs 68.4%, *p-value* = 0.016) and a superior PPV (67.4% vs 65.0%, *p-value* = 0.444) (Table 2).

3.3. Secondary outcome

When [^{18}F]-FDG PET/MRI was compared with A-US, the sensitivity of A-US in detecting positive lymph nodes after PST was not significantly higher (63.3%, 95% CI 46.1-80.6 vs 53.3%, 95% CI 35.5-71.2; *p-value*: 0.405). Similarly, the specificity in identifying patients who converted to nodal-negative disease did not differ significantly between A-US and [^{18}F]-FDG PET/MRI (60.5%, 95% CI 45.0-76.1 vs 68.4, 95% CI 53.6-

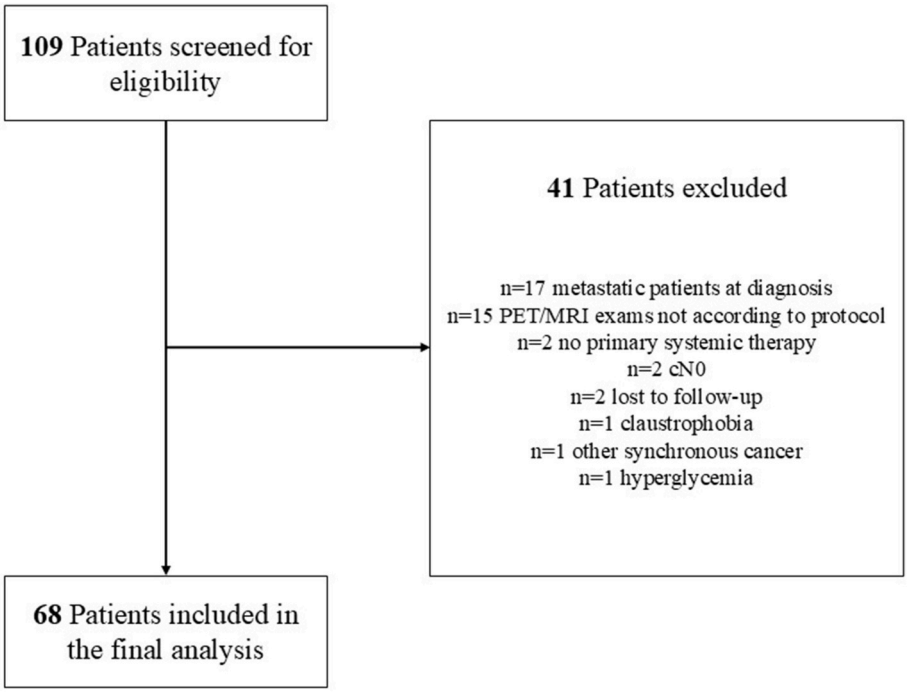

Fig. 1. SNB vs PET/MRI 1 trial flow-chart.

Table 2
Results and diagnostic accuracy of PET/MRI, PET and MRI in the overall population.

Axillary metastasis		PET/MRI		PET		MRI			
	All patients No.	Negative No.	Positive No.	Negative No.	Positive No.	Negative No.	Positive No.		
Yes	30	14	16	17	13	16	14		
No	38	26	12	27	11	33	5		
Accuracy		**PET/MRI** % (95% CI)		**PET** % (95% CI)		**MRI** % (95% CI)		**P-value** PET/MRI vs PET	**P-value** PET/MRI vs MRI
Sensitivity		53.3 (35.5-71.2)		43.3 (25.6-61.1)		46.7 (28.8-64.5)		0.250	0.500
Specificity		68.4 (53.6-83.2)		71.1 (56.6-85.5)		86.8 (76.1-97.6)		1.000	0.016
Positive predictive value		57.1 (37.2-75.5)		54.2 (32.8-74.5)		73.7 (48.8-90.9)		0.438	0.024
Negative predictive value		65.0 (50.2-79.8)		61.4 (47.0-75.8)		67.4 (54.2-80.5)		0.180	0.444

83.2, *p-value*: 0.317) (Table 3). Moreover, stratification by molecular subtype revealed no statistically significant differences in diagnostic performance between the two imaging modalities (*p-value*: >0.05) (Supplementary Table 1).

Table 3
Diagnostic accuracy of PET/MRI and US in the overall population.

Axillary metastasis		PET/MRI		US		
	All patients No.	Negative No.	Positive No.	Negative No.	Positive No.	
Yes	30	14	16	11	19	
No	38	26	12	23	15	
Accuracy		**PET/MRI** % (95% CI)		**US** % (95% CI)		**P-value** PET/MRI vs US
Sensitivity		53.3 (35.5-71.2)		63.3 (46.1-80.6)		0.405
Specificity		68.4 (53.6-83.2)		60.5 (45.0-76.1)		0.317
Positive predictive value		57.1 (37.2-75.5)		55.9 (39.2-72.6)		0.931
Negative predictive value		65.0 (50.2-79.8)		67.7 (51.9-83.4)		0.957

3.4. Exploratory outcomes

When evaluating the performance of [^{18}F]-FDG PET/MRI across molecular subgroups, the PPV was significantly higher in patients with luminal breast cancer (85.7%, 95% CI 57.2-98.2) compared with those with HER2-positive or triple-negative disease (28.6% 95% CI 8.4-58.1, *p-value*: 0.002). Conversely, in these latter subgroups, the NPV was greater (71.4% and 83.3%, respectively) than in patients with ER-positive/HER2-negative tumors (Table 4).

When assessing the performance of [^{18}F]-FDG PET/MRI compared with [^{18}F]-FDG PET or MRI alone across all molecular subtypes, significant differences were observed only in HER2-positive and triple-negative breast cancers, where the hybrid modality demonstrated higher specificity and PPV than MRI alone (88.6% vs 71.4%, *p-value*: 0.031; 50% vs 28.6%, *p-value*: 0.016) (Supplementary Table 2).

4. Discussion

This prospective single-arm interventional trial explored the diagnostic performance of hybrid [^{18}F]-FDG PET/MRI for axillary re-staging in clinically node-positive breast cancer patients treated with PST. In this cohort, [^{18}F]-FDG PET/MRI was able to detect 53.3% of residual

Table 4
Diagnostic accuracy of PET/MRI, according to molecular subtype.

Axillary metastasis		Luminal HER2- (n = 24)		Luminal HER2+, HER2+ and Triple Negative (n = 44)		P-value
	All patients No.	Negative No.	Positive No.	Negative No.	Positive No.	
Yes	30	9	12	5	4	
No	38	1	2	25	10	
Accuracy		% (95% CI)		% (95% CI)		
Sensitivity		57.1 (34.0-78.2)		44.4 (13.7-78.8)		0.694
Specificity		33.3 (0.8-90.6)		71.4 (56.5-86.4)		0.230
Positive predictive value		85.7 (57.2-98.2)		28.6 (8.4-58.1)		0.002
Negative predictive value		10.0 (0.2-44.5)		83.3 (70.0-96.7)		<0.001

macro-metastatic axillary lymph nodes with a specificity of 68.4%. To our knowledge, this study includes the largest population of node-positive breast cancer patients undergoing [^{18}F]-FDG PET/MRI before and after PST with histopathological confirmation from axillary surgery serving as the reference standard. Although the planned accrual was not achieved, thus limiting the statistical power of the analysis, these results confirm the technical feasibility of hybrid imaging in this setting and highlight the persistent challenges of accurately assessing residual nodal disease after PST.

In our cohort, more than half of the patients (55.9%) achieved axillary pCR following PST, consistent with previously reported data in biologically selected populations [1–3]. Despite these encouraging outcomes, accurate preoperative identification of nodal status after PST remains challenging. A recent meta-analysis by Samiei et al. reported that the diagnostic performance of US, MRI and PET/CT for assessing axillary response after PST remains limited, with sensitivities of 65%, 60%, and 38%, respectively [22]. Within this framework, the diagnostic accuracy observed for [^{18}F]FDG PET/MRI in our study appears comparable to that of other imaging modalities, but does not demonstrate clear superiority. These findings are comparable to those reported by de Mooij et al. [23], who evaluated the diagnostic accuracy of sequential [^{18}F]-FDG PET/MRI in predicting primary tumor and axillary lymph node response to PST. Although their overall qualitative assessment was poor—none of the 12 initially node-positive patients with residual disease were correctly identified among 26 axillae—the study demonstrated that integrating the absolute SUVmax of the most FDG-avid lymph node halfway through PST with its relative decrease improved prediction accuracy. This finding is consistent with earlier observations that SUVmax based prediction is more accurate early during PST—after one to three cycles—than at its completion [24–26].

The performance of [^{18}F]-FDG PET/MRI is different according to the setting and the clinical scenario. In fact, in another trial conducted by our group, the SNB vs PET/MRI 2 trial (ClinicalTrials.gov ID NCT04829643), [^{18}F]-FDG PET/MRI detected a high proportion (70.5%) of macro-metastatic axillary lymph nodes that had been missed by A-US in a population of clinically node-negative patients [11].

When [^{18}F]-FDG PET/MRI was directly compared with A-US, diagnostic performance was comparable, with sensitivities of 53.3% and 63.3% and NPVs of 65.0% and 67.7%, respectively, confirming that hybrid imaging currently provides no additional value for axillary re-staging after PST These findings are consistent with recent data from the AXSANA registry, in which A-US demonstrated a sensitivity of 46.4% (95% CI 43.8–49.0%) and an NPV of 64.3% (62.2–66.3%) among 3,428 node-positive breast cancer patients who underwent PST [5]. Consequently, ultrasound remains the most widely available non-invasive modality for axillary staging, although its performance is substantially limited in the post-PST setting. Interestingly, both the AXSANA registry and our results suggest an association between imaging performance and tumor biology.

Although the hybrid modality did not demonstrate incremental value over [^{18}F]-FDG PET or MRI alone in the overall post-PST population, exploratory subgroup analyses suggested differential performance according to molecular subtype. In particular, higher specificity and PPV were observed in HER2-positive and triple-negative disease. These observations are biologically plausible, given differences in metabolic activity across subtypes, but must be interpreted with caution due to small subgroup sizes and limited statistical power. As such, these findings should be regarded as hypothesis-generating rather than confirmatory. This subtype-dependent improvement suggests that in an unselected post-PST population, the added value of hybrid imaging may be limited when relying solely on qualitative interpretation. Future optimisation of PET/MRI for axillary evaluation may require tailored interpretation strategies—incorporating metabolic, morphological, and potentially radiomic quantitative biomarkers—rather than a one-size-fits-all qualitative approach.

Ideally, the combination of [^{18}F]-FDG PET/MRI and A-US may enhance sensitivity, as previously highlighted by Morawitz et al. The authors proposed the use of [^{18}F]-FDG PET/MRI as the preferred modality for ruling out axillary lymph-node metastases, while recommending A-US as the most appropriate tool for confirming suspected nodal involvement [27]. This complementary approach may represent a pragmatic and clinically feasible strategy for axillary re-staging, potentially allowing accurate identification of patients who could safely minimize the extent of axillary surgery without compromising oncological safety. However, such multimodal workflows should be evaluated through ad-hoc designed trials in order to facilitate the transition toward personalised, less invasive surgical management, in line with current de-escalation trends in breast cancer care [4,28,29].

Importantly, despite growing interest in hybrid molecular imaging, the present study underscores that the role of [^{18}F]FDG PET/MRI after PST remains uncertain. Its moderate sensitivity, combined with high cost, limited availability, and lack of demonstrated superiority over established imaging modalities, precludes routine use in this setting at present [24–26]. However, PET/MRI may retain a potential role in selected clinical scenarios where both PET and MRI are already indicated, offering logistical advantages rather than clear diagnostic gains.

Beyond the use of [^{18}F]-FDG, emerging evidence suggests that alternative radiotracers—particularly those targeting tumour proliferation, receptor expression, or immune-microenvironmental features—may further enhance nodal assessment in the post-neoadjuvant setting. Agents such as [^{18}F]-FES, [68Ga]-FAPI, or immuno-PET tracers could help overcome some biological limitations of FDG, particularly in low-glycolytic luminal or lobular tumors [30–32]. Additionally, AI-driven analytical approaches, including radiomics and deep-learning-based feature extraction, may unlock latent information within PET/MRI datasets that is not appreciable through visual assessment alone. Integrating advanced radiotracers with AI-enhanced PET/MRI analysis could therefore markedly improve accuracy in assessing residual nodal disease, representing a promising avenue for future research and clinical translation [33–36].

5. Strengths and limitations

This trial has several strengths, including the largest homogeneous population of node-positive breast cancer patients evaluated with sequential [^{18}F]-FDG PET/MRI both before and after PST, the dual, independent assessment of [^{18}F]-FDG PET and MRI components, and the use of histopatological analysis of axillary lymph nodes as the reference standard. The implementation of a dedicated axillary [^{18}F]FDG PET/MRI protocol further enhanced the methodological robustness of the study. Nevertheless, several limitations must be acknowledged. A major limitation of this study is the lower-than-planned patient accrual relative to the original sample-size calculation. Several factors contributed to reduced enrolment. First, the COVID-19 pandemic substantially limited

hospital access and patient willingness to undergo additional, non-routine research examinations, particularly advanced imaging procedures. Second, a period of technical downtime of the hybrid PET/MRI system interrupted its clinical availability for several months, resulting in additional limitations to recruitment. Finally, evolving treatment paradigms during the study period also affected eligibility. The introduction of genomic testing to guide adjuvant treatment decisions in routine clinical practice led to an increased use of upfront surgery in node-positive patients with luminal breast cancer, as those with low-risk genomic profiles could potentially avoid chemotherapy [37]. In earlier practice, these patients would more frequently have been treated with primary systemic therapy. As a consequence, the study population was enriched for HER2-positive and triple-negative breast cancers, potentially limiting the generalisability of the findings and precluding adequately powered subgroup analyses. The single-centre design, the lower-than-planned enrolment and the exploratory nature of subgroup analyses represent very important limitations, as they reduce the statistical power of the study and limit the generalisability of our findings to broader clinical settings. Furthermore, the high cost and limited availability of [^{18}F]-FDG PET/MRI remain major barriers to the widespread implementation of PET/MRI outside of research settings. Taken together, these factors necessitate cautious interpretation of the results, which should be regarded as hypothesis-generating.

6. Conclusions

In conclusion, this prospective single-arm study demonstrates that [^{18}F]FDG PET/MRI is feasible for axillary assessment after PST but shows limited sensitivity and no clear diagnostic advantage over A-US or PET or MRI alone. While hybrid imaging may provide complementary information in selected patients and biological subgroups, its role after PST should currently be considered exploratory. Larger, methodologically robust studies, ideally incorporating novel radiotracers and AI-enabled analysis, are required to clarify whether PET/MRI can meaningfully contribute to axillary decision-making and to define its optimal clinical indications within sustainable and evidence-based care pathways.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2026.104875.

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