diagnostics

MDPI

Article

Metabolic Response on Preoperative [^{18}F]FDG PET/CT as a Predictor of Pathological Complete Response After Neoadjuvant Dual HER2 Blockade: A Multicentre Real-World Study

Ayberk Bayramgil [1,*], Mehmet Haluk Yücel [2], Ezgi Türkoğlu [3], Ali Kaan Güren [4], Bedirhan Ulufer [5], Burçin Çakan Demirel [6], Anıl Yıldız [7], Nazım Can Demircan [4], Ömer Fatih Ölmez [2], Ahmet Bilici [2], Melike Özçelik [1] and Yunus Emre Altıntaş [1]

1 Department of Medical Oncology, Ümraniye Training and Research Hospital, University of Health Sciences, Istanbul 34764, Türkiye; drmelike.ozcelik@gmail.com (M.Ö.); yunusaltintas1688@gmail.com (Y.E.A.)
2 Department of Medical Oncology, Faculty of Medicine, Medipol University, Istanbul 34214, Türkiye; mhalukyucel@gmail.com (M.H.Y.); olmezof@gmail.com (Ö.F.Ö.); ahmetknower@yahoo.com (A.B.)
3 Department of Medical Oncology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul 34865, Türkiye; ezgiturk_90@hotmail.com
4 Department of Medical Oncology, School of Medicine, Marmara University, Istanbul 34899, Türkiye; alikaanguren@gmail.com (A.K.G.); ncdemircan@gmail.com (N.C.D.)
5 Department of Medical Oncology, Institute of Oncology, Istanbul University, Istanbul 34093, Türkiye; bedirhanulufer@hotmail.com
6 Department of Medical Oncology, Bağcılar Training and Research Hospital, Istanbul 34200, Türkiye; burcin.cakandemirel@gmail.com
7 Department of Medical Oncology, Başakşehir Çam and Sakura City Hospital, Istanbul 34303, Türkiye; anilyildiz@live.com
* Correspondence: ayberkbayramgil@gmail.com

Abstract

Background/Objectives: The accurate prediction of pathological complete response (pCR) before surgery could inform surgical planning in HER2-positive breast cancer. We assessed how accurately the change in the primary tumour maximum standardised uptake value (SUVmax) between baseline and preoperative [^{18}F]FDG PET/CT predicts pCR after neoadjuvant chemotherapy with trastuzumab and pertuzumab. **Methods**: We retrospectively studied 260 patients with stage I–III HER2-positive breast cancer from five centres who had PET/CT within 1 week before neoadjuvant therapy and within 1 week before surgery. The percentage reduction in SUVmax (ΔSUVmax) was analysed as a continuous variable against pCR (ypT0/is ypN0); breast and axillary pCR were secondary endpoints. Incremental value over a prespecified clinicopathological model was assessed with bootstrap optimism correction, and an optimal threshold was explored with the Youden index. **Results**: pCR occurred in 130 patients (50.0%), and 165 (63.5%) had no residual uptake. ΔSUVmax discriminated pCR with an area under the curve (AUC) of 0.68 (95% confidence interval [CI] 0.63–0.74; adjusted odds ratio per 10-percentage-point increase in ΔSUVmax, 1.50, 95% CI 1.26–1.77) and raised the optimism-corrected AUC of the clinicopathological model from 0.68 to 0.75. The Youden-optimal threshold was 100% (no residual uptake); thresholds of 89–93% performed almost identically. No residual uptake had a positive predictive value of 64% (80% in oestrogen receptor [ER]-negative [<1%] vs. 52% in ER-positive [>10%] tumours) and a negative predictive value (NPV) of 74%. None of the 12 patients with ΔSUVmax < 30% achieved pCR (NPV 100%, 95% CI 76–100). ΔSUVmax was also associated with breast pCR (AUC 0.69) and axillary pCR (AUC 0.68). Preoperative SUVmax alone discriminated pCR similarly (AUC 0.69), and the baseline scan did not demonstrate additional predictive value beyond it. **Conclusions**: Preoperative metabolic response adds modestly to clinicopathological factors in predicting pCR after dual HER2 blockade. The absence

Check for updates

Academic Editor: Marko Buta

Received: 4 November 2026
Revised: 20 November 2026
Accepted: 25 November 2026
Published: 27 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

of residual uptake does not reliably indicate pCR, particularly in ER-positive disease, and preoperative PET/CT cannot replace surgical pathology.

Keywords: HER2-positive breast cancer; neoadjuvant therapy; pertuzumab; [^{18}F]FDG PET/CT; pathological complete response; oestrogen receptor

1. Introduction

Human epidermal growth factor receptor 2 (HER2)-positive disease accounts for 15–20% of breast cancers, and neoadjuvant chemotherapy combined with HER2-directed antibodies is the standard approach for stage II–III tumours [1]. Adding pertuzumab to trastuzumab increased pathological complete response (pCR) rates in NeoSphere [2], and in its 5-year analysis, patients who achieved pCR had longer progression-free survival [3]. pCR is associated with long-term outcomes in HER2-positive disease [4], and residual invasive disease after neoadjuvant therapy is now an indication for adjuvant trastuzumab emtansine [5].

Knowing before surgery whether a patient is likely to have achieved pCR could help plan the extent of breast and axillary surgery. In initially node-positive disease, the reliability of less extensive axillary staging after neoadjuvant therapy depends on nodal response [6]. Conventional imaging judges response mainly by size, which correlates imperfectly with residual disease. [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) measures tumour glucose metabolism and has been associated with pathological response in one meta-analysis that pooled breast cancer subtypes and treatment regimens [7].

In HER2-positive disease, most PET studies have examined early interim scans. In TBCRC026, the change in maximum standardised uptake value normalised to lean body mass (SULmax) at cycle 1, day 15, of chemotherapy-free trastuzumab and pertuzumab in tumours with oestrogen receptor (ER) expression ≤ 10% predicted pCR with an AUC of 0.72 [8]. AVATAXHER and PHERGain used early PET response to adapt neoadjuvant treatment [9–11]. Much less is known about the scan obtained at the end of neoadjuvant therapy, shortly before surgery, in patients treated with chemotherapy and a dual HER2 blockade. It is also unclear whether the predictive value of such a scan differs by ER status, which strongly influences pCR rates in HER2-positive disease.

We therefore assessed in a multicentre real-world cohort treated with neoadjuvant chemotherapy plus trastuzumab and pertuzumab how accurately the change in primary tumour SUVmax between baseline and preoperative PET/CT predicts pCR, whether it adds to routinely available clinicopathological factors, and whether its predictive values differ by ER status.

2. Materials and Methods

2.1. Study Design and Patients

This retrospective cohort study included patients with HER2-positive breast cancer who received neoadjuvant chemotherapy with trastuzumab and pertuzumab and underwent surgery between September 2015 and October 2025 at five centres in Istanbul, Türkiye (Ümraniye Training and Research Hospital, Kartal Dr. Lütfi Kırdar City Hospital, Medipol University Hospital, Marmara University Hospital and Bağcılar Training and Research Hospital). Patients were identified retrospectively from institutional records, and all received trastuzumab and pertuzumab. Eligible patients had histologically confirmed invasive carcinoma, stage I–III disease according to the American Joint Committee on Cancer (AJCC)

8th edition [12], [^{18}F]FDG PET/CT both before neoadjuvant therapy and before surgery, and a surgical pathology report. Patients with de novo metastatic or bilateral breast cancer were excluded. Baseline and preoperative [^{18}F]FDG PET/CT were part of routine practice at all participating centres, and all consecutive patients who met these criteria were included; no patient was excluded because a baseline or preoperative scan was missing.

2.2. Pathology

Pre-treatment core biopsies were assessed at each centre. HER2 positivity was defined as immunohistochemistry (IHC) 3+, or IHC 2+ with gene amplification in in situ hybridisation (ISH) [13]. ER status was classified as negative (<1%), low (1–10%) or positive (>10%) according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommendations [14]; progesterone receptor (PR) was considered positive at ≥1%.

pCR was defined as the absence of residual invasive carcinoma in the breast and axillary lymph nodes (ypT0/is ypN0). Breast pCR was defined as ypT0/is, and axillary pCR was ypN0; nodal micrometastases (ypN1mi) were counted as residual disease. Axillary pCR was analysed only in clinically node-positive patients (cN1–3).

2.3. Treatment

Most patients received four cycles of an anthracycline and cyclophosphamide (doxorubicin–cyclophosphamide every 2 or 3 weeks, or epirubicin-based combinations), followed by weekly paclitaxel or thrice-weekly docetaxel given with trastuzumab and pertuzumab. Other patients received six cycles of docetaxel, carboplatin, trastuzumab and pertuzumab (TCHP), or a taxane with trastuzumab and pertuzumab without an anthracycline. Regimens were chosen according to institutional practice.

2.4. PET/CT and Metabolic Response

Baseline PET/CT was performed within 1 week before the start of neoadjuvant therapy and preoperative PET/CT within 1 week before surgery, according to institutional protocols. The maximum standardised uptake value (SUVmax) of the primary tumour was recorded on both scans. SUVmax values were taken from the clinical PET/CT reports of local nuclear medicine physicians, who were unaware of the surgical pathology because all scans preceded surgery. When the preoperative report described no uptake suggestive of a residual tumour at the primary site, preoperative SUVmax was recorded as 0 (no residual uptake). Otherwise, the SUVmax given in the report was recorded, so faint or equivocal uptake was classified according to the interpretation of the reporting nuclear medicine physician. The metabolic response was calculated as ΔSUVmax (%) = (baseline SUVmax − preoperative SUVmax)/baseline SUVmax × 100; positive values indicate a decrease in uptake.

Scans were acquired by each centre's own PET/CT system according to EANM Research Ltd. (EARL) standards [15], with regular calibration and quality control. Acquisition followed each centre's standard clinical protocol based on the EANM procedure guidelines [15], which specify an FDG uptake period of approximately 60 min; individual uptake times were not available for analysis. Each patient's baseline and preoperative scans were acquired on the same system.

2.5. Covariates

The following baseline variables were prespecified as clinicopathological covariates: ER category, HER2 IHC score (3+ vs. 2+/ISH-amplified), histological grade (1–2, 3, or not reported), Ki-67 (continuous), clinical T category (cT1–2 vs. cT3–4), clinical N category (cN0, cN1, cN2–3), regimen (anthracycline-based vs. anthracycline-free) and baseline

SUVmax (log-transformed). Grade was not reported in 54 patients (20.8%) and was kept as a separate category; no other model variable had missing values.

2.6. Statistical Analysis

ΔSUVmax was prespecified as a continuous variable, and no data-derived threshold was used in the primary analyses; threshold optimisation was performed only as an exploratory analysis (described below). Discrimination for pCR was summarised as the area under the receiver operating characteristic curve (AUC) with 95% confidence intervals (CIs) from 2000 bootstrap resamples. Associations were estimated with logistic regression and expressed as odds ratios (OR) per 10-percentage-point increase in ΔSUVmax. Linearity was checked by adding a quadratic term. Because many tumours had no residual uptake, we also tested whether an indicator for no residual uptake added information beyond linear ΔSUVmax.

The multivariable model included all prespecified covariates regardless of univariable significance (130 events, 12 parameters). In univariable models, each categorical variable was entered with all its categories, using the same reference category as in the multivariable model. The incremental value of ΔSUVmax was assessed with a likelihood ratio test and the difference in AUC between the clinicopathological model with and without ΔSUVmax, with a 95% confidence interval from 1000 bootstrap resamples. Apparent AUCs and calibration slopes were corrected for optimism with 1000 bootstrap resamples [16]. To assess what the paired scans added to the preoperative scan alone (an analysis added during peer review), we compared the AUCs of preoperative SUVmax and ΔSUVmax in 2000 paired bootstrap resamples and fitted a model in which preoperative SUVmax (log-transformed after adding 1 because many values were 0) replaced the baseline SUVmax and ΔSUVmax; the added value of the baseline SUVmax and ΔSUVmax over this model was tested with a likelihood ratio test.

To describe clinical performance without optimising a threshold, sensitivity, specificity, a positive predictive value (PPV), and a negative predictive value (NPV) were reported at prespecified ΔSUVmax thresholds of 30% (the magnitude of decrease used by the PET Response Criteria in Solid Tumors (PERCIST) to define partial metabolic response, although PERCIST criteria are based on SULpeak rather than SUVmax [17]), 50%, 70%, 90% and 100% (no residual uptake), with Wilson 95% confidence intervals. Subgroup analyses were performed by ER category, and effect modification was tested with an interaction term between ΔSUVmax and ER > 10% vs. ≤10%, the cut-off used to define the ER-negative population in TBCRC026 [8].

As an exploratory analysis, we identified the ΔSUVmax threshold that maximised the Youden index (sensitivity + specificity − 1), testing every observed value as a threshold (test-positive if ΔSUVmax ≥ threshold). Youden values were compared exactly as integer counts, and when several thresholds shared the maximum, the highest was chosen. Stability was assessed in 10,000 bootstrap resamples; in each, the threshold was re-derived and applied to the patients not drawn in that resample (out-of-bag) to estimate its sensitivity and specificity without optimism.

Secondary endpoints were analysed with the same approach. Sensitivity analyses restricted the cohort to a baseline SUVmax ≥ 2.5 and ≥4.0, truncated ΔSUVmax at 0% to limit the influence of increases in uptake, used ypT0 ypN0 as the pCR definition, and replaced ΔSUVmax with the binary indicator of no residual uptake.

Baseline characteristics were compared with the Mann–Whitney U test, the chi-squared test, Fisher's exact test, or a Monte Carlo exact test for sparse tables. Tests were two-sided at $\alpha = 0.05$. Analyses were performed in Python 3.13 (Python Software Foundation, Beaverton, OR, USA) using NumPy 2.5, pandas 3.0, SciPy 1.18, and scikit-learn 1.9 with fixed random

seeds, and rerunning the code reproduces all results exactly. The analysis code is available from the corresponding author on request. Reporting follows the Standards for Reporting of Diagnostic Accuracy Studies (STARD) 2015 statement [18].

2.7. Ethics

The study was approved by the Ümraniye Training and Research Hospital Scientific Research Ethics Committee (18 June 2026; approval no. B.10.1.TKH.4.34.H.GP.0.01/316). Institutional permissions were obtained from all participating centres, and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived because of the retrospective design.

3. Results

3.1. Patients and Pathological Response

The cohort comprised 260 women with a median age of 50 years (interquartile range [IQR] 42–58) (Table 1). ER was negative in 81 tumours (31.2%), low in 17 (6.5%) and positive in 162 (62.3%). Of the 226 clinically node-positive patients (86.9%), 119 had biopsy-confirmed nodal disease. An anthracycline-based regimen was given to 239 patients (91.9%), TCHP to 16 (6.2%), and a taxane with trastuzumab and pertuzumab alone to 5 (1.9%). The median interval from the end of neoadjuvant therapy to surgery was 42 days (IQR 29–56).

Table 1. Baseline characteristics by pCR status.

Characteristic	All (n = 260)	pCR (n = 130)	No pCR (n = 130)	p
Age, years, median (IQR)	50 (42–58)	50 (43–58)	49 (38–59)	0.225
Menopausal status				
Premenopausal	119 (45.8)	55 (42.3)	64 (49.2)	0.342
Perimenopausal	26 (10.0)	16 (12.3)	10 (7.7)	
Postmenopausal	115 (44.2)	59 (45.4)	56 (43.1)	
Histological type				
Invasive carcinoma NST	241 (92.7)	124 (95.4)	117 (90.0)	0.191
Lobular	8 (3.1)	2 (1.5)	6 (4.6)	
Other	11 (4.2)	4 (3.1)	7 (5.4)	
Histological grade				
1–2	97 (37.3)	41 (31.5)	56 (43.1)	0.155
3	109 (41.9)	60 (46.2)	49 (37.7)	
Not reported	54 (20.8)	29 (22.3)	25 (19.2)	
Ki-67, %, median (IQR)	40 (25–60)	40 (25–69)	40 (25–59)	0.178
Oestrogen receptor (ER)				
Negative (<1%)	81 (31.2)	54 (41.5)	27 (20.8)	<0.001
Low (1–10%)	17 (6.5)	13 (10.0)	4 (3.1)	
Positive (>10%)	162 (62.3)	63 (48.5)	99 (76.1)	
Progesterone receptor				
Negative (<1%)	121 (46.5)	76 (58.5)	45 (34.6)	<0.001
Positive (≥1%)	139 (53.5)	54 (41.5)	85 (65.4)	
HER2 status				
IHC 3+	222 (85.4)	119 (91.5)	103 (79.2)	0.008
IHC 2+/ISH-amplified	38 (14.6)	11 (8.5)	27 (20.8)	
Clinical T category				
cT1	45 (17.3)	23 (17.7)	22 (16.9)	0.640
cT2	176 (67.7)	91 (70.0)	85 (65.4)	
cT3	26 (10.0)	10 (7.7)	16 (12.3)	
cT4	13 (5.0)	6 (4.6)	7 (5.4)	
Clinical N category				
cN0	34 (13.1)	22 (16.9)	12 (9.2)	0.169
cN1	150 (57.7)	76 (58.5)	74 (56.9)	
cN2	43 (16.5)	19 (14.6)	24 (18.5)	
cN3	33 (12.7)	13 (10.0)	20 (15.4)	

Table 1. *Cont.*

Characteristic	All (n = 260)	pCR (n = 130)	No pCR (n = 130)	p
Clinical stage				
I	6 (2.3)	4 (3.1)	2 (1.5)	0.102
II	154 (59.2)	84 (64.6)	70 (53.9)	
III	100 (38.5)	42 (32.3)	58 (44.6)	
Neoadjuvant regimen				
Anthracycline → taxane + HP	239 (91.9)	118 (90.8)	121 (93.1)	0.007
TCHP	16 (6.2)	12 (9.2)	4 (3.1)	
Taxane + HP	5 (1.9)	0 (0.0)	5 (3.8)	
Baseline SUVmax, median (IQR)	9.2 (6.2–12.9)	8.8 (6.0–12.5)	9.8 (6.7–13.5)	0.227
Preoperative SUVmax, median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–0.0)	1.4 (0.0–2.8)	<0.001
ΔSUVmax, %, median (IQR)	100.0 (78.5–100.0)	100.0 (100.0–100.0)	89.1 (59.3–100.0)	<0.001
No residual uptake on preoperative PET				
Yes	165 (63.5)	105 (80.8)	60 (46.2)	<0.001
No	95 (36.5)	25 (19.2)	70 (53.8)	

Values are n (%) unless stated otherwise. Percentages are column percentages. ER, oestrogen receptor; HP, trastuzumab and pertuzumab; IHC, immunohistochemistry; ISH, in situ hybridisation; NST, no special type; SUVmax, maximum standardised uptake value; TCHP, docetaxel, carboplatin, trastuzumab and pertuzumab.

pCR was achieved by 130 patients (50.0%) and breast pCR by 140 (53.8%); 10 patients had ypT0/is with residual nodal disease. Among the clinically node-positive patients, 165 of 226 (73.0%) achieved axillary pCR. pCR was more frequent in ER-negative and HER2 IHC 3+ tumours (Table 1).

3.2. Metabolic Response

The median baseline SUVmax was 9.2 (IQR 6.2–12.9) and did not differ by pCR status. Upon preoperative PET/CT, 165 patients (63.5%) had no residual uptake; in the other 95, the median SUVmax was 2.5 (IQR 1.8–4.0). The median ΔSUVmax was 100% (IQR 78.5–100) overall, 100% in patients with pCR and 89.1% in those without ($p < 0.001$). Uptake increased in six patients (2.3%).

3.3. ΔSUVmax and pCR

ΔSUVmax discriminated pCR with an AUC of 0.68 (95% CI 0.63–0.74) (Figure 1). Preoperative SUVmax performed similarly (AUC 0.69, 95% CI 0.64–0.74), whereas the baseline SUVmax had no discriminative value (AUC 0.46, 95% CI 0.39–0.53). The difference in AUC between preoperative SUVmax and ΔSUVmax was 0.007 (95% CI −0.004 to 0.018). Each 10-point increase in ΔSUVmax was associated with higher odds of pCR (OR 1.46, 95% CI 1.25–1.71). The association was linear (quadratic term $p = 0.70$), and an indicator for no residual uptake did not add significantly to the linear ΔSUVmax ($p = 0.085$).

In the multivariable model, ΔSUVmax remained associated with pCR (adjusted OR per 10% 1.50, 95% CI 1.26–1.77; $p < 0.001$), together with ER > 10% (OR 0.27), HER2 IHC 3+ (OR 2.74), Ki-67 (OR 1.18 per 10%) and clinical nodal involvement (Table 2). Adding ΔSUVmax improved the model fit (likelihood ratio χ^2 35.6, $p < 0.001$) and increased the AUC from 0.73 to 0.79 (difference 0.064, 95% CI 0.029–0.107). After optimism correction, the AUC increased from 0.68 to 0.75, and the calibration slope of the full model was 0.80. A model in which the preoperative SUVmax replaced the baseline SUVmax and ΔSUVmax showed similar predictive performance (apparent AUC 0.80 vs. 0.79, difference 0.005, 95% CI −0.014 to 0.020; optimism-corrected AUC 0.76 vs. 0.75), and adding the baseline SUVmax and ΔSUVmax to it did not improve the fit (likelihood ratio χ^2 0.31, 2 degrees of freedom, $p = 0.85$).

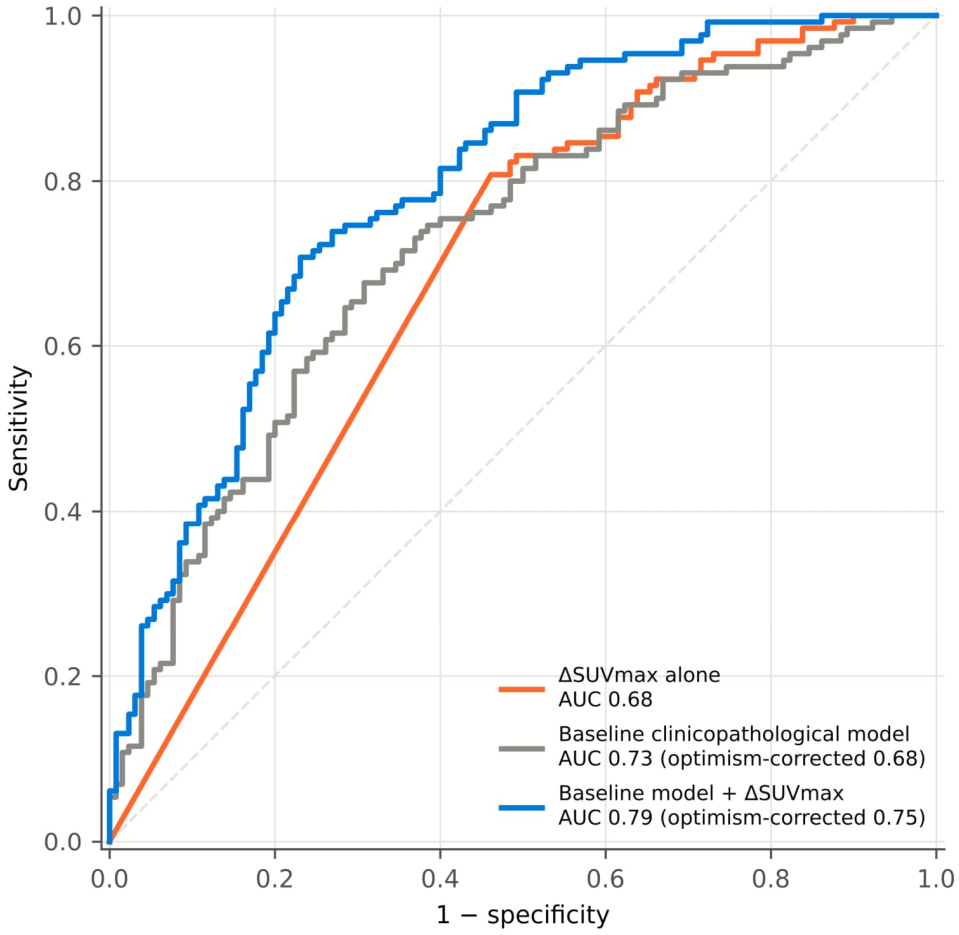


Figure 1. Receiver operating characteristic curves for pCR (ypT0/is ypN0) in 260 patients. ΔSUVmax alone (orange), the prespecified clinicopathological model (grey: ER category, HER2 IHC score, grade, Ki-67, clinical T and N category, regimen and baseline SUVmax) and the same model with ΔSUVmax (blue). Optimism-corrected AUCs are from 1000 bootstrap resamples. The straight segment of the ΔSUVmax curve reflects the 165 patients with no residual uptake (ΔSUVmax 100%). The dashed diagonal line represents the reference line for no discrimination (AUC = 0.50).

Table 2. Logistic regression for pCR.

Variable	Univariable OR (95% CI)	*p*	Multivariable OR (95% CI)	*p*
ΔSUVmax, per 10-percentage-point increase	1.46 (1.25–1.71)	<0.001	1.50 (1.26–1.77)	<0.001
ER-low (1–10%) vs. ER-negative	1.62 (0.48–5.46)	0.432	1.50 (0.38–5.90)	0.565
ER-positive (>10%) vs. ER-negative	0.32 (0.18–0.56)	<0.001	0.27 (0.14–0.52)	<0.001
HER2 IHC 3+ vs. IHC 2+/ISH+	2.84 (1.34–6.00)	0.006	2.74 (1.14–6.61)	0.024
Grade 3 vs. grades 1–2	1.67 (0.96–2.90)	0.068	1.33 (0.65–2.71)	0.431
Grade not reported vs. grades 1–2	1.58 (0.81–3.10)	0.178	1.28 (0.58–2.85)	0.545
Ki-67, per 10%	1.12 (0.99–1.26)	0.063	1.18 (1.02–1.37)	0.030
cT3–4 vs. cT1–2	0.65 (0.33–1.30)	0.226	0.78 (0.34–1.81)	0.565
cN1 vs. cN0	0.56 (0.26–1.21)	0.142	0.34 (0.13–0.91)	0.032
cN2–3 vs. cN0	0.40 (0.17–0.92)	0.031	0.29 (0.10–0.82)	0.020
Anthracycline-free vs. anthracycline-based regimen	1.37 (0.56–3.37)	0.496	0.90 (0.30–2.76)	0.860
Baseline SUVmax, per log unit	0.78 (0.50–1.21)	0.272	0.68 (0.39–1.19)	0.180

The multivariable model included all variables shown (130 events). Model performance: clinicopathological model without ΔSUVmax, apparent AUC 0.727, optimism-corrected AUC 0.682; with ΔSUVmax, apparent AUC 0.791, optimism-corrected AUC 0.753, optimism-corrected calibration slope 0.80. Likelihood ratio test for adding ΔSUVmax: χ^2 35.6, $p < 0.001$. Baseline SUVmax was log-transformed. OR, odds ratio.

3.4. Predictive Values at Prespecified Thresholds

None of the 12 patients (4.6%) with ΔSUVmax < 30% achieved pCR (NPV 100%, 95% CI 76–100) (Table 3); because this subgroup was small, the true NPV could be as low as 76%. As the threshold rose, specificity increased at the expense of sensitivity. No residual uptake had a sensitivity of 80.8%, specificity of 53.8%, PPV of 63.6% and NPV of 73.7%. Among the 95 patients with residual uptake, 25 (26.3%) achieved pCR, and within this group, ΔSUVmax discriminated poorly (AUC 0.61, 95% CI 0.49–0.73).

Table 3. Predictive performance of preoperative metabolic response for pCR.

Test Positive If	Test Positive, *n*	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
All patients (*n* = 260; pCR 130)					
ΔSUVmax ≥ 30%	248	100.0 (97.1–100.0)	9.2 (5.4–15.4)	52.4 (46.2–58.6)	100.0 (75.7–100.0)
ΔSUVmax ≥ 50%	234	96.9 (92.4–98.8)	16.9 (11.4–24.3)	53.8 (47.4–60.1)	84.6 (66.5–93.9)
ΔSUVmax ≥ 70%	210	92.3 (86.4–95.8)	30.8 (23.5–39.2)	57.1 (50.4–63.6)	80.0 (67.0–88.8)
ΔSUVmax ≥ 90%	171	82.3 (74.8–87.9)	50.8 (42.3–59.2)	62.6 (55.1–69.5)	74.2 (64.2–82.1)
No residual uptake (ΔSUVmax 100%)	165	80.8 (73.2–86.6)	53.8 (45.3–62.2)	63.6 (56.1–70.6)	73.7 (64.0–81.5)
ER-negative, <1% (*n* = 81; pCR 54)					
No residual uptake	54	79.6 (67.1–88.2)	59.3 (40.7–75.5)	79.6 (67.1–88.2)	59.3 (40.7–75.5)
ER-low, 1–10% (*n* = 17; pCR 13)					
No residual uptake	13	84.6 (57.8–95.7)	50.0 (15.0–85.0)	84.6 (57.8–95.7)	50.0 (15.0–85.0)
ER-positive, >10% (*n* = 162; pCR 63)					
No residual uptake	98	81.0 (69.6–88.8)	52.5 (42.8–62.1)	52.0 (42.3–61.7)	81.2 (70.0–88.9)

The thresholds in this table were prespecified, not derived from the data. Confidence intervals are Wilson intervals; AUC confidence intervals are bootstrap percentile intervals. AUC of continuous ΔSUVmax: ER-negative, 0.70 (95% CI 0.59–0.82); ER-low, 0.67 (0.39–1.00); ER-positive, 0.69 (0.62–0.75). Interaction between ΔSUVmax and ER > 10% vs. ≤10%: $p = 0.41$. Exploratory Youden analysis: the optimal threshold was 100% (Youden index, 0.35), and thresholds of 89–93% gave a Youden index of 0.34; in 10,000 bootstrap resamples, the optimal threshold was 100% in 57%, 85–99% in 40% and below 85% in 3%, with an out-of-bag sensitivity of 81% and specificity of 51%. NPV, negative predictive value; PPV, positive predictive value.

3.5. Exploratory Optimal Threshold

The threshold that maximised the Youden index was 100%, that is, no residual uptake (Youden index 45/130 = 0.35). Thresholds of 89.2%, 90.6% and 92.9% shared the second-highest value (44/130 = 0.34), a difference of one patient, and only nine patients had a ΔSUVmax between 89% and 100%. Across 10,000 bootstrap resamples, the optimal threshold was 100% in 57%, between 85% and 99% in 40%, and below 85% in 3% of the resamples (interquartile range: 89–100%); repeating the bootstrap with 20 other random seeds gave 56–58%, 39–41%, and 3%, respectively. Applied to the patients not drawn in each resample, the re-derived threshold had a sensitivity of 81% (95% interval 72–91%) and a specificity of 51% (36–64%).

3.6. ER Subgroups

The pCR rates were 66.7% in ER-negative, 76.5% in ER-low and 38.9% in ER-positive tumours. Discrimination by ΔSUVmax was similar in ER-negative (AUC 0.70, 95% CI 0.59–0.82) and ER-positive tumours (AUC 0.69, 95% CI 0.62–0.75), with no evidence of interaction ($p = 0.41$). Predictive values, however, differed markedly (Table 3, Figure 2). Among patients without residual uptake, pCR was achieved by 79.6% of those with ER-negative and 52.0% of those with ER-positive tumours. Among patients with residual uptake, pCR was still achieved by 40.7% (11 of 27) of those with ER-negative and 18.8% (12 of 64) of those with ER-positive tumours.

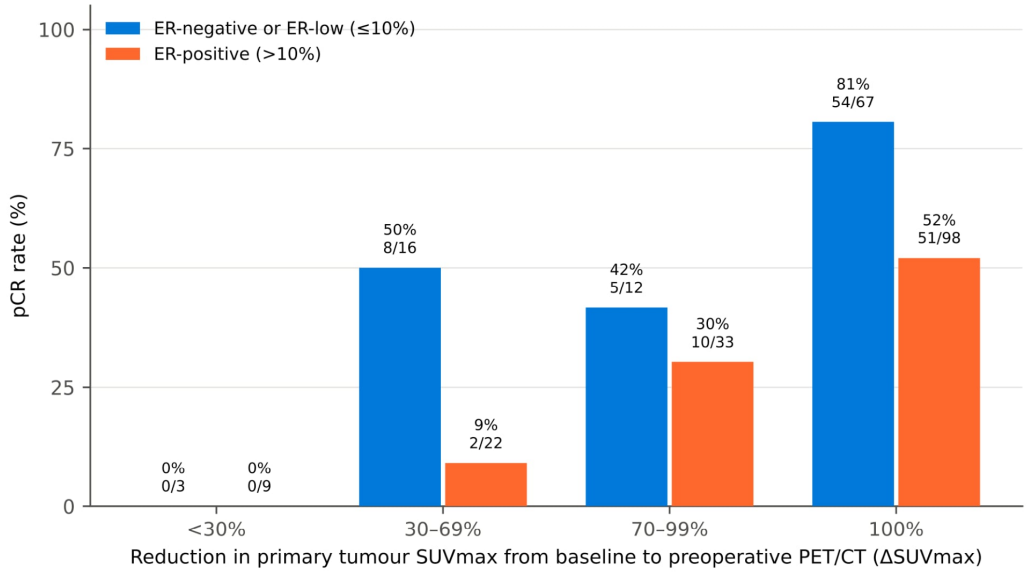


Figure 2. pCR rate by reduction in primary tumour SUVmax between baseline and preoperative PET/CT in tumours with ER ≤ 10% (blue, $n = 98$) and ER > 10% (orange, $n = 162$). Labels give the pCR rate and the number of patients with pCR over the number in each category. A percentage of 100% indicates no residual uptake on preoperative PET/CT.

3.7. Secondary Endpoints and Sensitivity Analyses

ΔSUVmax was associated with breast pCR (AUC 0.69, 95% CI 0.63–0.74; adjusted OR per 10% 1.51, 95% CI 1.28–1.78) and, in clinically node-positive patients, with axillary pCR (AUC 0.68, 95% CI 0.60–0.75; adjusted OR 1.23, 95% CI 1.09–1.38) (Table 4). In node-positive patients without residual uptake in the primary tumour, 83.9% had axillary pCR; among those with residual uptake, 54.2% still had axillary pCR (NPV 45.8%). The results were consistent when patients with a low baseline uptake were excluded, when increases in uptake were truncated, and when pCR was defined as ypT0 ypN0 (adjusted ORs 1.49–1.57; AUCs 0.68–0.69) (Table 4).

Table 4. Predictive performance of ΔSUVmax for secondary endpoints and in sensitivity analyses.

Analysis	*n*	Events	AUC of ΔSUVmax (95% CI)	Adjusted OR per 10-Point Increase (95% CI)
Primary analysis: pCR (ypT0/is ypN0)	260	130	0.68 (0.63–0.74)	1.50 (1.26–1.77)
Breast pCR (ypT0/is)	260	140	0.69 (0.63–0.74)	1.51 (1.28–1.78)
Axillary pCR (ypN0), cN1–3 only	226	165	0.68 (0.60–0.75)	1.23 (1.09–1.38)
Baseline SUVmax ≥ 2.5	256	127	0.69 (0.63–0.75)	1.54 (1.29–1.83)
Baseline SUVmax ≥ 4.0	240	119	0.69 (0.63–0.75)	1.57 (1.30–1.90)
ΔSUVmax truncated at 0%	260	130	0.68 (0.63–0.74)	1.51 (1.28–1.78)
pCR defined as ypT0 ypN0	260	125	0.68 (0.63–0.74)	1.49 (1.26–1.77)
No residual uptake (binary) instead of ΔSUVmax *	260	130	0.67 (0.62–0.73)	4.89 (2.63–9.09)

Adjusted ORs come from models including the covariates in Table 2 (for axillary pCR, cN2–3 vs. cN1 replaced the nodal categories). * OR for no residual uptake vs. residual uptake.

4. Discussion

In this multicentre cohort treated with neoadjuvant chemotherapy and dual HER2 blockade, the reduction in primary tumour SUVmax between baseline and preoperative PET/CT was associated with pCR independently of clinicopathological factors, but its discrimination was moderate (AUC 0.68). It added about 0.07 to the optimism-corrected AUC of a clinicopathological model. Two findings matter most, clinically. A poor metabolic response (ΔSUVmax < 30%) was never followed by pCR, although this rests on only

12 patients, and the lower 95% confidence limit of the NPV was 76%. Conversely, the absence of residual uptake was followed by pCR in only 64% of patients, and in only about half of those with ER-positive tumours.

The relationship between ΔSUVmax and pCR was graded and linear, but most of the information came from the distinction between no residual uptake and any residual uptake. Almost two-thirds of patients had no visible uptake before surgery, and among the remainder, the degree of reduction discriminated poorly. This is expected at the end of treatment: once most tumours have responded, residual disease is often small or low in cellularity and below the resolution of PET. The preoperative scan therefore behaves largely as a binary test, and its high sensitivity for pCR comes at the expense of limited specificity. Consistent with this, the exploratory Youden-optimal threshold was 100%, and thresholds between 89% and 93% performed almost identically. The bootstrap distribution of the optimal threshold is divided between these values, so the data identify a complete or near-complete metabolic response as the useful dividing line rather than a precise cut-off.

Most of this information was contained in the preoperative scan itself. Preoperative SUVmax discriminated pCR as well as ΔSUVmax, and a model in which preoperative SUVmax replaced the baseline SUVmax and ΔSUVmax performed as well as the full model; there was no evidence of added value from the baseline scan. This is consistent with an earlier study in which absolute SUVmax after two cycles predicted pCR better than its change from the baseline in HER2-positive tumours [19]. The baseline scan remains part of staging, but for predicting pCR at the end of treatment, it did not demonstrate additional predictive value.

Our estimate is close to that of TBCRC026, in which the change in SULmax at cycle 1, day 15, predicted pCR with an AUC of 0.72 [8]. That trial used an early scan, standardised acquisition and chemotherapy-free trastuzumab and pertuzumab in tumours with ER ≤ 10%, and so measured something different: the early sensitivity of the tumour to the HER2 blockade alone. AVATAXHER and PHERGain used an early PET response to adapt neoadjuvant treatment [9–11]. Early scans can still change therapy; a preoperative scan cannot. Its potential role is to inform surgical planning and the expectation of pCR during the few weeks before pathology becomes available. For that purpose, the threshold for acting is high, and a PPV of 64% is not sufficient to modify surgery on its own. A meta-analysis reported a pooled sensitivity of 82% and specificity of 79% for PET in predicting pathological response [7], but it combined subtypes and regimens and was not restricted to dual HER2 blockade.

No interim PET/CT was performed in our cohort, so we cannot tell whether an interim scan—for example, after three or four cycles—would have added information. Interim and preoperative scans answer different questions. An interim scan measures early sensitivity to treatment and can be used to adapt therapy, as in AVATAXHER and PHERGain [9–11], whereas a preoperative scan reflects the residual disease that surgery will remove. Whether combining the two improves prediction would need to be tested prospectively; in our data, most of the available information was already contained in the preoperative scan.

Predictive values depended strongly on ER status, even though discrimination did not. Because pCR is less frequent in ER-positive, HER2-positive tumours [20], the same test result carries a different probability of pCR. In our ER-positive patients, half of those with no residual uptake still had residual invasive disease, whereas in ER-negative tumours, about four in five of such patients achieved pCR. Conversely, residual uptake did not rule out pCR in ER-negative tumours, and 41% of which still achieved it. Lower proliferation and slower regression in ER-positive tumours may produce small residual foci with low FDG avidity. Interpreting a preoperative scan without considering ER status could therefore mislead. Tumours with ER 1–10% resembled ER-negative tumours in the pCR rate, in keeping with

evidence that ER-low tumours behave more like ER-negative disease [14,21]; with only 17 patients, we grouped them with ER-negative tumours for the interaction analysis, as in TBCRC026 [8].

These differences mirror those between breast cancer subtypes. FDG PET predicts responses best in highly proliferative tumours with high pCR rates, such as triple-negative and HER2-positive cancers, and less effectively in hormone receptor-positive, HER2-negative tumours, which often have low FDG uptake and rarely achieve pCR [22]. The most informative PET parameter also differs by subtype: in one study, the change in SUVmax after two cycles performed best in triple-negative tumours, whereas absolute SUVmax after two cycles performed best in HER2-positive tumours [19]. Breast MRI shows a similar pattern, with the lowest PPV for pCR in hormone receptor-positive, HER2-negative tumours [23]. Within HER2-positive disease, ER-positive tumours share some features of luminal tumours, which is consistent with the lower PPV that we observed in them.

For the axilla, no residual uptake in the primary tumour was followed by axillary pCR in 84% of clinically node-positive patients, but 16% of these patients still had residual nodal disease. Primary tumour PET response should therefore not be used on its own to select patients for less extensive axillary surgery. More than half of the patients with residual uptake also achieved axillary pCR, and the reliability of sentinel node procedures after neoadjuvant therapy depends on the technique [6]. Primary tumour PET response can complement, but not replace, surgical axillary staging.

Other information might improve prediction. Breast MRI is considered the most accurate imaging method after neoadjuvant therapy [22], but its accuracy for pCR also varies by subtype [23], and combining MRI with PET has been proposed [22]. Volumetric PET parameters such as metabolic tumour volume and total lesion glycolysis, standardised measurements such as SULpeak [17], and circulating tumour DNA are further candidates [22]. Whether better prediction is needed depends on its purpose. For counselling and surgical planning, an approximate probability of pCR may be enough. For omitting surgery, no imaging test, PET included, is accurate enough on its own: a trial of surgery omission used an image-guided vacuum-assisted biopsy of the tumour bed to confirm the absence of residual disease [24]. In that setting, PET/CT could at most help to select patients for biopsy.

The baseline SUVmax did not predict pCR, so the information lies in the preoperative scan rather than in initial tumour avidity. Excluding tumours with low baseline uptake, which produce unstable percentage changes, did not alter the results.

This study has limitations. It is retrospective, although both scans were part of routine practice and consecutive patients were included. Although acquisition followed EARL standards, images were acquired on different systems over ten years and were not centrally reviewed, so measurement variability may have weakened the associations. SUVmax rather than PERCIST SULpeak was used, and no visible uptake was recorded as zero rather than as a background value. The preoperative scan was performed about 5 weeks after the last treatment dose, and earlier or later scans may perform differently. No interim PET/CT was performed. Patient-level centre identifiers were not available for analysis, so clustering by centre could not be accounted for. Most patients received anthracycline-based chemotherapy, whereas anthracycline-free regimens are now widely used [25]. We did not compare PET with breast MRI or ultrasound, and the model has not been validated externally.

Prospective studies with harmonised PET acquisition should test whether preoperative metabolic response, interpreted according to ER status and combined with other imaging and biopsy, can guide surgical de-escalation.

5. Conclusions

After neoadjuvant chemotherapy with trastuzumab and pertuzumab, the reduction in primary tumour SUVmax in preoperative PET/CT is associated with pCR and adds modestly to clinicopathological predictors. Preoperative SUVmax alone carried similar information, and the baseline scan did not demonstrate additional predictive value beyond it. The best-discriminating threshold lay at a complete or near-complete metabolic response. A poor metabolic response may make pCR unlikely, although this was observed in only 12 patients. The absence of residual uptake does not reliably indicate pCR, especially in ER-positive tumours. Preoperative PET/CT should be interpreted in the light of ER status and cannot replace surgical pathology.

Author Contributions: Conceptualization, A.B. (Ayberk Bayramgil), A.Y. and Y.E.A.; data curation, A.B. (Ayberk Bayramgil), M.H.Y., E.T., A.K.G., B.U., B.Ç.D., A.Y., Ö.F.Ö. and A.B. (Ahmet Bilici); formal analysis, A.B. (Ayberk Bayramgil) and Ö.F.Ö.; investigation, Y.E.A. and M.Ö.; project administration, A.B. (Ayberk Bayramgil), A.B. (Ahmet Bilici), Y.E.A. and M.Ö.; validation, M.H.Y., E.T., A.K.G., B.U., B.Ç.D., A.Y. and N.C.D.; visualization, M.H.Y., E.T., A.K.G., B.U., B.Ç.D., A.Y., Y.E.A. and N.C.D.; writing—original draft preparation, A.B. (Ayberk Bayramgil) and M.Ö.; writing—review and editing, Y.E.A., N.C.D., A.B. (Ayberk Bayramgil), A.B. (Ahmet Bilici). All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Scientific Research Ethics Committee of Ümraniye Training and Research Hospital (approval no. B.10.1.TKH.4.34.H.GP.0.01/316; date of approval: 18 June 2026).

Informed Consent Statement: Patient consent was waived due to the retrospective design of the study, which used anonymised data from routine medical records.

Data Availability Statement: The data presented in this study are available on request from the corresponding author because they contain patient information that cannot be shared publicly. The analysis code is available from the corresponding author on request.

Acknowledgments: The authors thank the medical oncology, nuclear medicine, radiology and pathology departments of the participating centres for their contributions to data collection.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Loibl, S.; Gianni, L. HER2-positive breast cancer. *Lancet* **2017**, *389*, 2415–2429. [CrossRef] [PubMed]
2. Gianni, L.; Pienkowski, T.; Im, Y.H.; Roman, L.; Tseng, L.-M.; Liu, M.-C.; Lluch, A.; Staroslawska, E.; De La Haba-Rodriguez, J.; Im, S.-A.; et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* **2012**, *13*, 25–32. [CrossRef] [PubMed]
3. Gianni, L.; Pienkowski, T.; Im, Y.H.; Tseng, L.-M.; Liu, M.-C.; Lluch, A.; Starosławska, E.; De La Haba-Rodríguez, J.R.; Im, S.-A.; Pedrini, J.L.; et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): A multicentre, open-label, phase 2 randomised trial. *Lancet Oncol.* **2016**, *17*, 791–800. [CrossRef] [PubMed]
4. Spring, L.M.; Fell, G.; Arfe, A.; Sharma, C.; Greenup, R.; Reynolds, K.L.; Smith, B.L.; Alexander, B.; Moy, B.; Isakoff, S.J.; et al. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: A comprehensive meta-analysis. *Clin. Cancer Res.* **2020**, *26*, 2838–2848. [CrossRef] [PubMed]
5. von Minckwitz, G.; Huang, C.S.; Mano, M.S.; Loibl, S.; Mamounas, E.P.; Untch, M.; Wolmark, N.; Rastogi, P.; Schneeweiss, A.; Redondo, A.; et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N. Engl. J. Med.* **2019**, *380*, 617–628. [CrossRef] [PubMed]

6. Boughey, J.C.; Suman, V.J.; Mittendorf, E.A.; Ahrendt, G.M.; Wilke, L.G.; Taback, B.; Leitch, A.M.; Kuerer, H.M.; Bowling, M.; Flippo-Morton, T.S.; et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The ACOSOG Z1071 (Alliance) clinical trial. *JAMA* **2013**, *310*, 1455–1461. [CrossRef] [PubMed]
7. Tian, F.; Shen, G.; Deng, Y.; Diao, W.; Jia, Z. The accuracy of ^{18}F-FDG PET/CT in predicting the pathological response to neoadjuvant chemotherapy in patients with breast cancer: A meta-analysis and systematic review. *Eur. Radiol.* **2017**, *27*, 4786–4796. [CrossRef] [PubMed]
8. Connolly, R.M.; Leal, J.P.; Solnes, L.; Huang, C.-Y.; Carpenter, A.; Gaffney, K.; Abramson, V.; Carey, L.A.; Liu, M.C.; Rimawi, M.; et al. Updated results of TBCRC026: Phase II trial correlating standardized uptake value with pathological complete response to pertuzumab and trastuzumab in breast cancer. *J. Clin. Oncol.* **2021**, *39*, 2247–2256. [CrossRef] [PubMed]
9. Coudert, B.; Pierga, J.Y.; Mouret-Reynier, M.A.; Kerrou, K.; Ferrero, J.-M.; Petit, T.; Kerbrat, P.; Dupré, P.-F.; Bachelot, T.; Gabelle, P.; et al. Use of [^{18}F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [^{18}F]-FDG PET-predicted non-responders (AVATAXHER): An open-label, randomised phase 2 trial. *Lancet Oncol.* **2014**, *15*, 1493–1502. [CrossRef] [PubMed]
10. Pérez-García, J.M.; Gebhart, G.; Ruiz Borrego, M.; Stradella, A.; Bermejo, B.; Schmid, P.; Marmé, F.; Escrivá-De-Romani, S.; Calvo, L.; Ribelles, N.; et al. Chemotherapy de-escalation using an ^{18}F-FDG-PET-based pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain): A multicentre, randomised, open-label, non-comparative, phase 2 trial. *Lancet Oncol.* **2021**, *22*, 858–871. [CrossRef] [PubMed]
11. Pérez-García, J.M.; Cortés, J.; Ruiz-Borrego, M.; Colleoni, M.; Stradella, A.; Bermejo, B.; Dalenc, F.; Escrivá-De-Romaní, S.; Martínez, L.C.; Ribelles, N.; et al. 3-year invasive disease-free survival with chemotherapy de-escalation using an ^{18}F-FDG-PET-based, pathological complete response-adapted strategy in HER2-positive early breast cancer (PHERGain): A randomised, open-label, phase 2 trial. *Lancet* **2024**, *403*, 1649–1659. [CrossRef] [PubMed]
12. Amin, M.B.; Edge, S.B.; Greene, F.L.; Compton, C.C.; Gershenwald, J.E.; Brookland, R.K.; Meyer, L.; Gress, D.M.; Byrd, D.R.; Winchester, D.P. (Eds.) *AJCC Cancer Staging Manual*, 8th ed.; Springer: New York, NY, USA, 2017.
13. Wolff, A.C.; Hammond, M.E.H.; Allison, K.H.; Harvey, B.E.; Mangu, P.B.; Bartlett, J.M.S.; Bilous, M.; Ellis, I.O.; Fitzgibbons, P.; Hanna, W.; et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J. Clin. Oncol.* **2018**, *36*, 2105–2122. [CrossRef] [PubMed]
14. Allison, K.H.; Hammond, M.E.H.; Dowsett, M.; McKernin, S.E.; Carey, L.A.; Fitzgibbons, P.L.; Hayes, D.F.; Lakhani, S.R.; Chavez-MacGregor, M.; Perlmutter, J.; et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J. Clin. Oncol.* **2020**, *38*, 1346–1366. [CrossRef] [PubMed]
15. Boellaard, R.; Delgado-Bolton, R.; Oyen, W.J.G.; Giammarile, F.; Tatsch, K.; Eschner, W.; Verzijlbergen, F.J.; Barrington, S.F.; Pike, L.C.; Weber, W.A.; et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: Version 2.0. *Eur. J. Nucl. Med. Mol. Imaging* **2015**, *42*, 328–354. [CrossRef] [PubMed]
16. Steyerberg, E.W. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*, 2nd ed.; Springer: Cham, Switzerland, 2019. [CrossRef]
17. Wahl, R.L.; Jacene, H.; Kasamon, Y.; Lodge, M.A. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J. Nucl. Med.* **2009**, *50*, 122S–150S. [CrossRef] [PubMed]
18. Bossuyt, P.M.; Reitsma, J.B.; Bruns, D.E.; A Gatsonis, C.; Glasziou, P.P.; Irwig, L.; Lijmer, J.G.; Moher, D.; Rennie, D.; de Vet, H.C.W.; et al. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. *BMJ* **2015**, *351*, h5527. [CrossRef] [PubMed]
19. Groheux, D.; Majdoub, M.; Sanna, A.; de Cremoux, P.; Hindié, E.; Giacchetti, S.; Martineau, A.; de Roquancourt, A.; Merlet, P.; Visvikis, D.; et al. Early metabolic response to neoadjuvant treatment: FDG PET/CT criteria according to breast cancer subtype. *Radiology* **2015**, *277*, 358–371. [CrossRef] [PubMed]
20. Schettini, F.; Prat, A. Dissecting the biological heterogeneity of HER2-positive breast cancer. *Breast* **2021**, *59*, 339–350. [CrossRef] [PubMed]
21. Schrodi, S.; Braun, M.; Andrulat, A.; Harbeck, N.; Mahner, S.; Kiechle, M.; Klein, E.; Schnelzer, A.; Schindlbeck, C.; Bauerfeind, I.; et al. Outcome of breast cancer patients with low hormone receptor positivity: Analysis of a 15-year population-based cohort. *Ann. Oncol.* **2021**, *32*, 1410–1424. [CrossRef] [PubMed]
22. Gerosa, R.; Gelardi, F.; Tiberio, P.; Jacobs, F.; Benvenuti, C.; Gaudio, M.; Canzian, J.; Tinterri, B.; Zambelli, A.; Santoro, A.; et al. [^{18}F]FDG PET/CT as a biomarker for response evaluation in neoadjuvant treatment of early breast cancer: Could it become a game-changer in the scenario of the emerging (de)-escalation strategies? *Radiol. Med.* **2026**, *131*, 582–596. [CrossRef] [PubMed]
23. Janssen, L.M.; den Dekker, B.M.; Gilhuijs, K.G.A.; van Diest, P.J.; van der Wall, E.; Elias, S.G. MRI to assess response after neoadjuvant chemotherapy in breast cancer subtypes: A systematic review and meta-analysis. *npj Breast Cancer* **2022**, *8*, 107. [CrossRef] [PubMed]

24. Kuerer, H.M.; Smith, B.D.; Krishnamurthy, S.; Yang, W.T.; Valero, V.; Shen, Y.; Lin, H.; Lucci, A.; Boughey, J.C.; White, R.L.; et al. Eliminating breast surgery for invasive breast cancer in exceptional responders to neoadjuvant systemic therapy: A multicentre, single-arm, phase 2 trial. *Lancet Oncol.* **2022**, *23*, 1517–1524. [CrossRef] [PubMed]
25. van Ramshorst, M.S.; van der Voort, A.; van Werkhoven, E.D.; Mandjes, I.A.; Kemper, I.; Dezentjé, V.O.; Oving, I.M.; Honkoop, A.H.; Tick, L.W.; van de Wouw, A.J.; et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* **2018**, *19*, 1630–1640. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.