ELSEVIER

Seminars in
NUCLEAR
MEDICINE

^{18}F-FDG PET/CT for prediction of response in breast cancer

Mariza Vorster,[a,c] and Mike Sathekge[b,c]

Breast cancer remains one of the most heterogeneous malignancies, with marked variability in biology, therapeutic sensitivity, and clinical outcomes. As treatment strategies evolve toward individualized approaches, early and accurate assessment of response has become critical for optimizing outcomes and minimizing toxicity. Recent Findings: ^{18}F-FDG PET/CT provides a biologically grounded, non-invasive measure of tumour metabolism, heterogeneity, and early treatment adaptation. Baseline metrics such as SUVmax, metabolic tumour volume (MTV), and total lesion glycolysis (TLG)—reflect proliferative drive and aggressiveness, while early changes (ΔSUV, ΔMTV/TLG after 1−2 cycles) predict pathological complete response (pCR) with high negative predictive value. PET-derived nomograms integrating clinical, molecular, and metabolic data outperform clinicopathologic models alone. Radiomic and artificial-intelligence (AI) analyses further refine prediction by quantifying spatial heterogeneity and enabling subtype-specific modelling. Joint EANM/SNMMI guidelines and NCCN recommendations increasingly endorse ^{18}F-FDG PET/CT for staging and response monitoring in high-risk or locally advanced disease. ^{18}F-FDG PET/CT has transitioned from staging to precision-response prediction, particularly in HER2-positive and triple-negative breast cancer. Integration into AI driven nomograms supports adaptive, patient-tailored decisions that minimize toxicity and cost while maximizing benefit. Prospective multicentre validation aligned with EANM/SNMMI/NCCN guidance will consolidate PET's role in adaptive oncology.

Introduction

Breast cancer remains one of the foremost causes of cancer-related morbidity and mortality worldwide, exerting a profound clinical and economic toll on patients and health systems alike.[1] Despite substantial advances in surgical techniques, systemic therapies, and radiation strategies, outcomes remain heterogeneous, reflecting the biological complexity of the disease.[2] In this setting, the decision to initiate or continue cytotoxic chemotherapy carries weighty implications as ineffective therapy exposes patients to avoidable toxicity, erodes their quality of life, delays access to more effective alternatives, and inflates both direct (drug, infusion, hospitalization) and indirect (productivity, caregiving) costs-without conferring clinical benefit. Optimizing early treatment response prediction is therefore not only a scientific pursuit but also a clinical, ethical, and economic imperative.[3–5]

The intrinsic heterogeneity of breast cancer biology underpins much of the observed variability in therapeutic response. Molecular attributes such as estrogen and progesterone receptor expression, HER2 amplification, Ki-67 proliferation index, and intrinsic subtype (Luminal A/B, HER2-enriched, or triple-negative) govern tumor metabolism, growth kinetics, and chemosensitivity. Equally influential are intra-tumoral features such as hypoxia, stromal reactivity, and immune infiltration, which evolve dynamically under treatment pressure. Conventional anatomical imaging provides only a partial, delayed view of these processes, whereas metabolic imaging with positron emission

[a]Department of Nuclear Medicine at Inkosi Albert Luthuli Hospital, University of KwaZulu-Natal, KwaZulu-Natal, South Africa.
[b]Department of Nuclear Medicine, University of Pretoria & Steve Biko Academic Hospital, Private Bag X169, Pretoria 0001, South Africa.
[c]Nuclear Medicine Research Infrastructure (NuMeRI), Steve Biko Academic Hospital, Pretoria 0001, South Africa.
Corresponding author at: Department of Nuclear Medicine at Inkosi Albert Luthuli Hospital, University of KwaZulu-Natal. E-mail: VorsterM1@ukzn.ac.za

https://doi.org/10.1053/j.semnuclmed.2025.11.019

tomography (PET) captures them in real time, offering a more direct window into tumor biology.[6]

^{18}F-FDG PET/CT is uniquely suited for this purpose. By quantifying glucose metabolism, which is a hallmark of aggressive phenotypes driven by GLUT-1 upregulation, hexokinase activity, and HIF-1α signalling, it provides a sensitive functional assessment of tumor viability and therapeutic response. Baseline parameters such as SUVmax, metabolic tumor volume (MTV), and total lesion glycolysis (TLG), as well as early on-treatment changes (ΔSUV, ΔMTV/TLG after one or two cycles of chemotherapy), serve as surrogates for proliferation and hypoxia, correlating strongly with pathological complete response (pCR), progression-free survival, and overall survival across molecular subtypes.[7,8]

Beyond conventional semi-quantitative indices, texture and radiomic features derived from FDG PET reveal spatial heterogeneity, thereby capturing clonal diversity and microenvironmental complexity which may discriminate responders from non-responders more precisely. This is particularly relevant in HER2-positive and triple-negative disease, where early metabolic adaptation often precedes morphological change. Reliance on anatomical tumor shrinkage alone is therefor increasingly inadequate. Metabolic alterations occur earlier and should inform therapy decisions such as escalation, de-escalation, or regimen switching before irreversible resistance develops.[9]

To operationalize these multifactorial insights, predictive nomograms and machine-learning models provide a practical translational bridge. By integrating clinicopathologic variables (e.g., patient age, disease stage, tumor subtype, Ki-67), treatment characteristics, and PET-derived biomarkers (baseline MTV/TLG, early ΔSUV, heterogeneity indices), such models can generate individualized probabilities of pCR or therapeutic failure (Fig. 1). These tools refine patient counselling, minimize futile toxicity, optimize resource allocation, and enable biomarker-driven trial design. Importantly, nomograms incorporating early metabolic treatment response parameters outperform those that are based on clinical variables alone.[10]

Current SNMMI, EANM, and NCCN guidelines increasingly converge in recognizing ^{18}F-FDG PET/CT as integral to staging and treatment response assessment in locally advanced or biologically aggressive breast cancers—particularly from stage IIB up, in HER2-positive, and triple-negative subtypes. The 2024 EANM/SNMMI joint position statement highlights early metabolic assessment as a critical tool for adaptive therapy, while the NCCN supports its selective use in high-risk or equivocal cases where imaging results may alter management.[11,12]

Against this background, the current overview examines the role of ^{18}F-FDG PET in predicting treatment response in breast cancer, emphasizing how PET-augmented nomograms and AI-driven frameworks may advance precision oncology by improving outcomes while reducing the human and economic cost of ineffective chemotherapy.

Pathophysiology of breast cancer: visualizing heterogeneity and metabolic reprogramming with ^{18}F-FDG PET for predicting therapeutic response

Breast cancer represents a biologically diverse disease encompassing wide variation at the molecular, histopathological and metabolic levels. Clinically, it is stratified according to estrogen and progesterone receptor expression (ER/PR), HER2 amplification, and the proliferation index (Ki-67). Luminal A tumors (ER/PR-positive, HER2-negative and low Ki-67) typically exhibit slower growth with a more favourable prognosis. Luminal B cancers retain ER positivity but often lose PR expression, may express HER2, and demonstrate high Ki-67, reflecting greater proliferative drive and higher treatment resistance. HER2-enriched and triple-negative breast cancers (TNBC), (defined by the absence of ER, PR, and HER2) represent the most aggressive phenotypes, characterized by rapid proliferation, limited therapeutic options, and poorer outcomes.[13–15]

This biological diversity translates into complex pathophysiology driven by dysregulated signalling networks. Aberrant steroid hormone pathways, HER2-mediated proliferation, cyclin-dependent kinase activation (e.g., CDK9 in luminal B/HER2+), and upregulation of inflammatory mediators such as COX-2 and prostaglandins also contribute to tumor progression.[15,16] Metabolic reprogramming (most prominently a shift toward aerobic glycolysis) further facilitates uncontrolled proliferation, invasion, and therapeutic resistance. Enhanced glycolysis in breast cancer is sustained through upregulation of glucose transporter-1 (GLUT-1), increased hexokinase II activity, and stabilization of HIF-1α under hypoxia. Activation of PI3K/AKT/mTOR and MYC

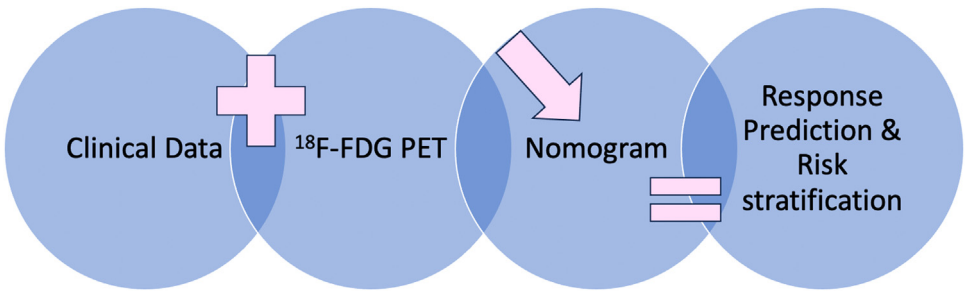

Fig. 1 Process and determinants in response prediction and risk stratification.

signalling consolidates this glycolytic phenotype, leading to increased lactate production and acidic microenvironments that favour invasion and immune evasion.[13–15] Lipid and amino acid metabolic rewiring complements these processes, maintaining energy balance and biosynthetic flux during treatment-induced stress. Collectively, these pathways explain the marked ^{18}F-FDG avidity observed in HER2-positive and triple-negative tumors, in contrast to the lower metabolic activity typically seen in better differentiated (e.g. luminal A) disease.[17]

Baseline PET parameters, such as SUVmax[18] metabolic tumor volume (MTV)[19] and total lesion glycolysis (TLG)[20] correlate strongly with adverse biological and clinicopathologic features. This includes high Ki-67, hormone receptor negativity, nodal involvement, and larger primary tumour size. In early HER2-positive disease, higher SUVmax corresponds to increased HER2 expression, larger tumors, and nodal positivity, while FDG-negative tumours often correspond to smaller, lower-grade lesions with favourable gene-expression profiles (e.g., low PAM50 recurrence risk).[21,22]

Importantly, FDG avidity reflects more than just tumour cell metabolism. It also captures host–tumour interactions, immune activation, and stromal remodelling within the tumor microenvironment (TME).[23] Uptake heterogeneity therefor mirrors spatial variations in hypoxia, angiogenesis, and inflammatory infiltration.

Stromal COX-2/prostaglandin[16] signalling and cytokine-mediated feedback loops amplify metabolic flux, contributing to treatment resistance and recurrence. Radiomic and texture analyses of FDG uptake patterns have thus emerged as non-invasive markers of clonal diversity and microenvironmental reactivity.[23]

At the cellular level, therapy itself drives metabolic adaptation. Exposure to chemotherapy, radiation, or targeted agents induces stress responses that are characterized by increased glycolysis, mitochondrial reactivation, and lipid metabolism shifts. Under these conditions, polyploid giant cancer cells (PGCCs) may emerge. These are large, multinucleated, therapy-resistant entities that enter transient senescence to later produce diploid, stem-like progeny that repopulates the tumor. Their survival is critically dependent on HIF-1α-driven glycolysis, making persistent post-therapy metabolic activity on FDG PET a potential signature of resistant clones rather than residual bulk disease.[24]

Beyond the tumor, systemic inflammation and host metabolism increasingly influence outcome. Elevated FDG uptake in the spleen and visceral adipose tissue (VAT) serves as a surrogate of immune activation and inflammatory tone. Composite models that integrate tumor SUV with splenic SUV, VAT uptake, circulating cytokines, and microbiome signatures outperform single-parameter metrics in predicting recurrence and survival. This underscores the importance of the bidirectional relationship between tumour and host metabolism.[25,26]

Imaging with ^{18}F-FDG PET/CT thus enables comprehensive, whole-body, non-invasive visualization of these intertwined pathophysiologic processes. It captures the molecular aggressiveness, adaptive resistance and systemic context that determine therapeutic outcomes. Among the key semi-quantitative parameters, the SUVmax remains the most widely validated (and used) predictor of treatment response and survival, anchoring metabolic imaging as a cornerstone in precision oncology (Fig. 2).[18,27]

^{18}F-FDG PET/CT for prediction of therapeutic response

^{18}F-FDG PET/CT (through its quantification of glucose metabolism) provides a dynamic, biologically grounded window into tumour aggressiveness and therapeutic sensitivity. Its avidity mirrors glycolytic reprogramming as a hallmark of oncogenic signalling and resistance potential. Thus serving as a powerful surrogate for tumour biology and treatment response across breast cancer subtypes.[28,29]

The SUVmax of the primary tumour correlates with aggressive features such as size, nodal involvement, hormone receptor negativity, high Ki-67 index, histologic grade, and increased HER2 expression to function as an integrated phenotypic risk marker. Beyond a pure binary HER2 classification (positive vs negative), radiomic signatures from FDG PET can non-invasively differentiate HER2-overexpression from HER2-low and HER2-zero phenotypes with externally

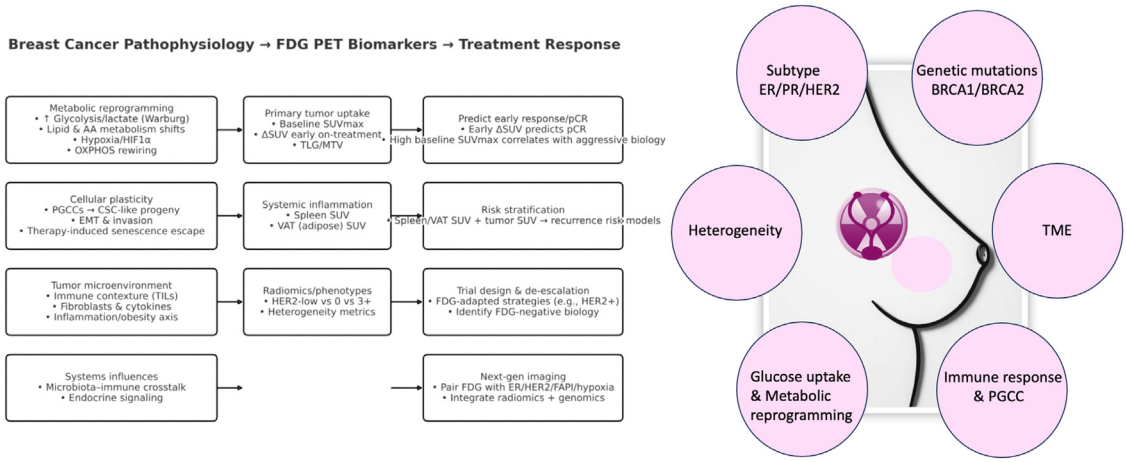

Fig. 2 Aspects of breast cancer pathogenesis that can be imaged with ^{18}F-FDG PET.

validated performance. This supports PET's potential role as a genomic surrogate when biopsy is limited or tumour heterogeneity is pronounced. Additionally, it is both impractical and unethical to biopsy every lesion, highlighting the advantage of whole-body PET imaging for characterization and mapping of disease heterogeneity.[30–33]

A 2022 study by Gong et al. included 51 HER2-positive metastatic breast cancer patients and evaluated the role of FDG PET during chemotherapy by capturing spatial heterogeneity (HI-inter, HI-intra), to predict pyrotinib response. Their results revealed that high heterogeneity during treatment response evaluation could indicate evolving resistance, as baseline high HI predicted significantly shorter PFS (10.6-11.2 vs. 25.3 months). These findings highlight the spatial ^{18}F-FDG uptake as a biomarker for response during targeted chemotherapy, providing a method to assess intra-tumoural variability mid-treatment to guide treatment decisions in heterogeneous tumors.[34] It also suggests the possibility of using FDG PET as a surrogate predictor of treatment response in the absence of FES-PET.

Baseline metabolic burden

Quantitative baseline PET semi-quantitative parameters such as SUVmax, SUV mean, metabolic tumour volume (MTV), and total lesion glycolysis (TLG) provide important prognostic insights prior to treatment initiation. A high baseline SUVmax or increased MTV/TLG independently predict a worse progression-free and overall survival, thus reflecting proliferative drive, tumour hypoxia, and overall disease burden.[35]

In early HER2-positive disease, SUVmax correlates positively with HER2 expression and Ki-67, confirming that metabolic activity parallels oncogenic signalling intensity. Baseline MTV thresholds have also been shown to identify patients unlikely to achieve pathological complete response (pCR) despite standard neoadjuvant chemotherapy (NAC), aiding risk-adapted therapy selection.[30–31]

A study of 286 Primarily pre-therapeutic patients by Najid et al., links baseline Total metabolic tumour volume (TMTV) to response during neoadjuvant chemotherapy (NAC). Their results indicated that a high TMTV (>9.0 cm^3) was associated with no-pathological Complete Response (pCR) (OR=2.4, $p < 0.01$). This implies that interim PET/CT could monitor TMTV changes during NAC to refine predictions, as high baseline TMTV also predicted shorter RFS (HR=4.0, $p < 0.01$). This suggests a role for serial PET imaging to evaluate evolving burden and supports using ^{18}F-FDG PET/CT during neoadjuvant chemotherapy (NAC) to track metabolic changes, potentially identifying non-responders early for intensified or changed therapies.[36]

Early metabolic response assessment represents one of FDG PET's most transformative applications. Reductions in SUVmax or TLG after one or two NAC cycles strongly correlate with pCR and survival, which is well before morphological changes usually occur.[37]

Kitajima et al. conducted a prospective study which included 33 patients with recurrent or metastatic breast cancer who underwent FDG PET/CT imaging both at baseline and after one cycle of systemic therapy. Early responses were evaluated using EORTC criteria. Responders (complete/partial metabolic response) showed a mean SUVmax reduction of 55.8%, while non-responders had minimal change (+0.47%, $p < 0.0001$), consistent across lesion sites like lymph nodes, bone, lung, and liver. Early PET/CT predicted progression-free survival (PFS), with responders having significantly longer PFS ($p = 0.0038$), highlighting its utility for early identification of ineffective therapies during treatment.[38] Their study demonstrated that ^{18}F-FDG PET/CT performed after just one cycle of chemotherapy detects metabolic changes earlier than anatomical imaging, which enables timely therapy modifications in metastatic settings. This approach could potentially reduce toxicity from prolonged ineffective chemotherapy and improve overall survival (OS) by guiding switches to alternative regimens.[38]

A recent retrospective analysis by Akkaya and colleagues of 109 breast cancer patients compared changes in Dynamic Contrast-enhanced (DCE)-MRI and ^{18}F-FDG PET/CT parameters during neoadjuvant therapy (NAC) to predict pathological response. During treatment, changes in PET SUV mean was the strongest predictor (AUC 0.724), outperforming DCE-MRI. Post-NAC SUV mean was also significant ($p = 0.003$, AUC 0.673). Patients with a partial treatment response demonstrated a higher change in wash-out rate on MRI ($p = 0.024$), but PET/CT delta parameters better distinguished complete vs. partial response, suggesting superior monitoring of metabolic shifts during NAC.[39]

These results emphasize the role of ^{18}F-FDG PET/CT in assessing response changes during NAC, with delta metrics providing complementary prognostic information to baseline values. Use of FDG PET could enhance mid-treatment evaluations, allowing for adaptive strategies in non-responders and improving pathological outcomes.[39]

The PHERGain trial is a randomised, open-label, phase 2 trial that took place in 45 hospitals in seven European countries. Patients with HER2-positive, stage I–III A invasive, operable breast cancer with at least one PET-evaluable lesion underwent baseline imaging and follow-up imaging after 2 treatment cycles.[40,41] In a sub-study, named RESPONSE, clinicopathological and molecular predictors of ^{18}F-FDG-PET disease detection were evaluated.[42] Baseline ^{18}F-FDG uptake demonstrated a median SUVmax of 7.2 (range, 1–39.3). Higher SUVmax values correlated significantly with adverse tumor characteristics, including advanced stage, larger primary lesion size, lymph node metastasis, hormone receptor–negative phenotype, overexpression of HER2, elevated Ki-67 proliferation index, and higher histologic grade ($p < 0.05$). Patients with ^{18}F-FDG-negative disease exhibited smaller tumors ($p = 0.014$), absence of nodal involvement, and lower histologic grade compared with FDG-avid PET counterparts ($p < 0.01$). While stromal tumor-infiltrating lymphocyte (sTIL) levels did not differ between 42 matched FDG positive and negative cases ($p = 0.73$), FDG-negative tumors were characterized by a reduced risk of recurrence and a lower prevalence of the PAM50 HER2-enriched subtype ($p < 0.05$). Distinct transcriptional profiles were further noted, with differential expression of genes associated with cancer metabolism

between FDG-negative and FDG-positive groups. The researchers further demonstrated that patients with early HER2-positive breast cancer who achieved a greater than 40% decrease in SUVmax after two therapy cycles could safely omit further chemotherapy while continuing anti-HER2 therapy and achieving equivalent three-year event-free survival. Across subtypes, an early SUVmax decline of 50−88% predict pCR with negative predictive values exceeding 95%.[42,43]

Notably, a minority (an estimated 15%) of HER2-positive tumours in the PHERGain study were FDG-negative at baseline. These tumours demonstrated lower glycolytic and hypoxia gene expression and were predominantly non−HER2-enriched subtypes. This highlights that FDG captures only one dimension of tumour metabolism and that complementary tracers such as ^{18}F-FLT (proliferation), ^{68}Ga-FAPI (stromal activation), or ^{18}F-FES (estrogen receptor imaging) can provide additional mechanistic insights.[41−43]

Even as early as 2013, a meta-analysis by Mghanga and colleagues demonstrated moderately high sensitivity and specificity of FDG PET in early detection of responders from non-responders. Fifteen studies with a total of 745 patients were included and the results were as follows: The pooled sensitivity and specificity of FDG-PET was 80.5% (95% CI, 75.9%−84.5%) and 78.8% (95% CI, 74.1%−83.0%), respectively, and the positive predictive and negative predictive values were 79.8% and 79.5%, respectively. After 1 and 2 courses of chemotherapy, the pooled sensitivity and false-positive rate were 78.2% (95% CI, 73.8%−82.5%) and 11.2%, respectively; and 82.4% (95% CI, 77.4%−86.1%) and 19.3%, respectively. Based on these promising results, the authors suggested the application of FDG PET in the evaluation of breast cancer response to neoadjuvant chemotherapy after either the first or second course (improved accuracy) in patients with breast cancer.[44]

A 2023 review by Oliveira et al. included 13 studies published between 2018 and 2023 that evaluated baseline ^{18}F-FDG PET heterogeneity features for predicting pathological response to neoadjuvant systemic therapy (NAST) in breast cancer. Eight studies (57.1%) linked heterogeneity to pCR, varying by subtype. As expected, heterogeneity was higher in the more aggressive forms (TNBC/HER2+) and was associated with non-pCR. Heterogeneity was lower in luminal and associated with pCR. Baseline FDG PET in neoadjuvant therapy captures intertumoral variability, aiding in response prediction, although inconsistent cutoff values limit reproducibility.[45]

The metabolic response of the axillary lymph node involvement mirrors primary tumour behaviour (See Fig. 3). Post-neo-adjuvant chemotherapy lymph node SUVmax of less than 4.9 predicts axillary pathologically complete response (pCR) with negative predictive values approaching 95%, particularly in HER2-positive and triple-negative subtypes. While histopathology remains essential for confirmation, PET enables rational selection for axillary de-escalation strategies.[46]

A 2021 systematic review and meta-analysis by Samiei et al. of 13 studies (2380 patients) evaluated non-invasive imaging post-neoadjuvant systemic therapy (NST) for axillary response in node-positive breast cancer. For ^{18}F-FDG PET-CT (209 patients), pooled sensitivity, specificity, PPV, and NPV were 38%, 86%, 78%, and 49%, respectively, indicating limited accuracy for detecting axillary pCR (39.5% rate). FDG PET-CT's role in neoadjuvant therapy is modest for post-NST axillary assessment, outperformed by MRI (NPV 58%) but better than ultrasound (NPV 50%), suggesting complementary use. The authors also highlighted FDG PET-CT's challenges in differentiating residual disease from inflammation post-NST, advocating for advanced techniques or AI to enhance its predictive value in neoadjuvant settings.[47]

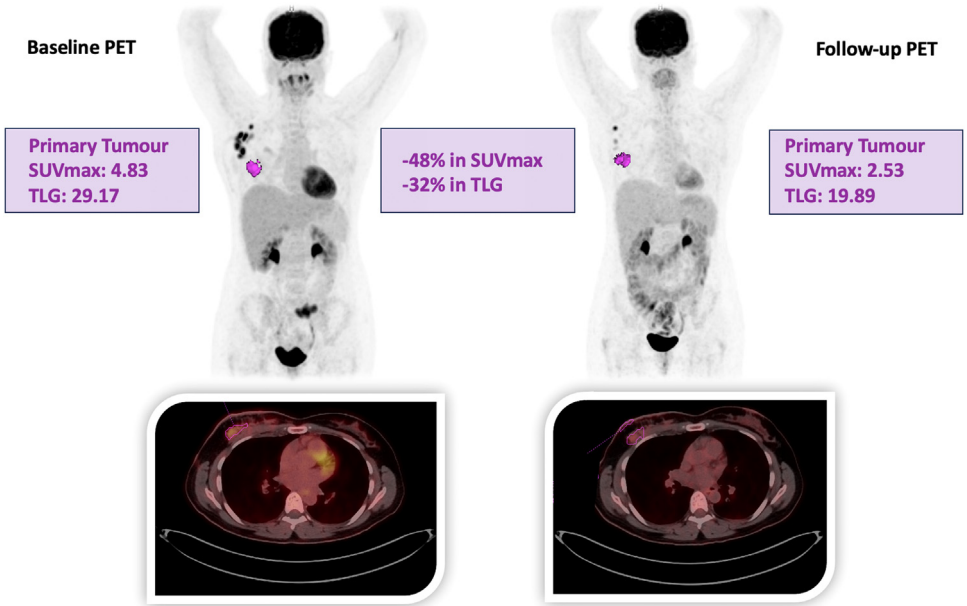

Fig. 3 42-yr-old woman with Grade II ductal carcinoma of the right breast (ER+, PR+, HER2+ and Ki-67 of 20%). The follow-up PET/CT scan demonstrates good response to therapy in line with the significant decrease in SUVmax and TLG noted in the primary breast tumour.

In this prospective RISAS trial sub-study of 185 clinically node-positive breast cancer patients, baseline ^{18}F-FDG PET/CT assessed axillary disease extent (limited vs. advanced) to predict axillary pCR post-neoadjuvant systemic therapy (NST). Overall axillary pCR was 29.7%, with no significant predictive value from axillary extent (OR 0.75, $p = 0.404$), but molecular subtypes showed differences: lowest in HR+/HER2- (7%), highest in HER2-enriched (OR 40, $p < 0.001$). Baseline FDG PET/CT in neoadjuvant therapy predicts axillary response subtype-specifically, guiding de-escalation in aggressive subtypes. The study found significant ORs for axillary pCR in HR+/HER2+ (14.82), HER2-enriched (40), and TNBC (6.91) vs. HR+/HER2-, emphasizing FDG PET/CT's utility in NST planning for tailored axillary management, though not influenced by baseline extent.[48]

Beyond local effects, systemic FDG uptake in spleen and bone marrow provides a non-invasive index of immune activation. Elevated baseline or therapy-induced uptake correlates with inflammatory cytokine profiles, while normalization accompanies favourable response. These systemic parameters enrich prognostic models that integrate tumour and host metabolism.[49–51]

Although primarily designed to evaluate baseline associations, a study of 47 patients by Tokac et al. with advanced breast cancer suggests a potential role for ^{18}F-FDG PET/CT in monitoring treatment dynamics. Whole-body metabolic parameters- in particular WB-MTV and WB-TLG, correlated significantly with circulating tumor DNA (ctDNA) alterations, linking metabolic tumor burden to molecular disease activity ($r = 0.563$, $p < 0.001$). These findings suggest that serial PET/CT acquisitions during chemotherapy could mirror ctDNA kinetics and provide complementary insight into treatment response. Despite its cross-sectional design, the persistence of correlations after excluding ctDNA-negative cases ($r = 0.500$ for WB-MTV) reinforces this potential utility. Integrating ^{18}F-FDG PET/CT with ctDNA analysis may therefore enable real-time assessment of tumor burden evolution, improving early identification of resistance or progression and informing adaptive therapeutic strategies in advanced disease.[52]

A retrospective study by Özdemir et al., that included 92 patients with germline BRCA1 or BRCA2 mutation profiles who underwent FDG PET imaging, demonstrated that patients with BRCA-positive BC had significantly higher SUVmax ($p = 0.039$), larger tumor size ($p = 0.025$), and presence of axillary nodal metastases ($p = 0.023$) than patients with BRCA-negative BC. Although the Ki-67 index was higher in the BRCA-positive group than BRCA-negative group, this difference was not statistically significant. In both the BRCA-positive and negative groups, SUVmax, Ki-67 index, and tumor size, grade, and stage were all significantly correlated with each other. The results of their study showed a strong association between BRCA mutations and SUVmax, indicative of a worse prognosis.[53]

A 2023 systematic review by Caracciolo et al. consists of 14 studies (842 patients) and compared MRI and ^{18}F-FDG PET/CT for pathological complete response (pCR) assessment post-neoadjuvant chemotherapy (NAC) in breast cancer. PET/CT showed superior sensitivity (>80% in TNBC/HER2+), while MRI had higher specificity and their combined use enhanced overall performance. FDG PET/CT in neoadjuvant therapy excels in early functional response detection, though end-NAC underestimates due to inflammation. This review advocates for prospective trials with PET/MRI and radiomics for improved accuracy, positioning FDG PET/CT as complementary to MRI for personalized NAC evaluation.[54]

The 2022 seminars article on the topic of FDG PET's role in response evaluation in metastatic breast cancer described the higher accuracy of PET compared to CT/bone scintigraphy in detecting progression or regression. Using PERCIST criteria, PET/CT during treatment identified changes earlier, leading to better survival through therapy switches (based on retrospective evidence). The authors recommended the use of quantitative methods like SUVmax and MTV for serial monitoring and advocated for FDG PET/CT as a standard for response assessment during MBC chemotherapy and highlighted the need for prospective studies.[55]

^{18}F-FDG PET/CT is poised to transcend its staging role to function as an integrative biomarker of treatment biology, thereby quantifying proliferative glycolysis, clonal heterogeneity, and immune-metabolic context. Baseline semi-quantitative parameters (in particular MTV and TLG) stratify risk and often outperform dynamic contrast-enhanced MRI. This highlights PET's ability to capture metabolic adaptation beyond pure perfusion changes. Early changes in SUV max guide adaptive decisions; and post-therapy imaging refines surgical and adjuvant strategies. At completion of neo-adjuvant chemotherapy, post-treatment SUV max, SUL peak, and tumour-to-liver ratio (TLR) distinguish minimal residual disease from partial or non-response.

Metabolic predictors vary with tumour biology. In hormone receptor−positive/HER2-negative cancers, textural heterogeneity indices outperform absolute SUVs, reflecting subtler metabolic activity. In HER2-positive disease, changes in SUVmax remain the most robust marker of anti-HER2 efficacy, whereas in TNBC, baseline SUVmax and MTV best predict outcomes (See Table 1 for the predictive utility of commonly used PET metrics and their clinical implications in breast cancer).

When fused with radiomics, molecular subtype, and host biomarkers (splenic uptake, VAT metabolism, cytokines, microbiome), PET-based parameters provide a multidimensional framework for predicting therapeutic response. Ultimately, ^{18}F-FDG PET/CT embodies the shift toward adaptive oncology; minimizing futile toxicity, guiding escalation or de-escalation, and anchoring precision medicine in biologically meaningful endpoints.

Nomograms and predictive models: integrating PET-derived biomarkers into precision oncology

Nomograms translate complex, multidimensional data into individualized predictions through simple graphical or algorithmic tools.[56] In breast cancer, conventional models

Table 1 Predictive utility of commonly used PET metrics and their clinical implications in breast cancer.

PET Metric	Predictive Utility	Clinical Implication
SUVmax/TLG	Baseline indicator of metabolic aggressiveness and tumour burden	High SUVmax (>7) associates with HR-negative and HER2-positive disease, high Ki-67, and poor prognosis
ΔSUV (1−2 cycles)	Early metabolic response marker	Reduction > 40 % after initial cycles predicts pCR (NPV > 95 %); supports early de-escalation or regimen change
MTV (Metabolic Tumour Volume)	Quantifies total metabolically active tumour load	Independent prognostic factor for PFS/OS; baseline and residual MTV correlate with recurrence risk
Radiomic heterogeneity indices	Capture spatial complexity and clonal adaptation	Identify resistance niches (e.g., PGCC-rich or hypoxic regions); augment AI-based predictive models
Splenic and VAT SUV	Reflect systemic immune activation and inflammatory tone	Integration with tumour SUV enhances recurrence-risk stratification and overall survival prediction
Tumour-to-Liver Ratio (TLR)	Normalised measure of metabolic intensity	Reduces inter-scanner variability; incorporated into radiomic nomograms predicting pCR
Composite AI/Radiomic Models	Combine metabolic, geometric, and textural features	Improve prediction accuracy (AUC 0.80−0.94) for pCR, axillary pCR, and survival endpoints
ΔMTV / ΔTLG (Post-NAC)	End-of-therapy residual-burden markers	Distinguish RCB 0/I from RCB II/III; inform surgical extent and adjuvant strategy

traditionally incorporate tumor size, nodal status, receptor profile, and proliferation indices to estimate recurrence risk, survival, or pathologic complete response (pCR).[57] While such clinicopathologic models remain valuable, they often overlook the biological heterogeneity and dynamic treatment adaptation that characterize modern oncologic care.

^{18}F-FDG PET/CT introduces a biologically grounded dimension to predictive modelling by quantifying tumor metabolism and systemic host response. PET-derived parameters, such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) capture glycolysis, total disease burden and intra-tumoural heterogeneity. Incorporating these metrics into multivariate nomograms significantly improves predictive accuracy for pCR, recurrence, and survival compared with clinicopathologic features alone.[58–60]

A multicentre study led by Chen included 193 breast cancer patients at the end of neoadjuvant chemotherapy that were divided into pathological complete remission vs non-complete. Nomograms that combined pre- and post-neoadjuvant chemotherapy (NAC) PET parameters with molecular subtype, Ki-67, and nodal burden achieved area-under-the-curve (AUC) values exceeding 0.90 for pathologically Complete Response (pCR) prediction, with excellent calibration and decision-curve utility. Patients who demonstrated early declines in SUVmax, MTV, or TLG demonstrated markedly higher pCR rates, underscoring the clinical value of early metabolic response assessment. Similarly, radiomics-based tumor-to-liver ratio (TLR) models harmonized across scanners achieved AUCs of 0.70–0.77, emphasizing the importance of pre-processing for reproducibility across platforms.[61]

PET-based nomograms also extend beyond primary tumor evaluation. Models incorporating metabolic and radiomic features of axillary lymph nodes predict nodal pCR with AUCs around 0.80, improving further when combined with clinical variables such as HER2 status and stage. These tools can safely guide omission of axillary lymph-node dissection (ALND) in up to 70% of patients, reducing morbidity and preserving oncologic safety. Such precision-guided de-escalation aligns with the broader trend toward tailored, toxicity-conscious cancer care.[62]

PET-augmented nomograms also demonstrate prognostic utility for long-term outcomes. A model integrating tumor subtype, TNM stage, and peripheral immune-inflammatory markers (lymphocytes, eosinophils, red-cell distribution width, platelet–large-cell ratio) achieved a concordance index of 0.83, accurately predicting 3-, 5-, and 7-year survival. Another model combining splenic SUVmax—a surrogate of immune activation—with total MTV achieved a C-index of 0.91 for 5-year recurrence-free survival, outperforming TNM staging. These findings highlight the contribution of systemic immune-metabolic markers to risk stratification and follow-up planning.[63]

Modern nomograms increasingly incorporate artificial intelligence and machine learning to accommodate non-linear relationships and high-dimensional data. Algorithms such as support vector machines, gradient boosting, and generalized additive models improve discrimination and calibration across multicentre datasets while maintaining interpretability. Radiomic PET features further expand predictive potential by quantifying spatial heterogeneity in glucose metabolism, reflecting clonal diversity and microenvironmental complexity. When combined with clinical and molecular data, these hybrid models achieve robust external validation and superior prognostic performance compared with logistic regression-based approaches.

Radiomics and artificial intelligence for treatment response prediction with ^{18}F-FDG PET/CT

Conventional semi-quantitative PET metrics (SUV, MTV, TLG) summarize uptake but fails to reflect the important aspect of spatial heterogeneity. Radiomics restores that nuance by converting routine PET/CT into high-dimensional descriptors of intensity, texture, shape, and wavelet patterns, thereby capturing tumour complexity, hypoxia surrogates, and microenvironmental variations that often underlie resistance.

Across prospective and retrospective cohorts, pre-treatment FDG radiomics consistently predicts pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) and stratifies survival. Baseline heterogeneity indices correlate with stage and outperform single clinicopathologic variables (e.g., Ki-67 or subtype alone). Volumetric–textural features (MTV, TLG, entropy) add independent value (particularly in luminal B and HER2-positive disease) by reflecting metabolic burden and clonal diversity rather than size alone.[64–66]

Emerging geometric descriptors quantify how metabolism is distributed within the lesion. Normalized distances from the hottest voxel to the tumour centroid (NHOC) or perimeter (NHOP) capture metabolic asymmetry; NHOCmax, NHOPpeak independently predict pCR and PFS, providing interpretable, morphology-linked markers of invasion.[67]

Multimodal AI: from images to individualized probabilities

Machine-learning models that fuse PET radiomics with clinical, histologic, and genomic inputs outperform single-modality approaches-particularly in Triple Negative Breast Cancer (TNBC), where texture features (entropy, skewness, kurtosis) and proliferation signatures drive prediction.[68] Dual-phase/dynamic PET further strengthens performance: retention indices derived from early–delayed SUV/TLG changes track residual disease and survival, and, when embedded as time-series radiomics, quantify treatment-induced metabolic adaptation in near-real time.[69]

Model credibility hinges on harmonization. EANM/SNMMI recommendations regarding scanner calibration, voxel resampling, and feature harmonization (e.g., ComBat/Limma) should be routine.[70] PERCIST-aligned lesion selection with SUL peak normalization improves inter-centre comparability and enables pooled validation.[71] Systematic reviews now report pooled AUCs around 0.80 for AI-assisted FDG PET response prediction; residual heterogeneity reflects retrospective designs and inconsistent segmentation—solvable with prospective, protocolized pipelines.[65,66]

Accuracy without transparency stalls translation. Explainable frameworks in the form of nomograms show which features drive each prediction, supporting clinician trust, regulatory appraisal, and bedside use. If deployed in user-friendly software, these tools have the potential to convert a standard PET/CT into an individualized probability of pCR or non-response that can guide escalation or safe de-escalation.

In summary, radiomics and AI have the potential to elevate ^{18}F-FDG PET/CT from a metabolic snapshot to a quantitative decision platform. Heterogeneity metrics, geometric asymmetry (NHOC/NHOP), kinetic features and multimodal ML collectively predict pCR and survival- especially in HER2-positive and triple-negative disease. With rigorous harmonization and prospective validation, these models may become integral to adaptive oncology in selecting the right therapy early, curtailing futile toxicity, and personalizing NAC pathways with the precision our patients deserve.

Advantages, limitations, and future directions

Nomograms remain among the most practical and interpretable predictive tools that offer excellent calibration, transparency, and cost-effectiveness. Nonetheless, challenges persist, such as data heterogeneity, feature overfitting, and limited standardization across centres. These are increasingly mitigated through AI-based feature selection, scanner harmonization, and global multicentre groups adopting federated learning frameworks.

Future multimodal nomograms may integrate PET/CT with genomic, transcriptomic, and liquid-biopsy data to enable adaptive therapy decisions in real time. Within nuclear medicine, ^{18}F-FDG PET–guided predictive modelling is poised to redefine response evaluation—transforming nomograms from static risk calculators into dynamic, biologically informed instruments of precision oncology.

^{18}F-FDG PET/CT has evolved beyond its initial role as a mere staging tool to become a pivotal instrument in precision oncology. Its unique capacity to quantify tumor metabolic heterogeneity, glycolytic reprogramming, intra-tumoral dynamics, and host–tumour microenvironment interactions (such as immune activation reflected by splenic or visceral adipose uptake) has positioned it as a leading non-invasive biomarker of early treatment response in breast cancer.

Across molecular subtypes, baseline parameters such as high SUVmax, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) consistently mirror aggressive tumor biology, characterised by high Ki-67 expression and HR-negative, HER-2-enriched, or triple-negative phenotypes. Early metabolic shifts, in particular SUV reductions of 50–88% after one to two cycles of neoadjuvant chemotherapy, reliably predict pathological complete response with a negative predictive value in excess of 95%, progression-free survival, and recurrence, often surpassing conventional anatomical or clinicopathologic models.

When integrated into predictive nomograms, ^{18}F-FDG PET/CT transforms management paradigms from empiricism to precision. PET-augmented models enable timely therapy modulation by escalating treatment in metabolic non-responders while safely de-escalating in early responders, as demonstrated in PHERGain. Such a personalised approach

avoids futile toxicity, contains costs, and enhances patient-centred outcomes. These applications extend to axillary surgery avoidance, refined survival stratification through systemic immune-metabolic markers (e.g., splenic and marrow uptake), and improved trial design by enriching response-adapted endpoints.

To embed these advances into clinical routine, several priorities should be addressed, which include the following: prospective multicentre validation using standardized criteria (such as PERCIST) to confirm reproducibility and generalizability, multimodal fusion that integrates PET radiomics with circulating tumor DNA, transcriptomic and immune signatures, novel tracer integration (e.g. ^{18}F-FES for estrogen receptor mapping, ^{18}F-FLT for proliferation, ^{68}Ga-FAPI for stromal activity) to complement FDG in low-glycolytic subtypes, AI-driven harmonization, leveraging federated learning frameworks to standardize data across platforms while maintaining patient confidentiality and health-economic validations, as cost-effectiveness remains pivotal for broad adoption. Early analyses suggest >20% reductions in chemotherapy and toxicity-management expenditures through PET-guided adaptation.

Looking forward, adaptive oncology will likely increasingly rely on AI-assisted, data-fused decision systems in which metabolic imaging serves as a dynamic biomarker platform, guiding real-time therapy selection rather than retrospectively documenting response. As radiomics and artificial intelligence mature, ^{18}F-FDG PET/CT will transcend its diagnostic origins to become the cornerstone of biologically informed, precision-guided care, which may represent a paradigm shift reminiscent of the transformation heralded by alpha theranostics in prostate cancer.

Conclusion

^{18}F-FDG PET/CT provides quantitative insights into tumor biology, visualizing glycolysis, clonal evolution, tumor-microenvironment interactions, and systemic inflammation. PET biomarkers enable early response prediction, therapy adaptation, and avoidance of ineffective chemotherapy. Incorporated into nomograms, PET metrics in combination with clinical and genomic variables offer superior accuracy for pCR prediction, axillary de-escalation, survival stratification, and adaptive treatment. The addition of radiomics enables capturing of spatial heterogeneity as proxies for resistance which enables machine learning models to classify subtypes with high accuracy. Ultimately, PET-augmented, AI-enhanced strategies are an ethical, economic, and clinical imperative for dynamic, real-time personalized breast cancer management.

AI declaration

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process During the preparation of this work the authors used Grok AI in order to improve the language of select paragraphs. After using this tool/service, the author reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Mariza Vorster reports article publishing charges was provided by University of KwaZulu-Natal. Mariza Vorster reports a relationship with University of KwaZulu-Natal College of Health Sciences that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Mariza Vorster: Conceptualization, Data curation, Project administration, Resources, Software, Validation, Writing – original draft, Writing – review & editing. **Mike Sathekge:** Conceptualization, Writing – review & editing.

References

1. Kim J, Harper A, McCormack V, Sung H, Houssami N, Morgan E, Mutebi M, Garvey G, Soerjomataram I: Fidler-Benaoudia MM. Global patterns and trends in breast cancer incidence and mortality across 185 countries. Nat Med 31:1154-1162, 2025.
2. Sedeta, Ephrem Tadele, Bilain Jobre, and Boris Avezbakiyev. "Breast cancer: global patterns of incidence, mortality, and trends." 41:10528, 2023
3. Kerr AJ, Dodwell D, McGale P, Holt F, Duane F, Mannu G, Darby SC, Taylor CW: Adjuvant and neoadjuvant breast cancer treatments: a systematic review of their effects on mortality. Cancer Treat Rev 105:102375, 2022
4. Wang J, Wu SG: Breast cancer: an overview of current therapeutic strategies, challenge, and perspectives. Breast Cancer 15:721-730, 2023.
5. Jiahui L, Xingfeng L, Lijie W, Xuying L, Jinhua L, Yunxia F, Jiejun C: Breast cancer patients' experiences of coping with financial toxicity: a systematic review and qualitative meta-synthesis. Psycho-Oncol 34(1): e70075, 2025
6. Guo L, Kong D, Liu J, Zhan L, Luo L, Zheng W, Zheng Q, Chen C, Sun S: Breast cancer heterogeneity and its implication in personalized precision therapy. Exp Hematol Oncol 12(1):3, 2023
7. Ren Z, Zhao J, Li S, Yuan H: Targeting glucose transporter 1 (GLUT1) in cancer: molecular mechanisms and nanomedicine applications. Int J Nanomed 20:11859-11879, 2025.
8. Katal S, McKay MJ, Taubman K: PET molecular imaging in breast cancer: current applications and future perspectives. J Clin Med 13 (12):3459, 2024
9. Urso L, Evangelista L, Alongi P, Quartuccio N, Cittanti C, Rambaldi I, Ortolan N, Borgia F, Nieri A, Uccelli L, Schirone A: The value of semiquantitative parameters derived from 18F-FDG PET/CT for predicting response to neoadjuvant chemotherapy in a cohort of patients with different molecular subtypes of breast cancer. Cancers 14(23):5869, 2022
10. Hou X, Chen K, Wan X, Luo H, Li X, Xu W: Intratumoral and peritumoral radiomics for preoperative prediction of neoadjuvant chemotherapy effect in breast cancer based on 18F-FDG PET/CT. J Cancer Res Clin Oncol 150(11):484, 2024
11. Vaz SC, Woll JP, Cardoso F, Groheux D, Cook GJ, Ulaner GA, Jacene H, Rubio IT, Schoones JW, Peeters MJ, Poortmans P: Joint EANM-SNMMI guideline on the role of 2-[18F] FDG PET/CT in no special type breast cancer: (endorsed by the ACR, ESSO, ESTRO, EUSOBI/ESR, and EUSOMA). Eur J Nucl Med Mol Imaging 51(9):2706-2732, 2024

12. Gradishar WJ, Moran MS, Abraham J, Abramson V, Aft R, Agnese D, Allison KH, Anderson B, Bailey J, Burstein HJ, Chen N: Breast cancer, version 3.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 22(5):331-357, 2024
13. Mohammed AA: The clinical behavior of different molecular subtypes of breast cancer. Cancer Treat Res Commun 29:100469, 2021
14. Xiong X, Zheng LW, Ding Y, Chen YF, Cai YW, Wang LP, Huang L, Liu CC, Shao ZM, Yu KD: Breast cancer: pathogenesis and treatments. Signal Transduct Target Ther 10(1):49, 2025
15. Wolf DM, Yau C, Wulfkuhle J, Brown-Swigart L, Gallagher RI, Lee PR, Zhu Z, Magbanua MJ, Sayaman R, O'Grady N, Basu A: Redefining breast cancer subtypes to guide treatment prioritization and maximize response: predictive biomarkers across 10 cancer therapies. Cancer Cell 40(6):609-623, 2022
16. Sahu A, Raza K, Pradhan D, Jain AK, Verma S: Cyclooxygenase-2 as a therapeutic target against human breast cancer: a comprehensive review. WIREs Mech Dis 15(3):e1596, 2023
17. Liu Y, Zhou Q, Song S, Tang S: Integrating metabolic reprogramming and metabolic imaging to predict breast cancer therapeutic responses. Trends Endocrinol Metab 32(10):762-775, 2021
18. il Lee M, Jung YJ, Kim DI, Lee S, Jung CS, Kang SK, Pak K, Kim SJ, Kim HY: Prognostic value of SUVmax in breast cancer and comparative analyses of molecular subtypes: a systematic review and meta-analysis. Medicine 100(31):e26745, 2021
19. Urso L, Manco L, Castello A, Evangelista L, Guidi G, Castellani M, Florimonte L, Cittanti C, Turra A, Panareo S: PET-derived radiomics and artificial intelligence in breast cancer: a systematic review. Int J Mol Sci 23(21):13409, 2022
20. Ozawa H, Higuchi T, Fujimoto Y, Bun A, Fukui R, Kanaoka H, Nagahashi M, Kitajima K, Yamakado K, Miyoshi Y: Total lesion glycolysis levels as predictive indicators in patients with metastatic and recurrent breast cancer undergoing endocrine therapy with or without CDK4/6 inhibitor. Anticancer Res 42(10):4813-4824, 2022
21. Li Y, Liu C, Wang B, Hu X, Gong C, Zhao Y, Xie Y, Zhang Y, Song S, Yang Z, Wang B: Prediction of pretreatment 18F-FDG-PET/CT parameters on the outcome of first-line therapy in patients with metastatic breast cancer. Int J Gen Med 14:1797-1809, 2021.
22. Gebhart G, Keyaerts M, Guiot T, Flamen P, Ruiz-Borrego M, Stradella A, Bermejo B, Escriva-de-Romani S, Martínez LC, Ribelles N, Fernandez-Abad M: Optimal [18F] FDG PET/CT cutoff for pathologic complete response in HER2-positive early breast cancer patients treated with neoadjuvant trastuzumab and pertuzumab in the PHERGain trial. J Nucl Med 65(5):708-713, 2024
23. Kitajima K, Higuchi T, Fujimoto Y, Ishikawa E, Yokoyama H, Komoto H, Inao Y, Yamakado K, Miyoshi Y: Relationship between FDG-PET and the immune microenvironment in breast cancer. Eur J Radiol 158:110661, 2023
24. Saini G, Joshi S, Garlapati C, Li H, Kong J, Krishnamurthy J, Reid MD, Aneja R: Polyploid giant cancer cell characterization: new frontiers in predicting response to chemotherapy in breast cancer. Seminars in Cancer Biology, Vol. 81. Academic Press, 220-231, 2022
25. Seban RD, Rouzier R, Latouche A, Deleval N, Guinebretiere JM, Buvat I, Bidard FC, Champion L: Total metabolic tumor volume and spleen metabolism on baseline [18F]-FDG PET/CT as independent prognostic biomarkers of recurrence in resected breast cancer. Eur J Nucl Med Mol Imaging 48(11):3560-3570, 2021
26. Kim HJ, Kim D, Bae SJ, Ahn SG, Jeong J, Park WC, Ryu YH, Jeon TJ, Lee Y, Cha YJ, Yoon CI: 18F-FDG uptake of visceral adipose tissue on preoperative PET/CT as a predictive marker for breast cancer recurrence. Sci Rep 12(1):21109, 2022
27. Han S, Choi JY: Prognostic value of 18F-FDG PET and PET/CT for assessment of treatment response to neoadjuvant chemotherapy in breast cancer: a systematic review and meta-analysis. Breast Cancer Res 22(1):119, 2020
28. Lei P, Wang W, Sheldon M, Sun Y, Yao F, Ma L: Role of glucose metabolic reprogramming in breast cancer progression and drug resistance. Cancers 15(13):3390, 2023
29. Gandhi N, Das GM: Metabolic reprogramming in breast cancer and its therapeutic implications. Cells 8(2):89, 2019
30. Aktas A, Aslayan SO, Gurleyik MG, Gungor S: Correlations of primary tumor SUVmax and axillary lymph node SUVmax with molecular subtypes of invasive breast cancer. Indian J Surg 83(Suppl 2):468-474, 2021
31. Goyal N, Gokulakrishnan P, Murali A, Dennis LJ, Rangasami R, Dev B: Association of standardized uptake values of primary breast cancer on [18F] FDG PET/CT with immunohistochemistry and molecular subtypes: correlation of SUV of primary BC with molecular subtypes. Arch Breast Cancer 10:175-186, 2023.
32. Topuz ÖV, Arslan E, Usul G: Relation between primary tumor suvmax value, ki-67 proliferation index and axillary metastasis in patients with triple negative breast cancer. Bagcilar Med Bull 10 (1):51-57, 2025.
33. Gao Y, Yin L, Ma L, Wu C, Zhu X, Liu H, Liang L, Chen J, Chen Y, Ye J, Xu L: Comparative analysis of metabolic characteristics and prognostic stratification of HER2-low and HER2-zero breast cancer using 18F-FDG PET/CT imaging. Cancer Imaging 24(1):166, 2024
34. Gong C, Liu C, Tao Z, Zhang J, Wang L, Cao J, Zhao Y, Xie Y, Hu X, Yang Z, Wang B: Temporal heterogeneity of HER2 expression and spatial heterogeneity of 18F-FDG uptake predicts treatment outcome of pyrotinib in patients with HER2-positive metastatic breast cancer. Cancers 14(16):3973, 2022
35. Elsayed B, Alksas A, Shehata M, Mahmoud A, Zaky M, Alghandour R, Abdelwahab K, Abdelkhalek M, Ghazal M, Contractor S, El-Din Moustafa H: Exploring neoadjuvant chemotherapy, predictive models, radiomic, and pathological markers in breast cancer: a comprehensive review. Cancers 15(21):5288, 2023
36. Najid S, Seban RD, Champion L, De Moura A, Sebbag C, Salaün H, Cabel L, Bonneau C: Clinical utility of pre-therapeutic [18F] FDG PET/CT imaging for predicting outcomes in breast cancer. J Clin Med 12 (17):5487, 2023
37. de Mooij CM, Ploumen RA, Nelemans PJ, Mottaghy FM, Smidt ML, van Nijnatten TJ: The influence of receptor expression and clinical subtypes on baseline [18F] FDG uptake in breast cancer: systematic review and meta-analysis. EJNMMI Res 13(1):5, 2023
38. Kitajima K, Higuchi T, Yamakado K, Miyoshi Y: 18 Early assessment of tumor response using F-FDG PET/CT after one cycle of systemic therapy in patients with recurrent and metastatic breast cancer. Hell J Nucl Med 25(2):155-162, 2022
39. Akkaya H., Kelle A.P., Akkaya T.D., Özdemir S., Erişen K.K., Gülek B. Comparison of changes in dynamic contrast-enhanced magnetic resonance imaging and flourine-18 fluorodeoxyglucose positron emission tomography/computed tomography parameters from baseline to post-neoadjuvant therapy in predicting pathological response in breast cancer. Diagn Interv Radiol.
40. Pérez-García JM, Gebhart G, Borrego MR, Stradella A, Bermejo B, Schmid P, Marmé F, Escrivá-de-Romani S, Calvo L, Ribelles N, Martinez N: Chemotherapy de-escalation using an 18F-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 22(6):858-871, 2021
41. Pérez-García JM, Cortés J, Ruiz-Borrego M, Colleoni M, Stradella A, Bermejo B, Dalenc F, Escrivá-de-Romaní S, Martínez LC, Ribelles N, Marmé F: 3-year invasive disease-free survival with chemotherapy de-escalation using an 18F-FDG-PET-based, pathological complete response-adapted strategy in HER2-positive early breast cancer (PHERGain): a randomised, open-label, phase 2 trial. Lancet 403(10437):1649-1659, 2024
42. Llombart-Cussac A, Prat A, Pérez-García JM, Mateos J, Pascual T, Escrivà-de-Romani S, Stradella A, Ruiz-Borrego M, de Las, Heras BB, Keyaerts M, Galvan P: Clinicopathological and molecular predictors of [18F] FDG-PET disease detection in HER2-positive early breast cancer: RESPONSE, a substudy of the randomized PHERGain trial. Eur J Nucl Med Mol Imaging 51(9):2733-2743, 2024
43. Gebhart G, Keyaerts M, Guiot T, Flamen P, Ruiz-Borrego M, Stradella A, Bermejo B, Escriva-de-Romani S, Martínez LC, Ribelles N, Fernandez-Abad M: Optimal [18F] FDG PET/CT cutoff for pathologic complete response in HER2-positive early breast cancer patients treated with

neoadjuvant trastuzumab and pertuzumab in the PHERGain trial. J Nucl Med 65(5):708-713, 2024
44. Mghanga FP, Lan X, Bakari KH, Li C, Zhang Y: Fluorine-18 fluorodeoxyglucose positron emission tomography—computed tomography in monitoring the response of breast cancer to neoadjuvant chemotherapy: a meta—analysis. Clin Breast Cancer 13(4):271-279, 2013
45. Oliveira C, Oliveira F, Vaz SC, Marques HP, Cardoso F: Prediction of pathological response after neoadjuvant chemotherapy using baseline FDG PET heterogeneity features in breast cancer. Br J Radiol 96 (1146):20220655, 2023
46. de Mooij CM, Mitea C, Mottaghy FM, Smidt ML, van Nijnatten TJ: Value of 18F-FDG PET/CT for predicting axillary pathologic complete response following neoadjuvant systemic therapy in breast cancer patients: emphasis on breast cancer subtype. EJNMMI Res 11(1):116, 2021
47. Samiei S, de Mooij CM, Lobbes MB, Keymeulen KB, van Nijnatten TJ, Smidt ML: Diagnostic performance of noninvasive imaging for assessment of axillary response after neoadjuvant systemic therapy in clinically node-positive breast cancer: a systematic review and meta-analysis. Ann Surg 273(4):694-700, 2021
48. van Amstel FJ, de Mooij CM, Simons JM, Mitea C, van Diest PJ, Nelemans PJ, van der Pol CC, Luiten EJ, Koppert LB, Smidt ML, van Nijnatten TJ: Disease extent according to baseline [18F] fluorodeoxyglucose PET/CT and molecular subtype: prediction of axillary treatment response after neoadjuvant systemic therapy for breast cancer. Br J Surg 111(9):znae203, 2024
49. Wang Y, Li Y, Jiang H, Zuo C, Xu W: Elevated splenic 18F-fluorodeoxyglucose positron emission tomography/computed tomography activity is associated with 5-year risk of recurrence in non-metastatic invasive ductal carcinoma of the breast. Br J Radiol 97(1153):237-248, 2024
50. Bang JI, Yoon HJ, Kim BS: Clinical utility of FDG uptake within reticuloendothelial system on F-18 FDG PET/CT for prediction of tumor recurrence in breast cancer. PLoS One 13(12):e0208861, 2018
51. Şahin E, Elboğa U: Relationship between reticuloendothelial systems' FDG uptake level and clinicopathological features in patient with invasive ductal breast cancer. Radiol Med 122(10):785-792, 2017
52. Tokac RH, Tokac EC, Yararbas U, Aykut A, Durmaz A, Akin H, Argon AM: Cross-sectional analysis of metabolic tumor burden detected by F-18 FDG PET/CT and circulating tumor DNA in advanced breast cancer. Cancer Med 14(16):e71049, 2025
53. Özdemir S, Sılan F, Akgün MY, Aracı N, Çırpan İ, Öztürk FK, Özdemir Ö: Prognostic prediction of BRCA mutations by 18F-FDG PET/CT SUVmax in breast cancer. Mol Imaging Radionucl Ther 30(3):158, 2021
54. Caracciolo M, Castello A, Urso L, Borgia F, Marzola MC, Uccelli L, Cittanti C, Bartolomei M, Castellani M, Lopci E: Comparison of MRI vs. [18F] FDG PET/CT for treatment response evaluation of primary breast cancer after neoadjuvant chemotherapy: literature review and future perspectives. J Clin Med 12(16):5355, 2023
55. Hildebrandt MG, Naghavi-Behzad M, Vogsen M: A role of FDG-PET/CT for response evaluation in metastatic breast cancer? Seminars in Nuclear Medicine, Vol. 52. WB Saunders, 520-530, 2022
56. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP: Nomograms in oncology: more than meets the eye. Lancet Oncol 16(4):e173-e180, 2015
57. Obeagu EI, Obeagu GU: Predictive models and biomarkers for survival in stage III breast cancer: a review of clinical applications and future directions. Ann Med Surg 86(10):5980-5987, 2024
58. Li Y, Chen K, Jin L, Huang H: Development and validation of an 18F-FDG PET/CT radiomic nomogram for predicting axillary lymph-node status after neoadjuvant chemotherapy for breast cancer: a multicenter study. Ann Nucl Med 39:1326-1336, 2025.
59. Wang Y, Li Y, Jiang H, Zuo C, Xu W: Elevated splenic 18F-fluorodeoxyglucose positron emission tomography/computed tomography activity is associated with 5-year risk of recurrence in non-metastatic invasive ductal carcinoma of the breast. Br J Radiol 97(1153):237-248, 2024
60. Li Y, Liu C, Wang B, Hu X, Gong C, Zhao Y, Xie Y, Zhang Y, Song S, Yang Z, Wang B: Prediction of pretreatment 18F-FDG-PET/CT parameters on the outcome of first-line therapy in patients with metastatic breast cancer. Int J Gen Med 14:1797-1809, 2021.
61. Chen K, Wang J, Li S, Zhou W, Xu W: Predictive value of 18F-FDG PET/CT-based radiomics model for neoadjuvant chemotherapy efficacy in breast cancer: a multi-scanner/center study with external validation. Eur J Nucl Med Mol Imaging 50(7):1869-1880, 2023
62. Li Y, Chen K, Jin L, Huang H: Development and validation of an 18F-FDG PET/CT radiomic nomogram for predicting axillary lymph-node status after neoadjuvant chemotherapy for breast cancer: a multicenter study. Ann Nucl Med 39:1326-1336, 2025.
63. Obeagu EI, Obeagu GU: Predictive models and biomarkers for survival in stage III breast cancer: a review of clinical applications and future directions. Ann Med Surg 86(10):5980-5987, 2024
64. Ji J, Duan F, Liao Q, Wang H, Liu S, Liu Y, Huang Z: Artificial intelligence-based pathology to assist prediction of neoadjuvant therapy responses for breast cancer. Cancer Med 14(15):e71132, 2025
65. Chen Y, Sun Y, Chen Y, Zhang J, Zhang H, Liu K, Dong L, Zhang X, Zhou R, Wang J, Zhong Y: Artificial intelligence-assisted PET imaging for predicting neoadjuvant chemotherapy response in breast cancer: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging: 1-8, 2025. https://doi.org/10.1007/s00259-025-07536-0
66. Javanmard Z, Shahraki SZ, Safari K, Omidi A, Raoufi S, Rajabi M, Akbari ME, Aria M: Artificial intelligence in breast cancer survival prediction: a comprehensive systematic review and meta-analysis. Front Oncol 14:1420328, 2025
67. Hong SP, Lee SM, Yoo ID, Lee JE, Han SW, Kim SY, Lee JW: Clinical value of SUVpeak-to-tumor centroid distance on FDG PET/CT for predicting neoadjuvant chemotherapy response in patients with breast cancer. Cancer Imaging 24(1):136, 2024
68. Bülbül O, Bülbül HM, Göksel S: Relationship between [18F] FDG PET/CT texture analysis and progression-free survival in patients diagnosed with invasive breast carcinoma. Eur J Breast Health 21(4):356, 2025
69. Kupik O, Tuncel M, Kiratli PÖ, Akpinar MG, Altundağ K, Demirkazik FB, Erbaş B: Predictive value of dual-phase 18F-FDG PET/CT in the assessment of neoadjuvant chemotherapy response in patients with locally advanced breast cancer: a prospective comparative study with dynamic contrast-enhanced Magnetic resonance imaging. Turk J Oncol/Türk Onkol Derg 37(4):426-435, 2022
70. Schlumbohm S, Neumann JE, Neumann P: HarmonizR: blocking and singular feature data adjustment improve runtime efficiency and data preservation. BMC Bioinform 26(1):47, 2025
71. Castorina L, Comis AD, Prestifilippo A, Quartuccio N, Panareo S, Filippi L, Castorina S, Giuffrida D: Innovations in positron emission tomography and state of the art in the evaluation of breast cancer treatment response. J Clin Med 13(1):154, 2023