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REVIEW

Novel Molecular Imaging Approaches: Towards a Better Estimation of Response in Breast Cancer

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Abstract

The use of [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) in breast cancer response assessment and monitoring is well established. However, there are limitations not only to the use of [^{18}F]FDG PET/CT in breast cancer, but also deficiencies in the conventional imaging assessment of treatment response. Breast cancer is biologically heterogeneous, and heterogeneity of tumours limits the accuracy of [^{18}F]FDG PET/CT assessment in some subtypes of breast cancer. Increased understanding of tumour biology and the tumour microenvironment have led to the development of new, specific radio-tracers. These targeted tracers may offer a solution in terms of more accurate response assessment, and prognostication.

Key words: molecular imaging; molecular probes; breast cancer

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Introduction

Breast cancer is the most frequently occurring cancer in women globally, with high cancer-related morbidity (Siegel et al, 2018). Providing an accurate estimation of response to treatment is valuable, as it enables the reduction of breast cancer treatment-related morbidity and mortality. This is particularly important in the response assessment of neoadjuvant chemotherapy, as pathologic complete response (pCR) following neoadjuvant chemotherapy (NAC), is important in determining prognosis (Spring et al, 2020), and in the monitoring of metastatic disease, to allow the most effective treatment to be used (Angarita et al, 2022).

Therapy response assessment is increasingly reliant on positron emission tomography/computed tomography (PET/CT), most commonly [^{18}F]fluorodeoxyglucose (FDG) PET/CT. The introduction of [^{18}F]FDG PET/CT has revolutionised cancer care, and now represents the standard of care for diagnosis and assessment of treatment response in many cancers. Tumour [^{18}F]FDG accumulation reflects the up-regulated glycolytic pathway of cancer cells, offering advantages in that it is useful in many different cancer types, but with the significant disadvantage in that it is non-specific. There is false positive [^{18}F]FDG uptake in several benign conditions, including infection and inflammation (including sarcoidosis, radiation pneumonitis

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and post-operative surgical conditions). Conversely, some cancers will have false negative [^{18}F]FDG imaging, due to low glycolytic activity or small tumour size. False negatives can also be seen where a tumour borders an area of high [^{18}F]FDG physiologic uptake, such as the heart. While these are potential limitations of PET, in practice these are an infrequent problem with an experienced reporter who has the full relevant clinical details to hand. In addition, scanning hardware is improving and the advent of total body PET will improve sensitivity, contrast and spatial resolution, as well as overall image quality (Cook et al, 2025).

Breast cancer is a heterogeneous cancer, with tumour type, tumour stage, histological grade, and the presence of different receptors, such as estrogen receptors (ER), progesterone receptors (PR), and human epidermal factor receptors 2 (HER2), all important in determining specific treatment and prognosis. Increases in our understanding of tumour biology and the tumour microenvironment have led to the development of radiotracers which exploit the heterogeneity of breast cancer subtypes. These radiotracers offer a more specific method of not only evaluating the treatment response, but predicting response pre-treatment. This becoming increasingly important, as therapy resistance is now one of the biggest problems facing cancer patients, with a study estimating that treatment resistance contributes up to 90% of cancer-related deaths (Dhanyamraju, 2024). This review aims to discuss the current imaging assessment of treatment response in breast cancer, and cover recent advances in molecular imaging, highlighting how these could offer a better estimation of therapy response in breast cancer.

Deficiencies of Current Imaging Assessment

The Response Evaluation Criteria in Solid Tumours (RECIST) uses the objective measurement of changes in the diameter of target lesions to assess the treatment response. RECIST was created to standardise tumour response assessment using morphological imaging in clinical trials (Therasse et al, 2006). RECIST version 1.1 is now in use, in which specific objective criteria are applied to post-treatment imaging to assess the treatment response (Eisenhauer et al, 2009). A complete response involves the disappearance of all target lesions, and partial response involves a 30% or greater decrease in the sum of the diameters of the target lesions. Progressive disease involves a 20% or more increase in the sum of the diameters of the target lesion. Non-target lesions are not individually measured, and but should be described using standardised language, so the RECIST 1.1 response is clear.

RECIST 1.1 is widely used in the assessment of breast cancer treatment response, despite multiple limitations. One of these is that RECIST 1.1 considers certain lesions as non-measurable, such as bone metastases. Bone metastases are only assessable if they have a soft tissue component of $>$10 mm (which is rare), and sclerotic lesions are excluded. This means that bone metastases are mainly considered unmeasurable and qualitatively assessed, whereas they often represent a significant burden of metastatic disease. A second issue is that measurement of lesion size alone is a crude indicator of response. In breast cancer, treatments such as chemoradiation and neoadjuvant therapy aim primarily to shrink the tumour,

meaning that a size-based assessment of response has previously been appropriate. However, lesions may be responding to treatment but not decreasing in size, for example, a tumour may show necrosis, indicating response, although overall lesion size is unchanged. A further issue is that some treatments may not initially cause tumour shrinkage. Immune checkpoint inhibitors, such as programmed cell death protein 1 (PD-1), have revolutionised the systematic treatment of advanced solid tumours. In patients with metastatic triple-negative breast cancer, the combination of the PD-1 inhibitor, pembrolizumab, plus chemotherapy showed a significant improvement in progression-free survival versus the combination of placebo plus chemotherapy (Cortes et al, 2020). However, immunotherapy can cause atypical imaging patterns of response, such as pseudoprogression, where tumour shrinkage or stabilisation is observed after an initial increase in tumour size. Pseudoprogression can also be seen with bone flares, where osteoblastic healing responses cause increase in the size and density of lesions (Messiou et al, 2011), and in the brain, where radiologically, disease can look like tumour progression or recurrence, but is actually a treatment effect, such as swelling or post-contrast enhancement after surgery or radiotherapy.

In order to address these issues, in 2017, immunotherapy RECIST (iRECIST) was introduced for patients undergoing immunotherapy (Seymour et al, 2017). iRECIST allows pseudoprogression to be captured; however, further atypical responses, such as a dissociated response, in which a patient has both responding and non-responding lesions at the same time, are not. The presence of a dissociated response is seen with some systemic immunotherapy treatments, and is often associated with a favourable prognosis. Failing to capture this is an issue, as the rate of dissociated response reported in different studies ranges from 3.3–47.8% (Guan et al, 2022), meaning iRECIST may often be failing to capture a frequently occurring atypical response.

In summary, as an assessment measure of treatment response, RECIST 1.1 is late to show response or progression, as response is based primarily on the size of the lesion. Assessing the tumoural metabolic response to treatment with [^{18}F]FDG PET may allow an earlier assessment of treatment response than measuring tumour shrinkage. Metabolic response assessment can be evaluated using two sets of criteria: the European Organization for Research and Treatment of Cancer (EORTC) criteria (Young et al, 1999) and the Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST) (Wahl et al, 2009). Although the objective measurements these criteria use are slightly different, a study assessing the use of PERCIST vs. EORTC in the tumour response assessment has found very high agreement (Kim, 2016), and the use of [^{18}F]FDG PET/CT is well established in breast cancer treatment response assessment.

Early Response Evaluation With [^{18}F]FDG PET/CT

[^{18}F]FDG acts as a glucose analogue, and is used in conjunction with PET to localise tissues with altered glucose metabolism. [^{18}F]FDG accumulates in tis-

sues with high glucose demand, and the PET scanner detects the radiation emitted by [^{18}F]FDG to create images that show how the tracer is building up in the body. This is reflected via the measurement of standardised uptake values (SUV), i.e., the amount of [^{18}F]FDG that has accumulated in the tumour and associated nodes and/or metastases. New multidisciplinary guidelines on the role of [^{18}F]FDG PET/CT in breast cancer have been published (Vaz et al, 2024), acknowledging that quantitative PET features (SUV, metabolic tumour volume, and total lesion glycolysis) are valuable prognostic parameters, and that [^{18}F]FDG PET/CT may be useful in the assessment of early metabolic response, particularly in non-metastatic triple-negative breast cancer (TNBC) and HER2+ tumours.

[^{18}F]FDG PET/CT is often used to assess the response to NAC, which works in several ways, one of which is to decrease the primary tumour size preoperatively for operable patients, avoiding extensive mastectomy (Schegerin et al, 2009). With the antitumour effect of chemotherapy, cellular glycolysis decreases before the tumour begins to shrink morphologically (Ogston et al, 2003), meaning the [^{18}F]FDG PET/CT response is often visible before any anatomic change. Accurate response assessment is important, as pCR following NAC is an important prognostic factor for both disease-free survival and overall survival for breast cancer (Antonini et al, 2023). There have been several large meta-analyses evaluating the use of [^{18}F]FDG PET/CT in the assessment of NAC response, which reveal similar results. A meta-analysis with 781 patients found that [^{18}F]FDG PET/CT had a sensitivity of 0.840 (95% confidence interval (CI), 0.796–0.878) in evaluating response to NAC in patients with breast cancer (Cheng et al, 2012). A second meta-analysis involving 920 patients showed that [^{18}F]FDG PET/CT was able to predict histopathological response in primary breast lesions with a pooled sensitivity of 84% (95% confidence interval (CI), 78–88%), and a negative predictive value (NPV) of 91% (95% CI, 87–94%). In the response assessment of regional lymph nodes, the sensitivity and NPV of [^{18}F]FDG PET were 92% (95% CI, 83–97%) and 88% (95% CI, 76–95%), respectively (Wang et al, 2012). Additionally, a multivariate analysis of [^{18}F]FDG PET/CT parameters in breast cancer patients before and after NAC showed that the SUV_{max} of the primary breast cancer is an independent predictive factor for pCR (Sengoz et al, 2023).

Performing early interim [^{18}F]FDG PET/CT imaging could also aid response assessment. In locally advanced breast cancer, performing [^{18}F]FDG PET/CT after 3–4 cycles of NAC was shown to provide an early and accurate NAC response assessment, and also found that changes in SUV_{max} levels of the breast tumour and axillary lymph nodes may be predictive for pCR (Tatar et al, 2022).

It is well established that patients with TNBC have poor outcomes when pCR is not reached after NAC (Chen et al, 2017), meaning [^{18}F]FDG PET/CT could be especially useful in the early evaluation of response in these patients. In a study of 78 patients with TNBC, it was found that early metabolic change during NAC can predict pCR and event free survival (Groheux et al, 2016). The change in SUV_{max} after two cycles was more pronounced in patients who achieved pCR (–72% vs. –42%; $p < 0.0001$). Furthermore, treatment pathways could be altered according to [^{18}F]FDG PET/CT findings, which would allow patients to avoid the morbid-

ity associated with non-effective treatment. A multi-centre study has found that [^{18}F]FDG PET/CT could identify patients with early-stage HER2 positive breast cancer who were likely to benefit from dual HER2 blockade with trastuzumab and pertuzumab (Pérez-García et al, 2021) and not require additional cytotoxic chemotherapy, opening the door to the possibility of chemotherapy de-escalation using a pathological response-adapted strategy.

Metastatic Response Assessment With [^{18}F]FDG PET/CT

Accurate treatment response assessment is paramount in the context of metastasis, as it not only allows the most effective treatments to be selected, it also reduces the morbidity associated with ineffective chemotherapy or targeted therapy. This is becoming more and more important as metastatic breast cancer is becoming a chronic disease, with increasing numbers of women living longer with metastatic breast cancer (Mariotto et al, 2017).

In patients with metastatic breast cancer, systemic therapy response assessment by [^{18}F]FDG PET/CT is known to be more accurate than contrast-enhanced CT (CE-CT) (Le Goubey et al, 2021). In patients with biopsy-verified metastatic breast cancer, treated with first line therapy (80.5% receiving endocrine therapy as their first line treatment) and disease progression, progression was seen first on [^{18}F]FDG PET/CT CT in 78.2% of patients compared with CE-CT (Vogsen et al, 2023). The median time difference in detection of progression by [^{18}F]FDG PET/CT vs. CE-CT was 6 months (95% CI, 4.3–6.4 months), representing a clinically relevant delay.

[^{18}F]FDG PET/CT has also shown superiority at predicting survival in patients with metastatic disease. A comparison of CE-CT and [^{18}F]FDG PET/CT for response monitoring in metastatic breast cancer found that [^{18}F]FDG PET/CT is a better predictor of progression-free and disease-specific survival than CE-CT (Vogsen et al, 2023). 2-year progression-free survival for responders vs. non-responders as assessed by [^{18}F]FDG PET/CT was 59.1% vs. 14.3%, vs. 54.2% vs. 46.0% by CE-CT. Correspondingly, 2-year disease-specific survival was 84.6% vs. 61.9% as assessed by [^{18}F]FDG PET/CT, and 83.3% vs. 77.8% as assessed by CE-CT. Tumour response on [^{18}F]FDG PET/CT was significantly associated with progression-free (hazard ratio (HR): 3.49, $p < 0.001$) and disease-specific survival (HR: 2.35, $p = 0.008$), while no association was found for tumour response on CE-CT.

Early [^{18}F]FDG PET/CT may also be useful in early assessment of metastatic disease. Example imaging of this is shown in Fig. 1, where early response to endocrine treatment is observed with an 8-week [^{18}F]FDG PET/CT scan. A prospective study of 23 women with biopsy-proven ER-positive metastatic breast cancer evaluated the benefit of [^{18}F]FDG PET/CT in assessing therapy response at baseline, four and 12 weeks after starting new endocrine treatment (most commonly aromatase inhibitor plus palbociclib). They found there was a high correlation between percentage change in average SUV_{max} per participant at 4 weeks and 12 weeks ($r = 0.81$), and that at the 4-week time point, PET responders had longer

progression-free survival (14.2 months vs. 6.3 months; $p = 0.53$) and overall survival (44.0 months vs. 29.7 months; $p = 0.47$), compared with non-responders, suggesting the clinical utility of 4-week [^{18}F]FDG PET/CT as an early predictor of treatment failure in this patient group (Makhlin et al, 2022). This could be valuable in allowing stratification of patients, and avoiding the morbidity associated with non-effective treatment.

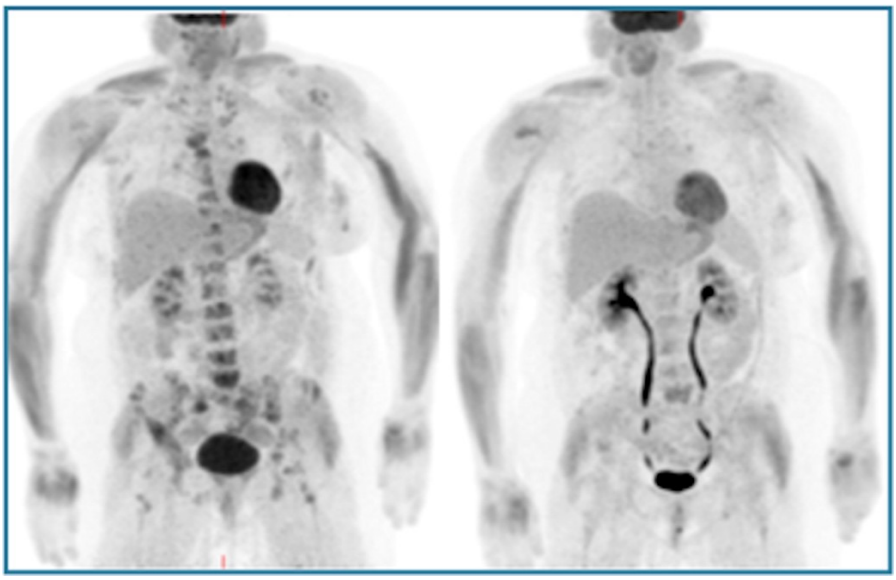

Fig. 1. Baseline (left) and 8-week [^{18}F]FDG PET scans of a woman with bone-predominant metastatic breast cancer on endocrine treatment showing an early partial metabolic response to treatment. The figure is from (Azad et al, 2019) [Springer], available under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). [^{18}F]FDG PET, [^{18}F]fluorodeoxyglucose positron emission tomography.

[^{18}F]FDG PET/CT may also be better than other advanced imaging in the assessment of bone metastases. A comparison of [^{18}F]FDG PET/CT, [^{18}F]-sodium fluoride (NaF) PET/CT and whole-body magnetic resonance imaging (WB-MRI) with diffusion-weighted imaging has been performed in the assessment of endocrine therapy response prediction at 8 weeks in patients with bone-predominant metastatic breast cancer. This found that while [^{18}F]FDG PET/CT and WB-MRI best predicted clinical non-progressive disease, and both [^{18}F]FDG and NaF PET/CT predicted progression-free survival at less than 24 weeks, there was a significant difference in the percentage change of [^{18}F]FDG SUV_{max} between patients with progression-free survival at less than 24 weeks and those with longer progression-free survival, suggesting [^{18}F]FDG may be the superior prognostic marker (Azad et al, 2019).

One potential issue with the long term use of repeated [^{18}F]FDG PET/CT imaging for treatment response monitoring is the associated cumulative radiation dose. All imaging which requires ionising radiation need to be justified by a trained practitioner under the Ionising Radiation (Medical Exposure) Regulations, so at each monitoring scan the risks vs. benefits of the imaging are taken into account. In the context of patients with cancer, many of whom will undergo radiotherapy as part of

their treatment pathway, the dose of ionising radiation of [^{18}F]FDG PET/CT imaging is comparatively very low, and the associated benefits of accurate and up to date imaging far outweigh the associated risks.

Prediction of Response With New Molecular Imaging Probes

Although [^{18}F]FDG is the most commonly used PET tracer in routine clinical practice for diagnosis and monitoring oncological therapy response, it is not a cancer-specific tracer, and the subtype of breast cancer can affect the glucose consumption, and therefore the uptake of [^{18}F]FDG (Liu et al, 2022). Although a hallmark of breast cancer is increased glucose consumption, breast cancer encompasses a heterogeneous group of cancers, including invasive ductal carcinoma (most common), invasive lobular carcinoma (second most common) and rarer subtypes including tubular, neuroendocrine, mucinous, apocrine, adenoid cystic, micropapillary, metaplastic, and medullary carcinoma, and different subtypes exhibit variability in the uptake of [^{18}F]FDG. The reasons behind this variability are not well understood in breast cancer; some reports have shown a positive correlation between the proliferation rate of a tumour and the [^{18}F]FDG uptake, with increasing SUV_{max} as the histological grade worsens (Tchou et al, 2010), however histological and immunohistochemical tissue analyses, including looking at factors such as tumour grade and differentiation, have been unable to explain the variability of [^{18}F]FDG across breast cancers (Avril et al, 2001). However, it is known that [^{18}F]FDG uptake is low in some histopathological types, such as invasive lobular cancer, luminal A (positive ER and a low proliferation index), and HER2 positive disease, meaning [^{18}F]FDG is less useful in the management of these cancer subtypes (Evangelista et al, 2023). These limitations have led to the development of new tracers which can target specific disease elements or processes, for example, the use of [^{89}Zirconium]trastuzumab PET/CT to assess patients with HER2 positive cancer.

These novel tracers offer many potential advantages when compared with [^{18}F]FDG PET/CT. A limitation of PERCIST for response assessment is that is it only applicable to [^{18}F]FDG avid lesions, and it has not been sufficiently validated to be applied to other tracers. Specific targeted molecular imaging probes, as detailed below, likely represent the future in assessment of breast and other cancer treatment response, and updated guidelines for standardisation of response are required to take these into account.

16α-[^{18}F]Fluoro-17β-Estradiol

16α-[^{18}F]Fluoro-17β-Estradiol ([^{18}F]FES) is a molecular imaging tracer which quantifies in vivo ER expression, meaning [^{18}F]FES PET/CT can non-invasively assess the ER status of several tumour lesions within the body at the same time. However, a disadvantage of [^{18}F]FES PET/CT is that there is high background physiological uptake in the liver, which limits the assessment of liver metastases.

A comparison of [^{18}F]FES PET/CT and [^{18}F]FDG PET/CT in patients with newly diagnosed ER-positive breast cancer found higher diagnostic sensitivity using [^{18}F]FES versus [^{18}F]FDG PET/CT (90.8% vs. 82.8%, respectively). The application of [^{18}F]FES in addition to [^{18}F]FDG PET/CT changed the management in 5/19 (26.3%) patients, with two changes in treatment objective (one from palliative to curative intent and one vice versa, two changes in surgical management, and one change in surgical management plus radiotherapy) (Liu et al, 2019). This analysis excluded liver lesions; nonetheless findings suggest that [^{18}F]FES may be a useful adjunct imaging to tailor treatment appropriately.

[^{18}F]FES PET/CT might also allow prediction of treatment efficacy. A phase II trial evaluating the efficacy and safety of adding fulvestrant, an ER antagonist, to NAC in patients with ER-positive/HER2 negative locally advanced breast cancer, found that the SUV_{max}, SUV_{mean} and total lesion-ER expression of [^{18}F]FES PET/CT in sensitive patients were significantly higher than those in non-sensitive patients ($p < 0.05$). Furthermore, there was significant correlation of these parameters with histopathological grade, and the pre- and post-treatment change in ER expression ($p < 0.05$) (Shao et al, 2025), suggesting [^{18}F]FES PET/CT could be used to stratify patients pre-treatment.

^{89}Zirconium [^{89}Zr]Trastuzumab (HER2) PET/CT

Evidence of heterogeneity in HER2 expression in breast cancers (Seol et al, 2012) has generated interest in whole-body assessment of HER2 status using molecular imaging via ^{89}Zirconium [^{89}Zr]trastuzumab (also known as HER2) PET/CT. Comparative imaging is seen in Fig. 2, evidencing the heterogeneity of HER2 expression.

The HER2-targeting trastuzumab emtansine (T-DM1) treatment in breast cancer exploits a tumour's HER2 status. The results of the ZEPHIR trial have now been published, in which patients with advanced HER2 positive breast cancer underwent HER2 PET/CT and [^{18}F]FDG PET/CT before T-DM1 initiation. They found 93/265 (35%) lesions were HER2 negative, and of these, 18 (19%) lesions (from 11 patients), responded anatomically after three T-DM1 cycles, resulting in an 81% NPV of the HER2 PET/CT. When combined with early metabolic response assessment using [^{18}F]FDG PET/CT, performed before the second T-DM1 cycle, NPVs of 91% and 100% were reached in predicting lesion-based and patient-based (RECIST 1.1) response, respectively (Mileva et al, 2024). It is therefore suggested that HER2 PET/CT, alone or in combination with early [^{18}F]FDG PET/CT, may be able to identify breast cancer lesions with a low probability of clinical benefit from T-DM1, allowing stratification of patients.

(4S)-4-(3-[^{18}F]fluoropropyl)-L-Glutamate

(4S)-4-(3-[^{18}F]fluoropropyl)-L-Glutamate ([^{18}F]FSPG) is a glutamate analogue taken up by the heterodimeric transporter system x_c^-. This transporter system represents a key step in the production of glutathione, one of the body's most abundant antioxidants, and is key in the development of a glutathione-based drug resistance. Multiple studies have already been published assessing the performance of

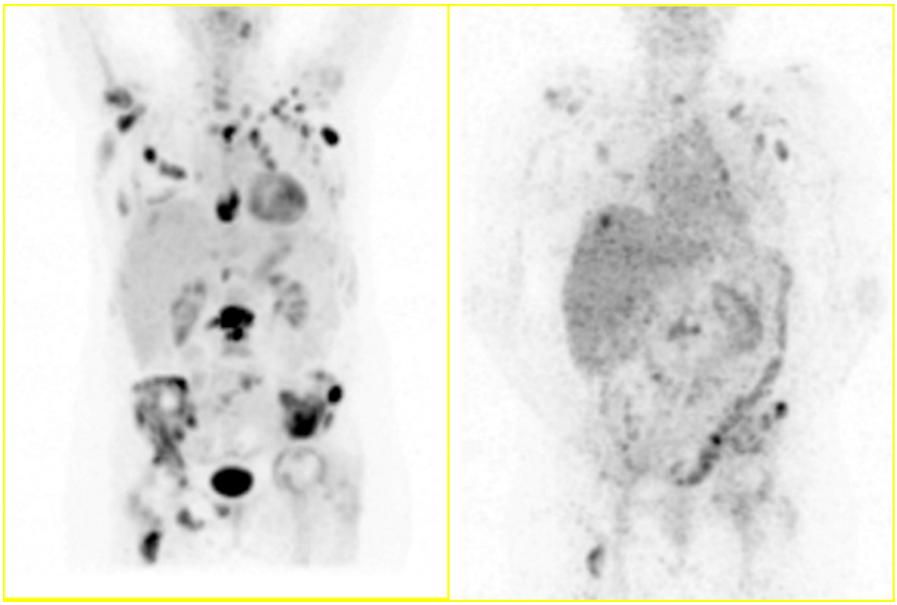

Fig. 2. [^{18}F]FDG (left) and [^{89}Zr]trastuzumab PET scans of a woman with metastatic breast cancer. The [^{18}F]FDG scan shows multiple active skeletal and nodal metastases, only a few of which show human epidermal factor receptors 2 (HER2) expression, revealing the heterogeneity of HER2 expression between metastases. Images from the authors' institution (King's College London and Guy's and St. Thomas' PET Centre, St. Thomas' Hospital, London, UK). [^{89}Zr], ^{89}Zirconium.

[^{18}F]FSPG as a diagnostic agent, including in breast cancer (Sharkey et al, 2023), however, the widespread use of [^{18}F]FSPG as a diagnostic probe has been limited by the heterogeneity of [^{18}F]FSPG uptake, likely caused by differential tumour response to oxidative stress (Sharkey et al, 2024).

As many cancer treatments rely on inducing oxidative stress in cancer cells, preclinical studies have exploited this characteristic, and have shown that [^{18}F]FSPG may offer an early and accurate assessment of treatment response. Changes in [^{18}F]FSPG retention following treatment occur before changes in both [^{18}F]FDG uptake and tumour volume (Greenwood et al, 2019; McCormick et al, 2019), suggesting that [^{18}F]FSPG could be a more sensitive assessor of treatment response than [^{18}F]FDG. Although not yet assessed in breast cancer, if similar findings were replicated in clinical trials, the use of [^{18}F]FSPG PET/CT could be valuable in predicting treatment resistance and providing an early imaging assessment of therapy response. One clinical trial evaluating the use of [^{18}F]FSPG in the diagnosis, prediction, and evaluation of treatment response in a variety of metastatic cancer types has been completed (NCT02599194), and publication of results is awaited.

^{68}Gallium [^{68}Ga] Fibroblast Activation Protein Inhibitor PET and Variants

Fibroblast Activation Protein Inhibitor (FAPI) PET uses a radiolabelled fibroblast activation protein (FAP) inhibitor to target cancer-associated fibroblasts. FAP is highly expressed in the stroma surrounding tumours and is a specific surface marker for cancer-associated fibroblasts. FAPI PET is useful in many different tumour types, and it has recently been shown that disease extent on [^{68}Ga]FAPI-46 PET/CT is a predictor of short overall survival in various solid tumours (Watan-

abe et al, 2024). A recent review of FAPI PET in breast cancer, including 172 patients, found that FAPI PET offers several advantages: it can detect more lesions than [^{18}F]FDG, the uptake is independent of the molecular and histopathological features of the cancer, and FAPI PET is more accurate than [^{18}F]FDG in detecting small lesions after chemotherapy (Evangelista et al, 2023), suggesting that FAPI PET may be a used as complementary imaging, especially for breast cancer types with low glucose metabolism.

In addition, early studies looking at response assessment with FAPI PET are promising. A small study of patients with invasive lobular breast cancer found a strong correlation between ^{68}Ga-FAPI tumour volume post-treatment and blood biomarkers in six patients before and after treatment (hormonal treatment in three patients, chemical in two patients and antibody-drug conjugates in one patient) (Eshet et al, 2023). There are also early studies assessing the use of FAPI PET in the evaluation of NAC response. Chen et al (2023) found that, in a study of 22 patients with newly diagnosed breast cancer, changes in ^{68}Ga-FAPI uptake after two cycles of NAC were predictive of pCR.

Radiomics and Artificial Intelligence

Increased use of [^{18}F]FDG PET/CT and other molecular imaging has provided extensive data, which has been harnessed by radiomics, which uses artificial intelligence (AI) to analyse the spatial distribution of pixel inter-relationships and signal intensities to extract elements, such as textural features. This process creates a high-dimensional data set that can be mined to identify complex patterns in images, which in turn can be used to predict underlying tumour biology and behaviour.

Radiomics may be able to assess the heterogeneity of uptake information of [^{18}F]FDG and other molecular imaging probes, which could then be exploited to predict or measure response more accurately than standard metrics. Radiomic signatures from [^{18}F]FDG PET images have been reported to be able to differentiate breast cancer factors, including HER2 expression (Moscoso et al, 2018) and triple-negative status (Soussan et al, 2014). It has been shown that extracting metabolic and texture features from [^{18}F]FDG PET/CT, and combining these features with clinical parameters, can predict pCR to NAC in patients with HER2 and triple-negative breast cancer (Payan et al, 2024). In this study, 128 patients with breast cancer had an [^{18}F]FDG PET/CT before starting treatment, and multiple models combining the various parameters (clinical, clinical plus metabolic, and clinical plus metabolic plus primary tumour blood flow) were developed, finding that baseline clinical data combined with global and texture tumour metabolism radiomic features assessed by [^{18}F]FDG PET/CT provided the best prediction of pCR after NAC in patients with breast cancer (mean balanced accuracy of 0.66 (clinical plus metabolic), 0.61 (clinical only), and 0.64 respectively (clinical plus metabolic plus tumour blood flow)). [^{18}F]FDG PET/magnetic resonance imaging (MRI) may offer additional benefits. In a study of 73 patients with newly diagnosed treatment naive breast cancer, multiparametric [^{18}F]FDG PET/MRI-based radiomics analysis was able to predict pCR with an NPV of 79.5% (Umutlu et al, 2022).

Several different AI methodologies have been used in the assessment of treatment response and prediction of treatment response with molecular imaging. PET imaging generates a huge amount of data, and AI could be used to assess imaging features to delineate which are the most predictive parameters in different cancer types. For example, in oesophageal cancer, convolutional neural networks, employed to hierarchically learn [^{18}F]FDG uptake patterns that are associated with histopathological response to NAC, were shown to have 80.7% sensitivity and 81.6% specificity in predicting non-responders (Ypsilantis et al, 2015). Convolutional neural networks may be able to extract PET parameters that could be prognostic of response to therapy. This could be applicable not only to [^{18}F]FDG PET, but also to newer tracers, to offer a bespoke predictive model for patients with different types of cancer, and particularly in situations where there are dissociated responses or pseudoprogression.

Conclusion

Molecular imaging with [^{18}F]FDG PET/CT has enabled an earlier, more sensitive and more specific assessment of treatment response than we have ever had previously with morphological modalities such as CT and MRI. Breast cancer encompasses a heterogeneous group of tumours, which exhibit variable [^{18}F]FDG uptake; increasing understanding of the tumour biology underpinning this heterogeneity has led to the development of novel molecular probes, targeted at a specific tumour target or process. In breast cancer, the development of molecular imaging probes which can non-invasively assess factors such as whole-body receptor status could radically change management, enabling not only better treatment response assessment, but also predicting therapy response and enabling de-escalation of therapy where appropriate. The use of these agents in conjunction with [^{18}F]FDG PET/CT may have the potential to provide a more sensitive and specific assessment of disease.

Molecular imaging generates a massive amount of data; this could be harnessed by AI to generate models which could predict treatment response based on an individual patient's tumour characteristics. This could carve a path forward to improved stratification of cancer patients, individualised treatment, and avoidance of the morbidity associated with non-effective cancer treatment.

Key Points

- The use of [^{18}F]FDG PET/CT in breast cancer response assessment and monitoring is well established.
- There are limitations not only to the use of [^{18}F]FDG PET/CT in breast cancer, but also deficiencies in the current imaging assessment.
- Breast cancer is biologically heterogeneous, and heterogeneity of tumours limits the accuracy of [^{18}F]FDG PET/CT assessment in some subtypes.
- Newer targeted tracers may offer a solution in terms of more accurate response assessment and prognostication.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

Both authors contributed to the conception and design of the review. The manuscript was drafted by ARS, and was reviewed and edited by GJRC. The final version has been approved by both authors. Both authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Images are selected to be non-identifiable. Written informed consent from patients was obtained as part of original imaging research studies.

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Conflict of Interest

The authors declare no conflict of interest.

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