

Role of Positron Emission Tomography for the Monitoring of Response to Therapy in Breast Cancer

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ABSTRACT

This review considers the potential utility of positron emission tomography (PET) tracers in the setting of response monitoring in breast cancer, with a special emphasis on glucose metabolic changes assessed with ¹⁸F-fluorodeoxyglucose (FDG). In the neoadjuvant setting of breast cancer, the metabolic response can predict the final complete pathologic response after the first cycles of chemotherapy. Because tumor metabolic behavior highly depends on cancer subtype, studies are ongoing to define the optimal metabolic criteria of tumor response in each subtype. The recent multicentric randomized AVATAXHER trial has suggested, in the human epidermal growth factor 2-positive subtype, a clinical benefit of early tailoring the neoadjuvant treatment in women with poor metabolic response after the first course of treatment. In the bone-dominant metastatic setting, there is increasing clinical evidence that FDG-PET/computed tomography (CT)

is the most accurate imaging modality for assessment of the tumor response to treatment when both metabolic information and morphologic information are considered. Nevertheless, there is a need to define standardized metabolic criteria of response, including the heterogeneity of response among metastases, and to evaluate the costs and health outcome of FDG-PET/CT compared with conventional imaging. New non-FDG radiotracers highlighting specific molecular hallmarks of breast cancer cells have recently emerged in preclinical and clinical studies. These biomarkers can take into account the heterogeneity of tumor biology in metastatic lesions. They may provide valuable clinical information for physicians to select and monitor the effectiveness of novel therapeutics targeting the same molecular pathways of breast tumor. *The Oncologist* 2015;20:94–104

Implications for Practice: ¹⁸F-Fluorodeoxyglucose (FDG)-positron emission tomography (PET) is a molecular imaging exam. It can monitor breast cancer response to therapy earlier than the tumor shrinking observed with conventional imaging. This review focuses on the advantages and limits of FDG-PET for early determination of response, both in the neoadjuvant and metastatic settings. It discusses the different PET timing and metabolic criteria to define response that have been evaluated in previous studies. The development of new radiotracers of specific molecular pathways of breast cancer cells is also a challenging and promising research area to monitor the effectiveness of the new target treatments emerging in breast cancer.

INTRODUCTION

Positron emission tomography (PET) allows noninvasive visualization and quantitative assessment of many biologic processes that are modulated during therapy of breast cancer. Of these, evaluation of glucose metabolism with ¹⁸F-fluorodeoxyglucose (FDG) is the most widely used and has an evolving role in breast cancer management [1]. Because glucose metabolic changes occur earlier than tumor shrinking [2], the ability of FDG-PET to predict treatment response in individual patients has been an active field of research for many years, particularly in the neoadjuvant setting. For the

same reason, but also in the context of the heterogeneity of breast cancer metastases, FDG-PET/computed tomography (CT) has been implemented in the follow-up of metastatic breast cancer. In all cases, accurate early differentiation of responders from nonresponders using FDG-PET/CT is clinically relevant to avoid unnecessary drug toxicities and to allow an early switch of noneffective treatment.

Besides FDG, new radiotracers of specific molecular pathways of breast cancer have recently emerged. These biomarkers of receptor expression, tumor cell proliferation, or

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angiogenesis may provide valuable clinical information to select the most efficient treatment and to monitor the effectiveness of novel therapeutics.

MATERIALS AND METHODS

We searched for studies that evaluated the value of PET for monitoring the response to therapy of breast cancer. The search was performed using the electronic database PubMed (<http://www.pubmed.com>) until May 2014. The search strategy included the keywords “PET” or “PET/CT”; “breast cancer” or “breast carcinoma”; “response” or “monitoring”; “neoadjuvant” or “primary” or “metastatic”; “chemotherapy” or “hormone therapy” or “endocrine therapy”; “HER2” or “triple negative” or “luminal”; “18F-FDG” or “FDG” or “FES” or “FLT” or “15O-water”; and “glucidic metabolism” or “blood flow” or “angiogenesis.” Studies were considered eligible if they included women with breast cancer who were initiated with chemotherapy or endocrine therapy either in the neoadjuvant or metastatic settings with baseline and interim PET. Both prospective and retrospective studies were included on the condition that they were published in English in a peer-reviewed journal. Except for the ACRIN 6688 and ZEPHIR trials, both presented at the 2014 American Society of Clinical Oncology (ASCO) meeting, unpublished data, case reports, abstracts, and letters were not sought.

We screened the titles and abstracts of all potentially relevant articles to determine eligibility. All studies matching the eligibility criteria were retrieved, and bibliographies were checked for other relevant publications. The bibliographies of relevant review articles were also hand-searched to identify additional studies. If few articles were available on a precise question being address in the present review, they are mentioned. If many articles were eligible, only the ones considered to be “major articles” are mentioned. Articles were considered major either because they correspond to first pilot studies that were later corroborated, because of their good design and high impact factor of the journal in which they were published, or because of a relatively higher number of women included compared with other studies. We also searched for meta-analysis.

Although systematic literature search protocols were applied to provide an overview of the area of the present subject, the PRISMA Statement guidelines could not be entirely applied because of the extended field of the topic, the methodological heterogeneity in the literature existing, and the lack of evidence on this subject. Moreover, combining data from these heterogeneous studies would not have been appropriate.

FDG-PET IN THE NEOADJUVANT SETTING

Neoadjuvant chemotherapy (NAC) is used in large but operable breast cancer to downstage the primary tumor and increase the rate of breast conservative surgery [3, 4]. NAC also provides the opportunity to evaluate *in vivo* the breast tumor sensitivity to therapeutics. Women who achieve a pathological complete response (pCR) in the breast and axillary nodes at the end of NAC seem to have significantly improved survival [5, 6]. However, this conclusion depends on breast cancer subtype [6]. Thus, pathological examination at the end of NAC has been used as a surrogate of survival for assessing treatment efficacy,

but pathological response cannot be determined until surgery. An earlier tumoral response assessment could allow for adjusting the treatment to the individual tumor response during NAC.

Because of delayed tumor shrinking and difficulties in differentiating residual fibrosis from active tumor, conventional imaging (CI) is of limited accuracy to assess the response to NAC [2]. Because glucose metabolism is increased in breast cancer, the monitoring of the metabolic response with FDG-PET has been proposed for the early prediction of pCR [7–15]. PET uptake measures can provide a continuous indicator of response and carries information beyond the standard dichotomous evaluations usually used in other response assessments. Although interesting papers published by Dunnwald et al. [16] have shown that FDG uptake kinetic analysis may hold an advantage over static uptake measures for response assessment, the most-used parameter is the percentage decrease of the tumor maximal standard uptake value (SUV) between baseline and post-treatment exam (Δ SUV). Indeed, this parameter is easier to measure than FDG kinetic parameters in routine practice and is more reproducible among centers than absolute SUV values [17]. A study by Schwarz-Dose et al. [12], prospectively including 104 women, found that a Δ SUV superior to 45% after the first cycle predicts a pathological response with a sensitivity of 73%, a specificity of 63%, a positive predictive value (PPV) of 36%, and a negative predictive value (NPV) of 90%. Similar results were found after the second cycle of NAC, using a threshold of 55%.

Three meta-analyses were published [18–20]: results indicate that FDG-PET has reasonable sensitivity to make early predictions regarding histopathological response to NAC in breast cancer, all tumor subtypes included. Mghanga et al. [20] included 15 studies (745 patients). The pooled sensitivity, specificity, PPV, and NPV were 80.5%, 78.8%, 79.8%, and 79.5%, respectively. Mghanga et al. concluded that FDG-PET is valuable for early monitoring of breast cancer response to NAC, with a trend toward a higher sensitivity after the second course than after the first course. This meta-analysis also underlined the great heterogeneity of the monocentric studies. Indeed, the definition of the pathological response largely varies from one study to another, considering or not axillary lymph nodes involvement (Table 1). Differences in PET timing were also observed. Consequently, the thresholds of Δ SUV to define metabolic response largely differ across studies, ranging from 40% to 88% SUV decrease (Table 1). In addition to the predictive value of FDG-PET, this exam also carries an independent prognostic value: a high tumor SUV can help discriminate patients at high risk of tumor relapse [21, 22].

Since the original works published by Sorlie and Perou [23–26], gene expression profiling has led to a new molecular classification of breast cancer. A more easy-to-use, biology-based classification has arisen in clinical practice [27–30]. Both classification systems demonstrated distinct breast cancer subtypes with predictive and prognostic significance. The influence of these entities on the tumor metabolic behavior became a matter of interest.

At baseline, FDG avidity correlates with high tumor grading, high mitotic activity, negative hormonal receptor status, tumor proliferation index assessed with Ki-67: it is thus a marker of tumor aggressiveness [9, 31]. A first paper of our

Table 1. Some of the studies evaluating the predictive value of Δ SUV with FDG-PET (CT) on tumor pathological response at the end of neoadjuvant chemotherapy

Study	Patients (n)	Tumor stage	Timing of interim PET	Optimal PET timing	Number of cycles of NAC	Histological scale	Definition of pathological responders	Axillary involvement considered	Pathological responders according to definition	Optimal SUV decrease cutoff	Accuracy
Schelling et al. (2000) [7]	22	Large (T \geq 3 cm) and LABC	After 1 and 2 cycles	One and or two cycles	2–4	Honkoop	pCR and pMRD	No	29%	55% (ROC)	88% (first cycle) and 91% (second cycle)
Rousseau et al. (2006) [8]	64	Stage II–III	After 1, 2, and 3 cycles	Two cycles	4–6	Sataloff	Sataloff TA-B	No	56%	40% (ROC)	77% (first cycle) and 87% (second cycle)
Berriolo-Riedinger et al. (2007) [9]	47	Large and LABC	After 1 cycle	One cycle	4–6	Sataloff	Sataloff TA IIA-B	Yes	23%	60% (ROC)	87%
McDermott et al. (2007) [10]	96	Large and LABC	After 1 cycle, midpoint, endpoint	Between one cycle and midpoint	6 or 8	Miller-Payne	Miller-Payne grades 4 and 5	No	Not indicated	24% after 1 cycle and 58% at midpoint (ROC)	65% (first cycle) and 78% (midpoint)
Schwarz-Dose et al. (2009) [12]	104	Large (T \geq 3 cm) and LABC	After 1 and 2 cycles	One or two courses, equally	4–6	Honkoop	pCR and pMRD	No	16%	45% after 1 cycle and 55% after 2 cycles (ROC)	65% (first cycle) and 64% (second cycle)
Duch et al. (2009) [15]	50	Stage II–III	After 2 cycles	After two cycles	4	Miller-Payne	Miller-Payne grades 4 and 5	No	22%	40% (ROC)	78%
Kolesnikov-Gauthier et al. (2012) [13]	63	Large and LABC	After 1 and 2 cycles	After 1 and 2 cycles	6	Sataloff	Sataloff TA	No	21%	15% prospectively defined (EORTC)	Not indicated (sensitivity = 36%, specificity = 100%)

Abbreviations: CT, computed tomography; EORTC, European Organization for Research and Treatment of Cancer; FDG, fluorodeoxyglucose; LABC, locally advanced breast cancer; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; PET, positron emission tomography; pMRD, pathological minimal residual disease; ROC, receiver operating characteristic curves; SUV, standard uptake value; T, tumor.

institution, confirmed by other studies, demonstrated that both the tumor metabolism at baseline and the metabolic response after the first cycle of treatment are highly dependent on the tumoral subtype [32–34]. Thereafter, different metabolic patterns have been identified in each of the three main biologic subtypes of breast cancer.

HER2-Positive Subtype

Approximately 20% of invasive breast cancers overexpress human epidermal growth factor 2 (HER2). This subtype is highly proliferative, but its prognosis has been strongly improved with the advent of trastuzumab [35–37]. Because new therapies are available in this subtype (i.e., dual anti-HER2 blockage, the addition of an antiangiogenic drug), the early identification of poor-responding women after a first line of trastuzumab/cytotoxic drugs is an important clinical issue.

Initial results were conflicting because two studies demonstrated a good value of early FDG-PET/CT to predict pCR [38, 39], contrasting with the results of Koolen et al. [40, 41]. The two positive studies found that absolute residual SUV at interim PET was the best predictive marker. Groheux et al. [38] found that a tumor and axillary SUV $<$ 3.0 after two cycles of NAC was a good predictor of a pCR (PPV = 92%, NPV = 88%, accuracy = 90%). Although Humbert et al. [39] found tumor SUV $<$ 2.1 to be the optimal cutoff after the first cycle (PPV, NPV, and accuracy = 76%). Contrary to Humbert et al., trastuzumab was introduced after four cycles of NAC in Groheux's study, explaining the lower early tumor response. Both studies found a lower predictive value of Δ SUV. Nevertheless, the strength of Δ SUV is to be less affected by technical factors than absolute SUV and to be more reproducible among centers in multicentric trials [17], and its predictive value can be improved by the exclusion of low metabolic tumors at baseline [39].

The neo-ALTTO study enrolled women with HER2+ breast cancer and compared metabolic response to neoadjuvant lapatinib and/or trastuzumab. In 66 women, FDG-PET/CT was performed at baseline; at weeks 2 and 6, pCR rate was twice as high for PET responders than nonresponders (week 2: 42% vs. 21%, $p = .12$; week 6: 44% vs. 19%, $p = .005$). The authors concluded that FDG-PET/CT is efficient for monitoring the tumor response to neoadjuvant anti-HER2 therapy alone [42].

Coudert et al. [43] planned the AVATAXHER multicentric phase 2 randomized trial to assess the benefit of adding bevacizumab after the second cycle of treatment in women who responding poorly (Δ SUV $<$ 70%) to trastuzumab/docetaxel. The addition of bevacizumab for women with a poor metabolic response increased the pCR rate from 24% to 43.8%. This is the first study suggesting that tailoring the NAC regimen to the early metabolic response might be of clinical benefit. The prognostic value of the metabolic response in this subtype has not been evaluated yet.

Triple-Negative Subtype

Approximately 15% of breast cancers are triple-negative (negative estrogen and progesterone receptors, no HER2 overexpression) [44]. It is a highly chemosensitive subtype with a pCR frequently reached, but the prognosis remains poor, particularly when pCR is not achieved at the end of NAC [6, 45, 46].

This aggressive subtype has the highest baseline SUV [32, 33, 47]. In the recent study of Groheux et al. [48], 50 patients were included. Interim FDG-PET/CT was performed after the second course of NAC. The mean Δ SUV of the primary tumor was -72% in the pCR group versus -38% in the non-pCR group ($p < .0001$). Using a 50% cutoff, Δ SUV was the best PET parameter to predict pCR, corroborating previous results [40, 49]. Interim PET was also associated with patient outcome: the 3-year event-free survival was 77.5% in metabolic responders (Δ SUV $\geq 42\%$) versus 47.1% in nonresponders (Δ SUV $< 42\%$).

The main limit is the heterogeneity of the NAC regimen used across studies and the usual switch to another regimen at midpoint of NAC in triple-negative (TN) breast cancer. Two previous studies showed that Δ SUV is dependent on the type and sequence of drugs used [32, 50]. Therefore, the observed metabolic response may not be sustained after the switch. Care must be taken when interpreting FDG-PET in settings of TN women with a midcourse switch.

Luminal/HER2-Negative Subtype

Despite a favorable prognosis, the luminal subtype usually has a low chemosensitivity. pCR is rarely achieved [29], and an intermediate tumor reduction allowing a conservative surgery is a more reasonable aim. Because NAC is controversial in this low chemosensitive subtype, there is a need for early biomarker to predict which luminal tumors will respond to NAC.

When primary tumor has a low pretherapy uptake, the ability of PET to detect it and to assess its response is limited [10, 51]: this limitation is usually observed in the luminal/HER2 subtype, which has the lowest baseline SUV and Δ SUV [32, 33]. Moreover, because pCR is rare in this subtype, previous studies failed to demonstrate its prediction with FDG-PET [41, 52, 53]. Koolen et al. [41] found that Δ SUV was predictive of "near pCR," allowing few scattered cells, but the prognostic value of this definition is controversial [6]. In this subtype, the metabolic tumor volume could be more accurate than the SUV to predict the response [52, 54].

Because pCR is very uncommon, a study of our institution directly assessed the prognostic value of PET [53]. We demonstrated that tumor metabolism at baseline, and changes after the first course were early surrogate markers of 5 years of patient survival, independently of the pathologic response. We were able to identify a subgroup of patients with a high risk of relapse (5-year relapse-free survival [RFS] of 33%) based on a high baseline tumor metabolism and a low metabolic response following one cycle of chemotherapy. In contrast, patients with a low baseline tumor metabolism or a high baseline tumor metabolism followed by a good metabolic response had a low risk of relapse (5-year RFSs of 93% and 88%, respectively). Moreover, the baseline tumor metabolism was strongly correlated with tumor proliferation index: low-metabolic luminal tumors had low Scarff-Bloom-Richardson grade and Ki-67 expression, contrary to hypermetabolic ones, which presented increased proliferation indexes and mainly belonged to the luminal B subtype.

FDG-PET IN THE METASTATIC SETTING

Contrary to the neoadjuvant setting, the pathological response generally cannot be obtained in the metastatic setting. Because a change in tumor size is an indicator of outcome in the treatment of many solid tumors [55], it is the most

frequently used surrogate endpoint to evaluate therapeutic effects in metastatic disease. Anatomic imaging is used for this purpose (predominantly ultrasound, CT, or magnetic resonance imaging [MRI]). The Response Evaluation Criteria in Solid Tumors (RECIST) have been defined [56] and updated [57] to standardize this response assessment.

However, criteria based on the size of tumors are limited because new targeted therapies are more cytostatic than cytotoxic. Moreover, change in tumor size is also not a good surrogate of bone lesion response, and the RECIST 1.1 criteria specify that bone lesions without soft tissue components cannot be considered as measurable [57]. This is a major limitation because bone is the preferential site of breast cancer metastases [58, 59].

In order to overcome this problem, the University of Texas M.D. Anderson Cancer Center has developed more specific response criteria for bone metastases response monitoring (MDA Criteria), combining quantitative (size measurement) and qualitative (sclerotic bone reaction) assessments [60, 61]. Despite such efforts, Hayashi et al. [62] found that the MDA criteria predicted progression-free survival at 6 months, but not earlier. Indeed, because morphologic imaging does not directly reflect tumor cell viability, but rather the secondary effect on bone adjacent tissue, morphologic changes are often delayed during chemotherapy [63] and do not seem to correlate with the presence of residual active tumor [64]. Moreover, a "flare" reaction can be assessed on CT or bone scan, corresponding to the sclerotic healing (Fig. 1), making the response evaluation difficult [60, 65].

In contrast, PET reflects cellular and molecular changes of tumor cells occurring before tumor shrinking, as demonstrated in 1993 by Wahl et al. [2]. In 2002, Stafford et al. [66] published preliminary results showing that changes in tumor FDG uptake with therapy were correlated with the overall clinical assessment of response ($p < .01$) and concluded that serial FDG-PET can help in bone response assessment. This was corroborated by Schwarz-Dose et al. [67], who included 11 patients with 26 metastatic lesions in first-line therapy: metabolic tumor changes, evaluated after the first and second courses of chemotherapy, correctly predicted the final clinical response in all women. Regarding the optimal timing for interim PET, Couturier et al. [68] had conflicting results: they found that PET changes after the third cycle of chemotherapy, but not after the first, predicting the clinical response after six cycles and overall survival. Tumor metabolic early change as a surrogate of survival in bone-dominant metastatic breast tumor response was later confirmed by Specht et al. [69]. A greater than 41% decline in SUV of the most hypermetabolic lesion at baseline was associated with a longer time to progression ($p < .005$). However, this study was retrospective with a large interval between PET exams ranging from 1 to 17 months. Cachin et al. [70] also found that a complete PET response after completion of high-dose chemotherapy (maximum three cycles) can more powerfully stratify for survival than conventional imaging (including CT).

Later, the development of integrated FDG-PET/CT has improved the accuracy of the response evaluation beyond that achievable by PET alone by adding information on bone morphological changes, particularly interesting for bone metastases (Fig. 1). Indeed, FDG uptake reflects the metabolic

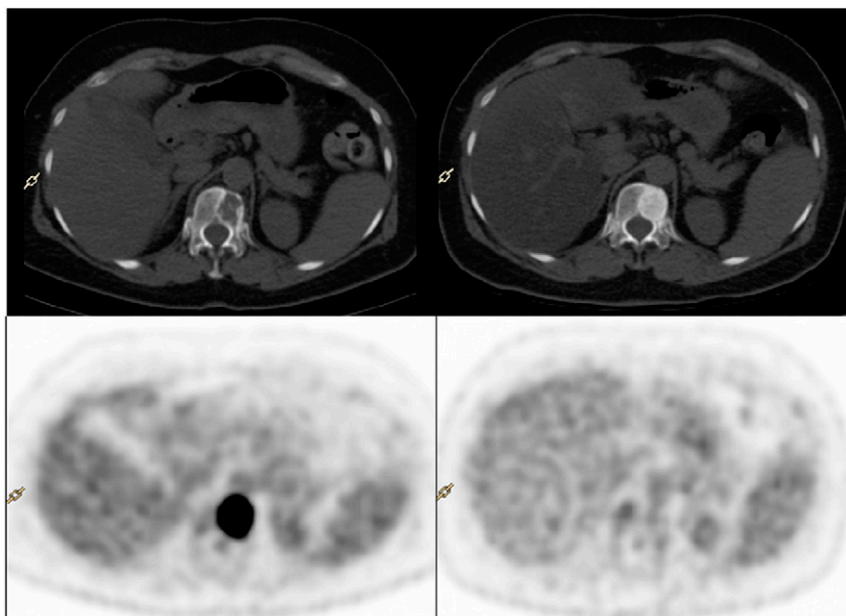


Figure 1. Example of fluorodeoxyglucose-positron emission tomography (PET)/computed tomography (CT) exam before (left) and after (right) 3 months of eribulin and trastuzumab therapy in a woman with an osteolytic metastases of breast cancer, located on TH12. After treatment, CT showed an important sclerotic reaction of the bone lesion, whereas PET showed no more metabolic activity. Both the anatomic and molecular imaging are in favor of a good response to systemic treatment.

feature of bone metastases independently of their CT pattern (osteoblastic and osteoclastic) [64].

Tateishi et al. [71] retrospectively compared the prognostic value of morphologic and metabolic changes in bones metastases in patients with metastatic breast cancer, both evaluated with a FDG-PET/CT. One hundred and two women treated with first-line hormone-chemotherapy were included. PET/CT was performed at baseline and after treatment (mean: 28 days; range: 21–38 days). Only the metastatic lesion that exhibited the most substantial uptake was selected as the target lesion for response. Results showed that an increase in CT attenuation and a decrease in SUV of bone metastases were associated with response duration. Multivariate analysis showed that a decrease in SUV of 8.5% or more was the only significant predictor of long response duration. This Δ SUV threshold differs from that of Specht's study (41%), possibly in relation with the difference of time between PET exams [69].

Thus, many studies have demonstrated that FDG-PET/CT is more accurate than morphologic CI for early monitoring of response to therapy, with a good prognostic stratification [64, 71]. FDG-PET/CT may emerge as a standard of care in bone metastatic breast cancer.

Evaluation of Response to Endocrine Therapy

Endocrine therapy is an efficient and low-toxicity treatment in metastatic hormone-positive (HR) breast cancer. It is often used as the first line treatment [72], but only 30%–50% of women with HR+ metastatic disease respond to first-line hormonotherapy [73, 74]. It may be explained by the heterogeneity of HR expression in the metastases, the sampling error of a one-site biopsy, and the presence of non-functional estrogen receptors (ERs). Thus, identification of other predictive biomarkers of the tumor hormone sensitivity remains an important clinical issue.

In responding tumors, an early increase in FDG uptake has been described 7–10 days after introduction of tamoxifen therapy [75]. This metabolic flare reaction may be explained by an initial increase in cell growth caused by an agonist effect of therapy and implies that ERs are functional. Thus, it is an early predictor of tumor sensitivity to endocrine therapy [75, 76]. In contrast, because antiaromatase therapy lowers estradiol level and thus reduces the tumor agonist effect, responding patients shows an early drop in tumor FDG uptake after antiaromatase induction [77]. Dehdashti et al. [78] demonstrated that an estradiol challenge (30 mg of estradiol), initiated before the antiaromatase therapy, can restore the metabolic flare that both predicts tumor response and longer overall survival. Only one study has evaluated the relevance of FDG-PET/CT for the delayed monitoring of metastatic breast cancer treated with endocrine therapy. PET/CT exams were performed at baseline and after 10 ± 4 weeks [79]. Using cutoffs of 25% SUV increase or decrease, progressive, stable, and partial metabolic response disease showed median progression-free survival times of 6, 27, and 20 months, respectively ($p < .0001$). FDG-PET/CT can thus be used for the delayed monitoring of response to hormone therapy, usually indicated for bone-dominant metastatic cancer, in which morphological modalities often fail to assess tumor response [60, 64].

Because antiaromatase therapy lowers estradiol level and thus reduces the tumor agonist effect, responding patients shows an early drop in tumor FDG uptake after antiaromatase induction. Dehdashti et al. demonstrated that an estradiol challenge, initiated before the antiaromatase therapy, can restore the metabolic flare that both predicts tumor response and longer overall survival

Limitations

All the studies previously mentioned were monocentric, and most of them were retrospective. They suffer from a lack of consensus on the optimal PET timing and metabolic criteria to use for response evaluation, compared with RECIST. Consequently, the 2012 NCCN Guidelines have pointed out this lack of standardization as a key limitation for using FDG-PET/CT in the metastatic setting of breast cancer, emphasizing the need of further prospective studies [80].

Currently, two sets of response criteria using PET are available: those developed by the European Organization for Research and Treatment of Cancer [81] and the PET Response Criteria in Solid Tumors (PERCIST) [82]. These criteria are still matters of debate. One first critical point is that the metabolic response is highly influenced by the cancer genomic and immunohistological subtype and by the treatment [32]. The optimal criteria therefore need to be adapted to each situation.

A second limit is that PERCIST, like RECIST, evaluates change of SUV only in the most active lesion(s), without considering the frequently observed intraindividual heterogeneity of the response among lesions in metastatic breast cancer. FDG-PET/CT being a whole body evaluation of metastases with a unique procedure is much more reliable than conventional imaging to identify a mixed response (Fig. 2). Huyge et al. [83] have performed serial FDG-PET/CT in women with bone-dominant metastatic breast cancer. Coexistence of responding and nonresponding metastatic lesions was observed in 43% of women with a trend toward an intermediate outcome in these patients, compared with women with homogeneous response or nonresponse.

To create the reproducibility that is needed in multicentric trials, further multicentric studies should thus be conducted to define robust standardized metabolic criteria in the monitoring of metastatic breast cancer, taking into account the various subtypes of breast cancer, the treatments used, and the heterogeneity of response among metastases.

NEW TRACERS OF OTHER MOLECULAR PATHWAYS FOR BREAST TUMOR RESPONSE EVALUATION

Recent identification of molecular alterations in key proteins involved in breast cancer cell proliferation has led to the development of new target therapies. Specific biomarkers are required to evaluate these molecular pathways.

Furthermore, breast cancer is a heterogeneous tumor made up of different cell clones [84, 85]. Imaging tracers have the advantage of taking into account the heterogeneity of tumor biology in metastatic lesions, whereas biopsies are subject to sample error.

Contractor et al. have recently demonstrated that changes in FLT-PET uptake within 2 weeks after initiating the first or second cycle of docetaxel can predict the anatomic response at midtherapy (after three cycles) with good sensitivity and is correlated with the decrease of circulatory tumor cells.

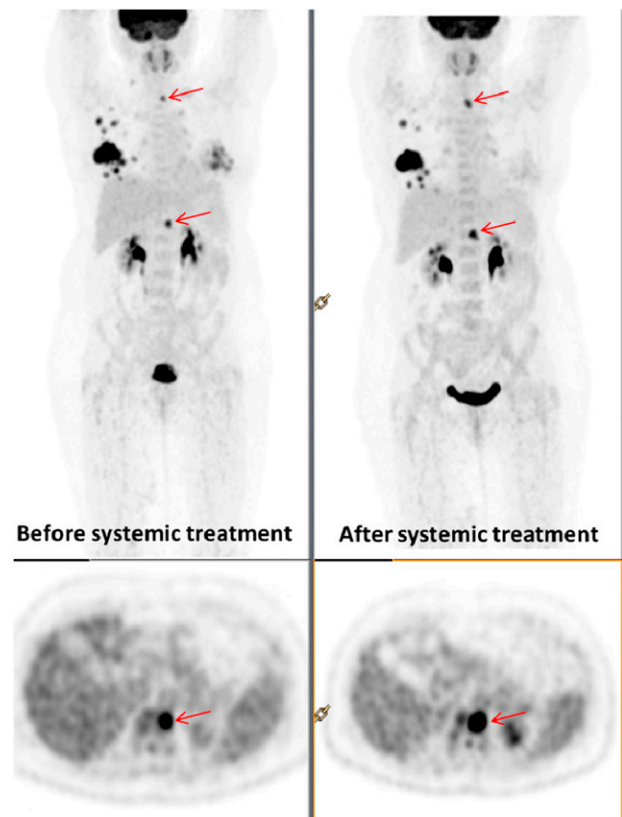


Figure 2. Discordant response between bone and visceral metastases on fluorodeoxyglucose (FDG)-positron emission tomography (PET) exams performed before (left) and after (right) 3 months of treatment with gemcitabine-trastuzumab. Baseline FDG-PET shows hypermetabolic activity in bilateral and multifocal breast tumors, lymph node involvement of right axilla, and bone metastases. After treatment, PET demonstrated an heterogeneous metabolic response with coexistence of responding (left breast, axillary nodes) and nonresponding metastatic bone lesions (red arrows, moderate increased in focal uptake of the two bone lesions).

Changes in Tumor Cell Proliferation

Proliferation is one of the key behaviors of cancer and is thus particularly attractive in cancer imaging. The most studied PET proliferation tracer is ^{18}F -fluorothymidine (FLT). Its uptake depends on the activity of thymidine kinase-1, overexpressed during the S phase of the cell cycle [86, 87]. Its use is limited by a lower uptake than FDG [88], and a high physiological uptake in the liver and in bone marrow limits its use for evaluating metastases in these organs [88]. The main advantage of FLT is its lower accumulation caused by tumor inflammation [89–91], which may reduce the false-positive effects of inflammatory reaction encountered with FDG-PET. Small studies have shown that FLT could reflect treatment effectiveness earlier than anatomic imaging [92–94]. Contractor et al. have recently demonstrated that changes in FLT-PET uptake within 2 weeks after initiating the first or second cycle of docetaxel can predict the anatomic response at midtherapy (after three cycles) with good sensitivity [93] and is correlated with the decrease of circulatory tumor cells [94]. In the neoadjuvant setting, the few studies are contradictory. A recent study including 20 women has reported disappointing results: FLT breast tumor uptake at

baseline was correlated with baseline Ki-67 ($p = .006$), but the decrease after the first cycle of NAC did not predict pathological response [95]. In contrast, preliminary results of the ACRIN 6688 multicentric trials, presented at the 2014 ASCO meeting, found that FLT-PET after the first cycle of NAC was marginally predictive of pCR in 51 women [96]. Further works are warranted to establish the exact clinical role of FLT for monitoring breast tumor response, compared with FDG.

Changes in Tumor Blood Flow and Angiogenesis

Angiogenesis is an important hallmark of tumor growth [97] and has become a therapeutic target in breast cancer. Imaging of changes in tumor flow during therapy is an important clinical issue to evaluate the efficacy of these drugs.

The Seattle group has assessed perfusion in breast cancer using ^{15}O -labeled water [34, 98–101]. They determined that blood flow decrease after 2 months of therapy can predict tumor response and outcome in women receiving NAC [99, 100]. Moreover, locally advanced breast cancer tumors with a baseline flow-glycolytic metabolism mismatch (low tumor blood flow but high glycolytic metabolism) are more resistant to therapy, predicting a low likelihood of pCR and higher risk of early relapse [98, 101]. This mismatch is more common in triple-negative tumors [34].

In a few papers, determination of tumor blood flow and metabolism with a single injection of FDG was suggested to be an alternative to the less available ^{15}O -water. Indeed, dynamic FDG-PET can indirectly evaluate blood flow using a two-compartment model [100, 102], but it requires an acquisition of 1 hour. Mullani et al. [103] used a shorter first-pass method to calculate blood flow by dynamic imaging 2 minutes after FDG injection: it was linearly correlated with the ^{15}O -water method. Cochet et al. [104] demonstrated that, in breast cancer, blood flow determined with this first-pass FDG method was correlated with tumor angiogenesis evaluated by immunohistochemistry.

Other molecular pathways have been studied. $\alpha_v\beta_3$ integrin is a protein expressed on activated endothelial cells during angiogenesis. It is involved in tumor growth, local invasiveness, and metastatic spread [105]. Promising PET tracers have been developed to image this protein: ^{18}F -galactorGD is the most studied one [105–107]. In breast cancer, a clinical study demonstrated elevated and highly variable $\alpha_v\beta_3$ expression in primary tumor, assessed with PET [105].

Vascular endothelial growth factor (VEGF) is a molecular target of the monoclonal antibody bevacizumab. When labeled with 89-zirconium (^{89}Zr), bevacizumab preserves its VEGF-binding properties. ^{89}Zr -Bevacizumab tumor uptake correlated with VEGF tumor levels [108] and might be valuable for prediction and evaluation of the effect of VEGF-targeting therapeutics. In the near future, the development of a PET/MRI integrated system will permit the combination of imaging of molecular targets using PET tracers and study of perfusion using MRI [109].

Estrogen Receptor Tumor Expression

Approximately 70% of women with breast cancer have ER-positive tumors. Currently, because distant metastases are numerous and not easily accessible for biopsies [110], patients with metastatic breast cancer are usually stratified according to the immunohistochemistry analysis of the primary tumor,

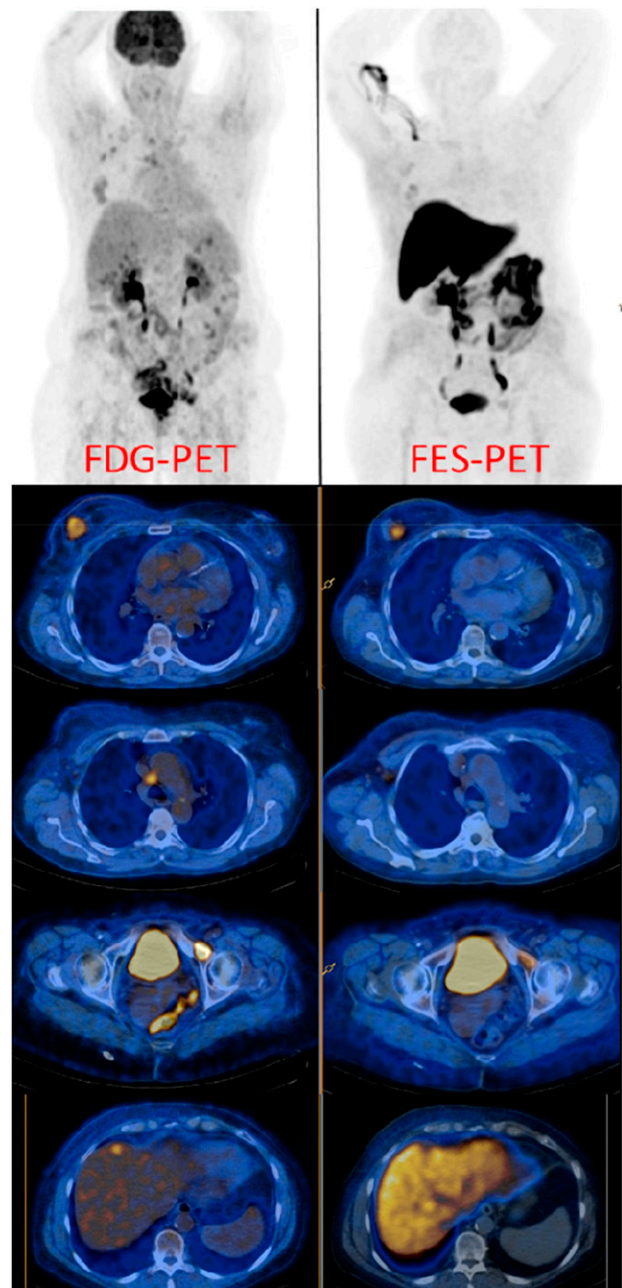


Figure 3. FDG-PET exam (left) and FES-PET exam (right) of a woman with metastatic breast cancer. The tumor lesions, assessed with FDG-PET, showed heterogeneous expression of estrogen receptors: primary breast tumor had a high but heterogeneous uptake pattern of FES, mediastinal nodes showed no significant FES uptake, and the bone metastasis on the left ischiopubic branch showed weak FES uptake. The liver metastasis was not evaluable with FES-PET because of the high physiological uptake of the liver (images are obtained from Estrotepredic Programme Hospitalier de Recherche Clinique, coordinator: Dr. K. Kerrou, Hôpital Tenon, Assistance-Publique–Hôpitaux de Paris, Paris; Eudract: 2011-005043-27).

Abbreviations: FDG, fluorodeoxyglucose; FES, $^{16\alpha}\text{-}^{18}\text{F}$ -fluoro- $^{17}\beta$ -estradiol; PET, positron emission tomography.

but approximately 40% of them have discordant ER expression across lesions [111]. PET with $^{16\alpha}\text{-}^{18}\text{F}$ -fluoro- $^{17}\beta$ -estradiol (FES) can characterize and quantify the in vivo functional status of ER expression in all tumor lesions within one patient (Fig. 3).

Table 2. Studies evaluating the prediction of response with FES-PET in women with estrogen receptor-positive breast cancer

Study	Number of patients	Stage	Main goal	Conclusions
Dehdashti et al. (1999) [76]	11 postmenopausal women	Metastatic breast cancer	To investigate whether FES and FDG-PET, performed both before and 7–10 days after initiation of tamoxifen, can predict hormonally responsive breast cancer	Increase in FDG uptake and the degree of ER blockage, evaluated by FES uptake decrease after the initiation of tamoxifen, predicted response
Mortimer et al. (2001) [75]	40 postmenopausal women	Locally advanced, recurrent, or metastatic	To investigate whether FES and FDG-PET, performed both before and 7–10 days after initiation of tamoxifen, can predict hormonally responsive breast cancer	Increase in FDG uptake, baseline FES uptake and decrease in FES uptake 7–10 days after the initiation of tamoxifen predicted response
Linden et al. (2006) [113]	47	Metastatic breast cancer	To quantify tumor FES uptake to predict response to salvage hormonal treatment in heavily pretreated metastatic breast cancer patients, predominantly treated with aromatase inhibitors.	Absence of FES uptake (SUV <1.5) predict failure of endocrine therapy; may help to guide treatment selection
Dehdashti et al. (2009) [78]	51 postmenopausal women	Locally advanced or metastatic	To predict the response to endocrine therapy (aromatase inhibitor or fulvestrant) with baseline FES-PET and FDG-PET before and after challenge with 30 mg of estradiol	Baseline FES uptake (SUV ≥2) and metabolic FDG flare after estradiol challenge can predict the response to therapy
Linden et al. (2011) [120]	30	Metastatic	To measure changes in FES uptake during treatment with aromatase inhibitor, tamoxifen, or fulvestrant	High decreases with tamoxifen and fulvestrant (54% average decline); lowest decrease after aromatase inhibitor (15% average decline)

Abbreviations: FDG, fluorodeoxyglucose; FES, 16α - ^{18}F -fluoro- 17β -estradiol; PET, positron emission tomography; SUV, standard uptake value.

Its sensitivity and specificity to detect ER+ lesions are evaluated at 84% and 98%, respectively [112]. Four studies reported the predictive value of FES tumor uptake for response to endocrine therapy in 138 patients with metastatic breast cancer [75, 76, 78, 112,] (Table 2). FES-PET was performed before introducing endocrine therapy. A tumor SUV higher than 1.5 at baseline predicts a clinical benefit with a PPV of 65% and a NPV of 88%. Thus, in patients with a previously ER+ tumor, low FES uptake in metastasis predicts nonresponse to endocrine therapy. One of these studies, including 40 women, also found that the decrease in FES uptake 7–10 days after induction of tamoxifen, corresponding to ER blockage, was greater in responders than nonresponders ($55\% \pm 14\%$ vs. $19\% \pm 17\%$, respectively) [75]. Nevertheless, the limited number of women included, the differences in optimal SUV cutoff, and the predictive value require additional studies.

Many other PET tracers are being evaluated, for example ^{89}Zr -trastuzumab [114–117]. The few studies published demonstrated a good uptake in HER2-positive liver, lung, bone, and brain metastases. The multicentric ZEPHYR trial, presented at the 2014 ASCO meeting, found promising first results for ^{89}Zr -trastuzumab as a predictive marker for trastuzumab/emtansine (T-DM1) therapy in HER2+ breast cancer [118]. Promising works are also ongoing in progesterone-receptor imaging [119].

CONCLUSION

FDG-PET is a promising early imaging biomarker of the efficacy of breast treatment. First studies demonstrated that, in the neoadjuvant setting, the metabolic response can predict final pCR after the first cycles of NAC. However, breast cancer is a heterogeneous disease, and following studies showed that tumor metabolic behavior highly depends on the various biologic subtypes of breast

cancer. In subgroup analysis, FDG-PET seems to correctly predict pCR in HER2-positive and TN subtypes, whereas it may rather be a surrogate marker of survival in luminal tumors. Rigorous prospective clinical trials are mandatory to define the optimal metabolic criteria of good and poor metabolic response for each of the three main biologic subtypes of breast cancer and answer questions about the optimal PET timing. Randomized clinical trials, evaluating different PET-based therapeutic strategies, are also needed to demonstrate a clinical benefit of an early tailoring of the neoadjuvant treatment.

In the metastatic setting, there is increasing clinical evidence that FDG-PET/CT is the most accurate and earlier imaging modality for assessment of the tumor response to treatment when both metabolic and morphologic tumor data are considered. Compared with other imaging modalities, whole-body FDG-PET/CT is particularly efficient in measuring bone metastasis response and may emerge as a standard of care.

Many therapies targeting specific molecular hallmarks of breast tumor cells have recently emerged, with encouraging and sometimes disappointing results. The concurrent development of new predictive surrogate markers of the efficacy of these treatments is required to reveal their true potential. In the future, new radiopharmaceuticals highlighting specific molecular pathways of an individual tumor may help physicians to select the optimal target therapy, leading to a more personalized treatment. The role of imaging biomarkers, compared with biological and molecular biomarkers of response (circulating tumor cells for example) will also have to be better defined.

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DISCLOSURES

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