Positron Emission Tomography and Neoadjuvant Therapy of Breast Cancer

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The increasing use of neoadjuvant therapy for breast cancer has led to the development of early surrogate markers of response. Positron emission tomography (PET) allows noninvasive study of fundamental biologic processes in the tumor; furthermore, PET provides various markers to assess tumor response early in the course of therapy. Numerous studies have shown that changes in tumor glucose metabolism during therapy are significantly correlated with final response and patient outcome. Moreover, new PET tracers that are currently being developed or under evaluation, providing specific information on tumor characteristics or receptor expression, will assist the development of new targeted anticancer agents.

Neoadjuvant therapy is now commonly used in patients with locally advanced breast cancer, as it improves surgical options and provides prognostic information (1,2). However, about 60%–90% of patients achieve clinical response, and complete pathological response is noted in 3%–30% of patients in most breast cancer trials (3,4). Thus, one of the greatest needs in neoadjuvant therapy of breast cancer is to find an early and accurate way to determine which patients are responding to therapy to avoid the toxicity and cost of ineffective therapy and to allow a change to more effective treatment for the individual patient. This is central to the concept of personalized medicine. In this setting, there is an increasing interest in functional imaging, particularly with positron emission tomography (PET). PET allows noninvasive visualization and quantitative assessment of many biologic processes that are modulated during therapy and generally precede morphologic changes. Of these, evaluation of glucose metabolism with ¹¹C-fluorodeoxyglucose (FDG) is the most widely used, based on the well known increased glucose requirement of cancer cells described as the Warburg phenomenon (5). Cellular uptake of FDG is influenced by multiple mechanisms involved in malignant cellular transformation, including both intrinsic cell function like increased proliferation and micro-environmental factors like hypoxia (via hypoxia-inducible factor, which activates glycolysis and the expression of glucose transporters) (6). Furthermore, multiple new PET tracers are under evaluation that could also play a role for prediction or early evaluation of response to therapy. Magnetic resonance imaging also provides functional imaging techniques like dynamic contrast-enhanced magnetic resonance imaging (7), diffusion-weighted imaging (8), and magnetic resonance spectroscopy (9), which have all shown promising results as surrogate markers of response to neoadjuvant therapy of breast cancer. We suggest the lecture of a recent review article on that field (10).

This article considers potential utility of PET tracers in the setting of neoadjuvant therapy of breast cancer with a focus on radiotracers that have been studied in the clinical arena (Table 1), and with the exclusion of neoadjuvant radiotherapy, because to our knowledge, the utility of PET tracers has not been studied in this setting.

PET and Cytotoxic Chemotherapy

Conventional cytotoxic chemotherapy is the most widely used therapeutic approach in the neoadjuvant setting and has been the scenario in which PET tracers, in particular FDG, have been most commonly evaluated. Indeed, it had been established almost 20 years ago that FDG tumor uptake generally decrease during and after chemotherapy; furthermore, residual tumor FDG uptake after completing neoadjuvant chemotherapy (NAC) predicts residual disease and is highly predictive of relapse (11–15). Moreover, early prediction of tumor response during the course of NAC using serial FDG PET scans has been most widely evaluated during the past 10 years, using a comparison to histopathology assessment of response from the post-surgery specimen as a gold standard. In particular, the degree of change in FDG tumor uptake between baseline and after one or two courses of NAC is correlated with histopathologic response after the completion of therapy (12,16–24). This approach appears to be of particular interest because it might offer an early opportunity to change therapeutic strategy in case of inefficacy. All these studies determined a threshold value of decrease in FDG uptake to predict response to NAC: This cutoff varies from 20% to 60% after one course of NAC, with sensitivity from 61% to 100% and specificity from 53% to 96% (12,16–19, 21), and from 40% to 55% of baseline uptake after two courses of NAC, with sensitivity from 69% to 100% and specificity from 30% to 95% (16, 17,21–24). Thus, this specific threshold value varies dramatically across studies, in particular when determined after only one course of chemotherapy. There are several factors that could explain such differences. First, there is a great heterogeneity regarding the definition of histological response, and all these studies do not take into account the phenotypic diversity of breast cancer. For example, it is
...well established that patients with triple-negative breast cancer have a higher pathological response rate to anthracycline-based treatment when compared with patients with non–triple-negative breast cancer (41,42), but patients who do not exhibit a pathological complete response have significantly worse survival if they have triple-negative breast cancer (43); for patients with hormone-positive breast cancer, obtaining a pathological complete response is less critical in term of survival. Thus, to determine an optimal threshold of decrease of FDG uptake, it appears worthwhile to define consensus criteria of pathological response, which take into account tumor characteristics (41).

These studies also exhibit a great heterogeneity concerning imaging protocol, data analysis, and the chemotherapy protocol used. A recent study showed that in a patient receiving sequential chemotherapy, the drug sequence (docetaxel followed by anthracyclines or the drugs in reverse order) could influence the decrease of tumor FDG uptake after four cycles of chemotherapy and then substantially modify the determination of a cutoff value (42). Thus, further large multicenter studies are required to standardize imaging protocols and define criteria for evaluating the significance of changes in FDG uptake that are adapted predicting benefit in a given breast cancer phenotype from a specific therapy. Importantly, as most biological processes are subject to homeostatic control, the concept of a threshold above which response is guaranteed and below which failure is assured is almost certainly too simplistic. Nevertheless, most therapeutic monitoring trials have used post hoc analysis to define such a threshold that best separates patients who do and do not achieve a response according to whatever gold standard has been selected.

Besides questions regarding how best to analyze changes in tumor glucose metabolism, FDG also has some important biological limitations. First, increased FDG is not a specific feature of malignant cells: The tendency of FDG to accumulate in inflammatory tissues can complicate the interpretation of mid-therapy images. Second, chemotherapy may cause an initial increase of FDG uptake because of the activation of energy-dependent cellular repair mechanisms. Thus, it has been recommended that assessment of tumor response should not be performed until several weeks after beginning of chemotherapy (43).

Given these limitations, more specific tracers are under evaluation, in particular tracers of cellular proliferation. Of these, 3′-deoxy-3′-18F-fluorothymidine (FLT), an analog of thymidine, is the most extensively studied. FLT uptake is dependent on the cellular activity of thymidine kinase. Because thymidine kinase activity generally reflects the proliferative state of the cell, the rate of cellular trapping of FLT provides an indirect measure of thymidine incorporation into DNA and therefore an approximate measure of cellular proliferation. It has been demonstrated that FLT uptake is significantly better than FDG uptake as a measure of tumor proliferation (34). Moreover, one of the particular interests of FLT, beyond specificity, is its capacity to predict very early response to therapy, 1 or 2 weeks following beginning of NAC (35).

Finally, beyond the choice of the tracer to determine response to NAC, an interesting option could be to combine simultaneous evaluation of multiple tumor characteristics. For example, Dunnwald et al. (20) suggested that the combined evaluation of glucose metabolism with FDG and perfusion with 18O-water could have an interest to predict survival following NAC, paving the way for a multimodality approach in this setting.

Table 1. Positron emission tomography tracer available for monitoring response of breast cancer to neoadjuvant therapy

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Function</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>18F-fluorodeoxyglucose (FDG)</td>
<td>Glycolysis</td>
<td>(11–33)</td>
</tr>
<tr>
<td>18F-fluorothymidine (FLT)</td>
<td>Proliferation</td>
<td>(34,35)</td>
</tr>
<tr>
<td>18F-16α-17β-fluoroestradiol (FES)</td>
<td>Estrogen receptor expression</td>
<td>(28–30)</td>
</tr>
<tr>
<td>11C-choline</td>
<td>Membrane synthesis</td>
<td>(36)</td>
</tr>
<tr>
<td>18Ga-labeled DOTA-2-Z-17β-estradiol (ABY-002)</td>
<td>HER2 expression</td>
<td>(37)</td>
</tr>
<tr>
<td>15O-water</td>
<td>Perfusion</td>
<td>(20)</td>
</tr>
<tr>
<td>18F-galacto-RGD</td>
<td>Integrin αvβ3 expression</td>
<td>(38)</td>
</tr>
<tr>
<td>18F-fluoromisonidazole (FMISO)</td>
<td>Hypoxia</td>
<td>(39)</td>
</tr>
<tr>
<td>18F-fluoropacitaxel (FPAC)</td>
<td>Paclitaxel distribution</td>
<td>(40)</td>
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PET and Endocrine Therapy

Neoadjuvant endocrine therapy has gained wide acceptance for estrogen receptor (ER)–positive breast cancer because of its recognized efficacy in the adjuvant setting and the fact that conventional cytotoxic chemotherapy may be less effective in ER-positive breast cancer. However, about 40% of patients with ER-positive breast cancer do not show an objective clinical response to neoadjuvant endocrine therapy. Thus, the development of ER imaging agents for PET, of which the most successful has been 18F-16α-17β-fluoroestradiol (FES), appears to be worthwhile. Indeed, the tumor uptake of FES PET appears to be predictive of clinical response to endocrine therapy (28–30). However, these studies were performed on metastatic disease or in mixed population of locally advanced and metastatic breast cancer.

FDG has also been used in the setting of monitoring response to endocrine therapy with intriguing results. Serial FDG PET showed that an early increase in FDG uptake in response to an estrogen agonist (performed from 1 to 10 days after administration) predicted the response to endocrine therapy and subsequent patient outcome (28,30), suggesting that this metabolic flare could be a marker for the activation of estrogen signaling in the tumor. Moreover, the combined in vivo evaluation of baseline ER expression (FES uptake) and metabolic flare reaction (early changes in FDG uptake) seems to have a complementary utility for predicting response to tamoxifen (28). In contrast, FDG uptake later (4 weeks) after beginning of neoadjuvant letrozole shows a decrease of tumor metabolism, well correlated with cell cycle response monitored by Ki67 (31). These changes in glucose metabolism during the course of endocrine therapy seems to be correlated with changes in cell proliferation, even if results of a recent preclinical study suggest that the initial increased uptake of FDG occurring after estrogen stimulation is mediated by nonnuclear ER and is associated with increased activity of PI3K/Akt pathway, a pathway important in mediating resistance to cell death (32). Thus, FDG...
uptake during neoadjuvant endocrine therapy is probably the result of numerous and complex in vivo influences and requires further clinical trials to be definitely accepted as a relevant marker of response, alone or associated to other imaging markers.

PET and Trastuzumab

Approximately 20% of breast cancer present an overexpression of the HER2, which is associated with response to the anti-HER2 antibody trastuzumab (Herceptin). In the setting of neoadjuvant therapy, the addition of trastuzumab to conventional cytotoxic chemotherapy improves the rate of complete response and of event-free survival. However, the various mechanisms of action of trastuzumab give rise to various mechanisms of resistance, and complete response rates remain at only about 40%.

A recent preclinical study showed a significant decrease of FDG uptake in tumor overexpressing HER2, 2 weeks after beginning of trastuzumab therapy (33). However, clinical information is lacking because most of the clinical studies evaluating the role of FDG PET monitoring of neoadjuvant therapy did not study trastuzumab or did not independently analyze patients receiving trastuzumab in association with chemotherapy compared with patients receiving only conventional chemotherapy (18).

Choline metabolism is closely associated with membrane metabolism and intracellular signaling. The incorporation of radiolabeled choline by tumor cells has been shown to be associated with proliferation; so it would be expected that therapy response might be accompanied by changes in the incorporation of \(^{11}C\)-Choline. Kenny et al. (36) demonstrated that uptake of \(^{11}C\)-Choline by four patients responding partially or completely to trastuzumab treatment was lower than pretreatment uptake, suggesting that \(^{11}C\)-Choline PET may be useful in detecting the response of breast cancer to trastuzumab treatment. This interesting option needs to be confirmed in larger populations.

Another option is to directly target HER2, given the idea that in vivo evaluation of HER2 expression before and during trastuzumab therapy could permit to both predict and monitor tumor response. However, this approach is limited by the size of antibodies targeting HER2 (like trastuzumab), limiting their tumor penetration and clearance. That is why smaller molecules with same affinity for the target, like diabodies or affibodies, are under development. Baum et al. (37) recently administered to three breast cancer patients \(^{68}Ga\)-labeled DOTA\(^{-}\)-Z\(^{\alpha\beta}\)-peptide (ABY-002), showing the feasibility of this approach.

Future Directions

Numerous novel targeted therapeutic agents have been recently developed, reflecting increasing evidence that breast cancer is a heterogeneous disease. However, this individualization of therapy has led the increasing need of tools to specifically characterize and rapidly evaluate treatment effects. Accordingly, different approaches can be considered for the development of new imaging agents. The first approach is to develop imaging of particular biological characteristics of cancerous lesions, such as angiogenesis or hypoxia.

Antiangiogenic agents such as bevacizumab are now approved by the US Food and Drug Administration for use in various cancers even though their role in neoadjuvant therapy is still under debate. PET imaging provides many tools to evaluate tumor perfusion, of which \(^{15}O\)-water is the more recognized. However, because of the 2-minute half-life of \(^{15}O\), only a few research centers with a cyclotron on-site are able to use \(^{15}O\)-water. An exciting alternative is imaging of the expression of the integrin \(\alpha\beta\), with \(^{18}F\)-galacto-RGD, as it is highly expressed on activated endothelial cells but also on breast cancer cells in lesions with neovascularization. The development of this imaging agent is based on the fact that many integrins, including \(\alpha\beta\), bind to the tripeptide sequence arginine-glycine-aspartic acid (single letter code RGD) of different matrix proteins. A generally elevated and highly variable uptake of \(^{18}F\)-galacto-RGD on primary and metastatic human breast lesions has been demonstrated (38). Nevertheless, the implications of this for monitoring antiangiogenic therapy have to be determined.

PET tracers that detect hypoxia may also be useful because hypoxic tumors tend to be more aggressive and less likely to respond to a large range of treatments. Of them, \(^{18}F\)-Fluoromisonidazole has been successfully tested in breast cancer patients (39).

The second approach, very limited for the moment in the clinical area, is direct radiolabeling of anticancer agents, providing unique means for personalized treatment planning. For example, \(^{18}F\)-Fluoroplatinaxel has been recently tested on normal volunteers and on a breast cancer patient, to evaluate in vivo multidrug resistance (40).

Conclusions

The potential of PET to provide surrogate markers of pathological response and survival in patients receiving neoadjuvant therapy of breast cancer has been increasingly recognized in recent years. Although PET is not currently routinely used in this role, its penetration into clinical practice could expand significantly as a result of increasing understanding of the mechanisms of malignant transformation at a molecular level and the range of targeted therapies being developed as a result of such investigations.

Representing the downstream effects of modulation of a number of oncogenic pathways, as well as being influenced by micro-environmental factors such as hypoxia, FDG provides a convenient integrated readout of therapeutic response to a wide range of agents from cytotoxic drugs to molecular targeted agents. It is, accordingly, by far the most studied tracer for this indication and generally provides information of both clinical and prognostic relevance. Nevertheless, despite encouraging results, there remains uncertainty regarding the degree of FDG change that constitutes a beneficial response to any given therapy and, as a corollary of this, when to alter treatment on the basis of such information. It is widely agreed that standardization of procedures is needed (imaging protocol, data analysis, cross-calibration of PET scanners . . .) before that FDG could be considered a routine tool. However, the nature of therapeutic response as a continuum rather than a dichotomy between response and drug resistance suggests that interpretation of the significance of changes in glycolytic metabolism in the temporal domain will require as sophisticated an approach as the complexity of the biological processes involved would suggest is required. It seems clear that the more marked and the earlier the reduction in FDG uptake, the greater
the likelihood of therapeutic benefit. Although a complete metabolic response is never an indicator of cure per se (because of PET’s inability to detect microscopic residual foci of disease), it is likely that cure will generally only be seen in patients achieving this degree of metabolic response at some time during their treatment course.

Although FDG PET response during therapy is likely to remain a useful prognostic biomarker, its ability to be a predictive biomarker of response to targeted agents in the context of personalized medicine is even more exciting.

New tracers are currently being developed for PET, providing specific information on tumor characteristics (proliferation, membrane synthesis, perfusion, hypoxia) and on receptor expression (ER, HER2, αvβ3). Several of these will assist the deployment of targeted anticancer agents by identifying patients likely to benefit from such treatment by virtue of imaging expression of a relevant receptor or protein. Furthermore, by demonstrating loss of the cells displaying the target, they will be able to inform on the efficacy of treatment and the need for ongoing therapy. Clearly, such modulation of the imaging target could reflect either extermination of the relevant cells or development of resistance through loss of protein expression. Accordingly, such imaging approaches may need to be combined with more generic readouts of tumor biology. Such combined assessment using multiple imaging probes is likely to lead to more precise assessment of tumor biology and more accurate prognostic stratification. Further, association of PET with other functional imaging techniques available in the field of breast cancer (such as ultrasound, magnetic resonance imaging, and optical imaging) is a promising approach to further enhance the monitoring of neoadjuvant breast cancer therapy in the future.

References


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