Measuring Tumor Metabolism by ^{18}F-FDG PET Predicts Outcome in a Multicenter Study: A Step Off in the Right Direction

As a widely used diagnostic tool, ^{18}F-FDG PET/CT combines anatomic imaging with functional imaging and provides qualitative and quantitative information about tumor metabolic activity by assigning a standardized uptake value (SUV) measurement of the relative uptake of ^{18}F-FDG in a given tumor. ^{18}F-FDG PET can serve as a prognostic marker (1–3) and is routinely used for diagnostic staging, for recurrence evaluation, and to assess response to therapy or disease progression in multiple malignancies including breast cancer (4,5). Notably, because of its high sensitivity in the detection of therapy-induced glucose metabolic rate changes that may not be evident in anatomic images, particularly early after treatment, ^{18}F-FDG PET has held promise as a biomarker of early response for decades (6–8). In this regard, ^{18}F-FDG PET can serve as an integral marker that allows for a response-adapted therapeutic strategy wherein identification of sensitive or resistant tumors as early as a few weeks after treatment initiation allows patients to avoid toxic and futile therapies and directs patients toward an aggressive or investigational approach in an effort to maximize their outcome (9). This strategy has certainly proven practice-changing for patients with non-Hodgkin lymphoma (3).

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In breast cancer, the neoadjuvant setting has been recognized as ideal for evaluating surrogate biomarkers for the prediction of pathologic complete response (pCR) to therapy and clinical outcome. In this context, ^{18}F-FDG PET has certainly served as a successful integrated marker—that is, a marker used to compare the efficacy of different treatments but not for directing change in therapy in a prospective setting (9,10). Although using PET to identify responding patients has been of interest, in some tumors, responding patients continue to derive further benefit from therapy, and tumors that are progressive on first-line therapy frequently continue to progress even with salvage or experimental regimens. Nevertheless, subjecting patients to futile therapy when resection or other novel promising therapies are available seems truly inappropriate. Hence, we read with interest the collaborative efforts of Connolly et al. (11) and the Translational Breast Cancer Research Consortium

(TBCRC), which are reported in this issue of *The Journal of Nuclear Medicine*. In this randomized phase II trial of a histone deacetylase inhibitor (HDACi), vorinostat, combined with neoadjuvant chemotherapy in human epidermal growth factor receptor 2–negative breast cancer, Connolly et al. demonstrate that a precipitous decline in SUV corrected for lean body mass (SULmax) on ^{18}F-FDG PET predicts pCR. The addition of HDACi (vorinostat) to *nab*-paclitaxel and carboplatin did not improve measured outcomes; however, a significant decline in the SULmax by nearly 50% measured by ^{18}F-FDG PET, performed 2 wk into therapy, was associated with pCR, now an acceptable intermediate predictor of disease-free and overall survival by the Food and Drug Administration (12). This decline in SULmax confirms the promise of noninvasive metabolic imaging in a neoadjuvant setting and suggests that ^{18}F-FDG PET can identify responding patients in a multicenter collaborative effort.

There are many steps toward the clinical utility of ^{18}F-FDG PET/CT for early response assessment, including demonstration of fidelity of ^{18}F-FDG PET across multiple platforms (13–15), appropriate pairing of tracer and metabolic pathway, convincing tissue correlates, and proof of feasibility in a multicenter trial. In this context, we applaud the work of the Hopkins group and TBCRC for using a uniform imaging protocol and careful standardization of study phantoms to certify sites with careful central review of the images. A concern in the trial, though, was that supplementary anthracycline-based chemotherapy was given in addition to the planned therapies in some patients, possibly diluting the results of the study. However, a retrospective subset analysis of these patients showed that excluding these patients revealed similar results. The findings by Connolly et al. (11) are concordant with the notion that metabolic responders have a higher likelihood to achieve a pathologic response. Additionally, although pCR was defined as no viable invasive cancer in the breast and axilla in this study, SULmax was calculated for breast lesions only and correlated with pathologic response.

^{18}F-FDG PET could be used to guide patient selection; such trials have been reported in Hodgkin disease (16), and esophageal cancer (17), and could lead to less treatment for responding patients and a reduction of toxicity and costs of treatment. In the work by Connolly et al., a 52% decline in SULmax predicted pCR to carboplatin and paclitaxel with or without vorinostat and could be considered an optimal cut point for these agents. Future trials could be designed to use SULmax as a predictive biomarker of response to help sort through which other agents in breast cancer can result in a meaningful response for an individual patient, using in vivo sensitivity of the tumor, and thus identify sensitive tumors and promising agents early. Given the plethora of biologic agents currently in development for the treatment of breast cancer, these findings are relevant and meaningful. However, a clear consensus of what constitutes a significant change or an optimal cut point in quantitative PET parameters for a particular therapy has yet to be reached (4). It is expected that lean body mass–normalized SUV (SULpeak (11,18))

changes using the PET Response Criteria in Solid Tumors, version 1.0, would provide results either similar to or more precise than SULmax (*18*). Others have suggested that volumetric measurements using total lesion glycolysis may be a more informative biomarker than the commonly used maximum SUV (*1*). The neoadjuvant setting is ideal to identify which agents can serve as an optimal treatment for an individual patient because tumors are untreated, easily visualized by imaging, and can help move the best biologic agent forward. Additionally, guided by the change in quantitative PET parameters, the neoadjuvant setting serves as a model platform to intensify therapies to increase the proportion of patients who can achieve a pCR (*19*).

Although high baseline SULmax allowed the appreciation of a significant decline and seems applicable to patients with aggressive tumors that are highly ^{18}F-FDG–avid, it may not be relevant for indolent tumor types, in which we may need to consider other tracers such as ^{18}F-fluorothymidine, a marker of cellular proliferation, or ^{18}F-fluoroestradiol PET (*20,21*). Yet, subsetting of tumor types makes completion of clinical trials difficult in single-center settings, hence the importance of this work by the nimble collaborative group the TBCRC.

Another significant challenge in the assessment of response is that currently we predominantly use the Response Evaluation Criteria in Solid Tumors, introduced by the National Cancer Institute and the European Association for Research and Treatment of Cancer, which defines response as a 30% decrease in the sum of the diameters of target lesions (*22*). It is not surprising that there has not been a consistent correlation between tumor response and patient survival using these arbitrary criteria and that they therefore have not served medical oncologists and therapy evaluation well; albeit we have not yet displaced this approach in clinical trials. Promising work is under way in this area (*18*) but needs further validation. Response assessment using PET imaging has correlated well with patient survival (*23*). The present study shows promise in evaluating tumor response in the breast, but more important, there is a pressing need to evaluate response in the bone in metastatic disease because this is a more challenging area to functionally measure.

In summary, in an era of promising alternative chemotherapies, emerging antibodies, biotherapies, and potential for treatment intensification, prospective evaluation of ^{18}F-FDG PET as an integrated biomarker of early treatment response is timely. Prospective studies will need to individualize new tracers, quantitative parameters, and optimal cut points for a particular therapy. Once these are validated, molecular imaging can be used as an integral biomarker for patient or therapy selection in late-stage clinical trials and clinical practice.

DISCLOSURE

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