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PET imaging for Treatment Response in Cancer

Janet F. Eary, MD

University of Washington, Department of Radiology University of Washington Medical Center, Box 356113, Seattle, WA, USA, jeary@u.washington.edu

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PET tumor surveys have become widely used in clinical practice. [F-18] fluorodeoxyglucose (FDG) is the most commonly used radiotracer for clinical indication of tumor staging and restaging after treatment. FDG PET consistently has exhibited better diagnostic performance than conventional imaging in adults and pediatric populations.^{1–4} More recently, a growing body of literature is reporting the use of FDG and other PET imaging agents in treatment response assessment.^{5–7} In many cases, FDG PET has proved to be a reliable means of noninvasively observing response in various treatments.

Additionally, reliable determination of past treatment changes, including recurrent tumors and differentiation of benign and malignant lesions, will reduce morbidity and the cost of care in anatomic imaging. The Response Evaluation Criteria in Solid Tumors (RECIST) are a useful means to report quantitative changes in tumor size on CT scans in many different tumors in response to treatment.^{8,9,10} Many tumor types, however, do not change size appreciably in response to treatment. Early changes that may indicate treatment regimen effectiveness also may not result in tumor change in size. FDG PET is a relatively sensitive indicator of treatment response in many tumors, indicating changes in metabolism that often precede or take the place of tumor size change. Fig. 1 shows some examples of FDG PET tumor response.

Recently, several cooperative groups have addressed the use of FDG PET as a biomarker for cancer treatment response. An early report by the European Organization for Research and Treatment of Cancer (EORTC) set criteria for treatment response according to changes in tumor FDG uptake compared to baseline.² These criteria include:

Complete response (CR)—[F-18] fluorodeoxyglucose uptake is comparable to baseline activity in all lesions

Partial response (PR)—all target lesions have greater than 25% decrease in standardized uptake variable (SUV)

Stable disease (SD)—target lesions have less than 25% increase or decrease in SUV

Progressive disease (PD)—at least one target lesion has greater than 25% increase in SUV, or new lesions appear (regardless of SUV changes in target lesions)

These criteria are in wide use today for clinical FDG PET imaging. A set of criteria for clinically significant changes in tumor FDG uptake, however, is based on consistent parameters for the FDG PET acquisition between studies in the same patient, and between patient imaging groups at different institutions. Development and evaluation of new cancer therapies could be enhanced by a set of validated biomarkers for treatment response. FDG PET meets these criteria in clinical studies, if imaging studies are conducted with patients on clinical therapeutic trials in a reliable and consistent manner.³ To address the consistency in FDG PET data for use as

a biomarker for treatment response, the National Cancer Institute (NCI) convened a group of experts who recommended a set of guidelines for FDG PET imaging. These consist of guidelines for FDG PET patient preparation, image acquisition parameters, and other scan aspects that are considered valuable when providing consistent scanning parameters for various patients with different cancer histologies. If cancer therapy gradually evolves toward new treatment agent combinations and the introduction of molecularly targeted therapies as expected, FDG PET will play an increasingly important role as a validated biomarker for treatment response.

A review of cancer treatment response begins with consideration of the pathological basis of the tumor process. Tumors are complex pathobiological processes that may exhibit a range of blood flow, cell proliferation rate, cell viability, inflammation, pH, and oxygenation level, among other various processes. Because of these processes, treatment response can differ significantly from a standard treatment combination or from treatments with different mechanisms of action. For example, standard cancer and radiotherapies result in direct cell killing, while others may result in cytostasis. Often cytostatic therapies may not show changes in cell metabolism, but they may stop cellular proliferation. Cellular necrosis fraction is considered the hallmark of treatment response to chemotherapy. Overinterpretation of tumor cellular necrosis in a tumor specimen, however, may result in cases where necrosis is present as a distinguishing feature of the primary tumor. Fig. 2 shows a primary tumor where significant necrosis is present prior to therapy. For this reason, reliable treatment response imaging requires a baseline pretreatment scan for comparison. Necrosis can take the form of coagulative necrosis, or hemorrhagic necrosis when response results in hemorrhage and its resolution. Scarring is a common treatment response and is also common in radiation treatment. Compared with necrosis, this treatment response is metabolically active and can cause significant FDG uptake. In cases where granulation tissue formation precedes scarring, the inflammatory cells present also may elevate the apparent tumor bed tissue metabolism. Activated white cells can show as much as a tenfold increase in FDG uptake. An important part of treatment response interpretation in FDG PET imaging is identifying the treatment agent mechanism, tumor type, and timing of the scan observation in relation to the course of treatment. Early after therapy, observations may reveal very different findings from those obtained after the biological mechanisms involved in treatment response have revealed a more static state. Radiation responses to tumor and surrounding tissues may have extremely different timescales in relation to the end of the final therapy dose.

Acquisition of the most reliable PET data requires considering several elements in patient preparation and acquisition parameters. As previously mentioned, there are numerous factors that can influence the ability to identify pathologic conditions and their changes in a patient over time. Numerous reports have shown that pathologic tissue focus size in FDG PET remains a limit to detection.¹¹ Even in tumors with hypermetabolism, such as lymphoma, as many as 20% of tumors less than 15 mm in diameter are undetectable. Newer detectors made from lutetium oxyorthosilicate (LSO) are improving lesion detectability limits and decreasing scan duration. This latter parameter, however, can decrease lesion sensitivity in low-contrast pathologic conditions. Large patient body size has contributed to increased levels of noise in image reconstruction, in which lesion detectability is decreased further with even small amounts of patient motion. Image artifacts also can limit scan interpretation. Respiratory gating helps to reduce motion artifact in imaging the chest and upper abdomen. Metallic implants and gastrointestinal contrast, however, can cause significant CT-based attenuation artifacts. Imaging in the pediatric population, where doses of radiotracers are much lower and imaging times shorter, have scan acquisition protocols that may compromise image data quality and therefore affect image interpretation.¹

There is increasing interest in using PET images for determining biologically relevant tumor volumes for radiotherapy. This is another specific application where image parameter protocols and patient preparation must be designed and executed carefully. As many of these scans also serve as baseline for treatment with multimodality therapy, accurate response assessments require consistency in order to provide maximum clinical utility.

Image interpretation is possible through several forms in clinical practice. Visual interpretation and comparison with normal tissues, or uninvolved sites, may be adequate for diagnosis and disease staging. Treatment response, however, likely is evaluated better with the use of a semiquantitative scale for tumor uptake, such as the tissue standardized uptake variable (SUV). The utility of this value lies in consistent patient preparation, scan parameters of injected dose, acquisition time (for FDG), time point of observation after therapy, and type of therapy. Many authors have commented on what may be the most clinically relevant form of SUV when analyzing tumors, which include correction for blood glucose, lean body mass, and average tumor uptake.⁷

Our group advocates the use of the SUV maximum (SUV_{max}) measurement for tumor characterization. With FDG, many reports state that tissue uptake correlates with tumor mitotic rate, cellularity, blood flow, and various cytogenetic abnormalities. Therefore, the tumor likely behaves according to the most aggressive of these tissue elements. In particular, an average tumor SUV, which can include nonviable or lower metabolic components such as fat or serous fluid, may not reflect the inherent malignant potential of the most biologically aggressive aspects of the tumor. The report of the tumor SUV_{max} also eliminates potential bias in region of interest designation for tumor mass evaluation. Only the maximum pixel values are reported, which makes a more objective measurement. For tumor response imaging, this is another means of standardizing the scan and a reporting procedure that increases the reliability and consistency of clinical assessment of treatment effectiveness.

LYMPHOMA

The lymphomas are perhaps the most studied cancer types for utility of FDG PET in treatment response evaluation. These tumors, while varying in their clinical aggressiveness, often show dramatic responses to most treatment combinations. Much of this disease eventually relapses, however, and patients eventually succumb to their disease; hence, it often is designated as a treatable but not curable disease. Effective treatment strategies can be identified for each patient if nonresponders can be identified accurately. Use of only anatomic imaging for lymphoma response imaging can be problematic, because enlarged tumor bearing lymph nodes often remain somewhat enlarged after treatment when compared with normal sizes.

FDG uptake is useful for lymphoma research, because it shows increased tumor metabolism and varying levels of associated inflammation. In response evaluation, scarring also can cause residual uptake; however, treatment response imaging in lymphoma has become well-established.^{12,13} Relatively high sensitivity and specificity of changes in lymphoma FDG uptake have been correlated with extended disease-free intervals.^{11,14–16} More significantly, residual uptake in known lymphoma sites identifies patients who have much earlier relapse of lymphoma.

The Imaging Subcommittee of International Harmonization Project in Lymphoma recently published its recommendations.¹¹ For response imaging, it recommended PET imaging 6 to 8 weeks following chemotherapy or protocols using immunotherapy/chemotherapy combinations. Response observations for radiotherapy responses are suggested when they are most reliable, usually 8 to 12 weeks after completion of treatment. The mediastinal blood pool was recommended as the comparison for positive lesions, whether using a visual or semiquantitative assessment. Previously, another working group found that the addition of

FDG PET to analyze disease stages significantly increased response assessment for prognosis more than using standard measures alone.¹⁶ Some of the most interesting research is observing the use of FDG PET for predictive outcome early in treatment. Responses predictive of better outcome have been observed as early as 1 day after chemotherapy and after the first therapy cycle.^{17,18} Newer combinations for targeted and conventional therapy for lymphomas will benefit from the use of FDG PET in early and likely post-treatment evaluation.

LUNG CANCER

Rapid progress also has been made in the use of FDG PET for lung cancer treatment response evaluation. Most patients receiving chemo-radiotherapy have shown distinct reduction in tumor metabolism with treatment. Complete responders have shown the greatest decreases.^{19,20} Weber and colleagues found that the sensitivity for differentiating residual tumor from complete pathologic response was 67%.²¹ These findings were supported by similar work by Cerfolio and colleagues, who showed that the change in tumor FDG uptake measured as SUV had a linear relationship with percent nonviable tumor cells in resected tumor specimens.¹⁹ These data also correlate with patient outcome.^{22–24} Early response to treatment in lung cancer also correlates with patient outcome. A reduction of 20% or more for response after one cycle of chemotherapy had a 95% sensitivity and a 74% specificity, a clinically significant difference in survival.²³ Other studies have shown the utility of FDG PET for identifying patients for resection after induction therapy.

BREAST CANCER

Similar to lymphoma and lung cancer, recent studies have found the utility in identifying breast cancer response early in primary treatment. These findings are particularly significant, because there are increasing therapeutic alternatives and many active clinical trials evaluating new treatment combinations. Smith and colleagues reported a 90% sensitivity for complete response prediction after a first cycle of chemotherapy.²⁵ Schelling and colleagues described a highly sensitive study result for identification of complete responders when the tumor SUV decreased by 55% or more when compared to baseline pretreatment levels.²⁶ Others have shown similar results.²⁷ Mankoff and colleagues pursued the concept of multiparameter imaging to more specifically define and identify tumor responses in breast cancer patients who had locally advanced disease.²⁸ Tumor metabolism measured with FDG, and tumor blood flow quantified with [O-15] water, were compared at baseline and after 2 months of chemotherapy. These parameter changes then were correlated with patient survival. As expected, responders showed greater changes in FDG uptake than nonresponders. Additionally, responders had significant decreases in tumor blood flow. Interestingly, nonresponders showed increases in blood flow. The change in tumor blood flow was highly predictive for disease-free and for overall survival. These findings suggest that a multiparameter imaging approach in PET may provide valuable, specific information about differences in tumors from patients who are responders or nonresponders. Treatment protocols that incorporate antivasculature strategies likely will be evaluated more precisely with this type of approach.

GASTROINTESTINAL CANCERS

Esophageal cancer shows variable clinical responses to neo-adjuvant therapy. Consequently, several investigators have demonstrated the reliability of FDG PET to identify pathological responses and to correlate these responses with clinical outcome. These data support the idea that changes in FDG uptake predict long-term and disease-free survival.^{29–32} Similar to findings for other cancers, decreases in FDG uptake between 50% and 60% from baseline indicated clinically significant treatment responses.^{33,34} Early in treatment, responses also have been identified in patients who have locally advanced disease.³⁵ Recently, in esophageal cancer, treatment protocols designed to select responders have been initiated. Lordick and

colleagues reported a trial where FDG PET responders continued therapy, and nonresponders did not. Significantly, after median follow-ups of approximately 2 years, the median survival in PET responders was not reached, and PET nonresponders had a median survival of 25.8 months.³⁶

GASTRIC CANCER

Similar to esophageal carcinoma, gastric adeno-carcinoma is another clinical situation where FDG PET has made a significant contribution to tumor staging.^{37,38} Because of this high level of specificity and tumor responsiveness to therapy, early response detection also has been described.^{39,40} In this study, after a decrease in FDG uptake by 35% or more and assessment after 14 days of therapy, histopathologic response after 3 months of therapy was identified correctly in 77% of the patients. As in lymphoma early treatment response, identification may facilitate the use of FDG PET as a response biomarker for new therapy combinations aimed at disease cure.

The case of gastrointestinal stromal tumor (GIST) therapy with imatinib and accurate disease monitoring with FDG PET recently has become a new paradigm for success in molecularly targeted therapy. High levels of accuracy for the use of FDG PET as a response biomarker. Clinical treatment with targeted molecules such as imatinib may not be curative, but allow control of the tumor for long periods of time. Recent experience has shown that GISTs later develop resistance to imatinib, which then warrants a therapy change to continue preventing disease progression. The use of FDG as a biomarker has been validated in several GIST tumor models. This is reflected in reduction of tumor GLUT-1 transporter in animal tumor models treated with imatinib. In imatinib-resistant tumors, no change in FDG uptake was observed. This result was translated to clinical trials, where GIST response to treatment using FDG has been observed with high sensitivity and specificity. FDG uptake thresholds of 40% to 69% decrease compared to baseline were used to report treatment response.^{41–45} Nonresponders also are identified.⁴⁶ Patients who had little FDG uptake after treatment had the expected better survival also.⁴⁷

SARCOMAS

Although sarcomas are relatively rare compared with lung, breast, and lymphoma tumors, their difficulties in treatment sensitivity and their poor survival for high-risk disease make them important tumors when evaluating imaging methods that may contribute to more effective therapy strategies. Bone tumors are more likely to have better outcomes if adequate surgical resection can be achieved. In the pediatric bone tumor population, where maximum treatment can be delivered more effectively, outcomes are better overall than in the adult population. However, children who have treatment-resistant disease, however, are difficult to identify until treatment failure becomes evident. Hawkins and colleagues found that FDG uptake in response to treatment was correlated significantly with histopathologic assessment in resected bone tumors.⁴⁸ Schulte and colleagues had similar findings.⁴⁹

In adult soft tissue sarcomas, where the role of neo-adjuvant chemotherapy remains incompletely described, FDG PET has been shown to be an effective measure of treatment response. In a series of patients who had localized extremity soft tissue sarcomas treated with adriamycin-based neo-adjuvant chemotherapy followed by resection, the change in FDG uptake from baseline after therapy was highly correlated with survival.⁵⁰ In a mixed group of bone and soft tissue sarcoma patients, the reduction in tumor FDG uptake correlated with percent tumor necrosis in the resected tumors.⁵¹

TUMOR PROGRESSION WITH [F-18] FLUORODEOXYGLUCOSE PET

Lack of treatment response progression often is noted through a lack of change in FDG uptake level or a significant increase in FDG uptake. Increased numbers of disease sites are clearly indicative of progression. Patients who undergo support with granulocyte colony-stimulating factors, however, may be difficult to evaluate for bone and marrow-based disease response or progression. This results in increased metabolism throughout the marrow space and significantly reduces sensitivity. FDG flare reactions have been noted in metastatic disease sites after initiation of successful hormonal therapy, which may cause imaging evaluation difficulty also.^{51,52} Increased number of lesions and increases in existing lesional FDG uptake, however, indicate tumor progression. Fig. 2 shows an example of this situation.

NEWER PET CANCER IMAGING METHODS

Much of the ongoing clinical evaluation in PET in cancer involves non-FDG imaging agents. Generally, the goal of this research is to identify and detect changes in tumor response to therapy through the use of imaging agents that are more specific than tissue glucose metabolism. [C-11] acetate is being evaluated by several groups worldwide for imaging prostate cancer, whose metabolism with FDG is unreliable.^{53,54} [C-11] and [F-18] cholines are being evaluated for the same purpose. Current results support promise for these tracers, as they provide images with low background and may represent changes in cell membrane synthesis, which is important in understanding treatment response mechanisms. Others continue to evaluate the use of labeled amino acids to evaluate this additional means of quantitative cell synthesis. Initial experience with brain tumors indicates that this may be a possibility also.³

Combinations of imaging agents that report on basic tissue characteristics are also under investigation for PET imaging. One of the best examples of those techniques is the ongoing work of Mank-off and colleagues cited earlier that combines FDG and blood flow imaging.²⁸ Tumor biology specific imaging agent combinations will be significant contributions when they identify patients who can benefit from newer treatment combinations such as those that incorporate antivascular therapy.^{40,55} Additionally, these imaging results will provide a means for understanding treatment response mechanisms in clinical trials.

SUMMARY

Imaging treatment response with FDG PET has been evaluated in numerous prospective and retrospective clinical studies. As a result, it is becoming established as a biomarker for treatment response and as a marker for patient outcome prediction. Newer imaging strategies aimed at further understanding the differences in treatment response between cancers and therapies are underway. An important tool for clinical trials, PET cancer imaging can contribute significantly to understanding the timing and basis for disease response in a patient.

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Fig. 1.

There are examples of tumor response on [F-18] fluorodeoxyglucose (FDG) PET images. (A) An image of the chest showing a large mass of axillary lymph nodes that contain metastatic carcinoma. The left image is a baseline study, and the right image shows a response to treatment with decreased FDG uptake. (B) Anterior views of the pelvis with a high-grade gluteal sarcoma. The left image was acquired before neo-adjuvant chemotherapy, and the right image shows a response in decreased FDG uptake. Heterogeneity in the responding tumor tissue also is noted. (C) Patient with metastatic Ewings sarcoma with widespread bony metastases prior to salvage treatment, on the left two images, and on the right two images, a postsalvage therapy whole-

body FDG survey shows increased metastatic sites with increased FDG uptake in previously existing sites. This is an example of tumor progression during therapy.

Fig. 2.

Large sarcoma in the thigh soft tissues, where there is significant necrosis present in several areas in the tumor. These areas do not show FDG uptake. (A) FDG PET images in three planes. (B) Correlative MRI of this tumor.