^{18}F-FDG PET as a Candidate for "Qualified Biomarker": Functional Assessment of Treatment Response in Oncology

In this issue, *The Journal of Nuclear Medicine* publishes National Cancer Institute (NCI) guidelines that are a step on the path toward qualifying ^{18}F-FDG PET as a biomarker to assess treatment response during NCI-sponsored trials. These guidelines, written by Shankar et al. (*1*), were developed in recognition of the growing use of ^{18}F-FDG PET in clinical trials sponsored by the NCI and of the importance of standardizing methodology for such use. Broad representation was obtained in the drafting of these guidelines by including PET experts throughout the country, as well as representatives from the U.S. Food and Drug Administration and Center for Medicare Studies.

See page 1059

The authors write, "With, this increasing clinical experience, it is becoming clear that ^{18}F-FDG PET may have an important role as a surrogate endpoint for assessing the clinical efficacy of novel oncologic therapies. At the same time, it has become equally clear that the potential of ^{18}F-FDG PET as such a tool will not be achieved unless standard protocols are developed so that data can be accumulated and compared across multiple clinical sites. Today, the methods of obtaining ^{18}F-FDG PET scans and assessing ^{18}F-

FDG metabolism and uptake vary.…" The guidelines focus on "patient preparation, image acquisition, image reconstruction, quantitative and semiquantitative image analysis, quality assurance, reproducibility, and other parameters important in ^{18}F-FDG PET studies before and after a therapeutic intervention." They cover the practical issues of ^{18}F-FDG PET in detail and therefore provide a valuable reference for a generally accepted approach to incorporating PET into clinical trials.

These guidelines are remarkable for the fact that they are the result of discussions by an NCI-supported consensus panel and were preceded by 2 summaries of similar provenance on the potential usefulness of ^{18}F-FDG PET (*2*) and by a review of the potential of molecular imaging for monitoring treatment response (*3*). The guidelines were preceded by a similar review by our European colleagues on the use of ^{18}F-FDG PET in evaluating treatment response (*4*). Thus, in the last few years, it is as though a pendulum has swung, allowing us to begin to look objectively on PET as a tool for the imaging of treatment response.

Why now? Formal recognition by the NCI of the potential importance of ^{18}F-FDG PET in monitoring treatment response has been motivated by the search for biomarkers as endpoints of clinical trials to help reduce the growing cost of obtaining new drug approvals. The hope is that ^{18}F-FDG PET may be a true surrogate that can be used in place of classic endpoints in evaluating treatment response. A second motivation has been dissatisfaction with the classic anatomy-based imaging methods for assessing treatment response, such as the WHO criteria or the Response Evaluation Criteria in Solid Tumors (RECIST) (*5*). A third motivation has been the growing evidence in major cancers that ^{18}F-FDG uptake represents important underlying cancer biology and is a predictor of aggressive tumor behavior and treatment response.

Oncology Biomarker Qualification Initiative (OBQI)

The cost of developing a drug runs to hundreds of millions of dollars, and only 1 in 5 drugs that enters clinical trials successfully emerges as a product. For this reason, the pharmaceutical industry and key federal agencies are interested in new approaches to drug discovery, development, and regulation that will reduce costs and shorten the process (*6*).

With this concern in mind, the Food and Drug Administration, Center for Medicare Studies, and NCI have entered into a Memorandum of Understanding (http://www.fda.gov/oc/mous/domestic/FDA-NCI-CMS.html) with a goal of "improving the clinical utility of biomarker technologies as diagnostic and assessment tools that facilitate the development of safer and more effective cancer therapies." These agencies will focus on biomarkers as possible endpoints of clinical trials. Biomarkers are biologic indicators of disease or therapeutic effects that can be measured through dynamic imaging tests and tests on blood, tissue, and other biologic samples. This initiative will bring together the strength of these 3 agencies, with the strong collaboration of the pharmaceutical industry, to determine the optimal use of biomarkers to evaluate treatment response. A February 2006 press release that accompanied the announcement of this initiative stressed the following

potential applications of biologic markers: they can determine if a patient's tumor is likely to respond at all to a specific treatment; they can assess after 1 or 2 treatments whether a patient's tumor is responding to treatment; they can determine more definitively if a tumor is dying, even if it is not anatomically shrinking in size; they can identify which patients are at high risk of tumor recurrence after therapy; and they can efficiently evaluate whether an investigational therapy is effective for tumor treatment. According to the press release, "The goal of OBQI is to validate particular biomarkers so that they can be used to evaluate new, promising technologies in a manner that will shorten clinical trials, reduce the time and resources spent during the drug development process, improve the linkage between drug approval and drug coverage, and increase the safety and appropriateness of drug choices for cancer patients."

Limitations of Current Response Assessment Methods

Current guidelines for anatomic assessment of response rely on surrogates for tumor measurements, such as 1-dimensional measurement of the longest tumor axis on an axial slice or the cross product of the longest tumor axis and the greatest perpendicular. Certain therapies may not exhibit an adequate degree of tumor shrinkage to be "captured" as a response according to these criteria, and many questions may arise about the use of 1- or 2-dimensional tumor measurement itself as a surrogate. The rules of RECIST governing response assessment may be of limited value in certain clinical settings and with certain tumor types (5,7). Additional, more complete consideration of volumetric parameters may be more useful (8).

¹⁸F-FDG PET as a Window on Cancer Biology

In human tumors, ¹⁸F-FDG PET uptake correlates with the rate of glycolysis, which is known to be markedly greater in neoplastic tissues than in the normal tissues from which neoplasia arises. Both qualitative and quantitative information is useful in ¹⁸F-FDG PET (9). Among the many available quantitative parameters, a variant of the standardized uptake value is most widely used, and its calculation is included in the standard software provided by all major manufacturers of PET scanners.

¹⁸F-FDG PET has been found to be useful in numerous malignancies, and the Center for Medicare Studies has approved reimbursement, primarily for staging and detection of recurrence, for 8 tumor types. It is estimated that in 2005 in the United States alone, more than a million patients were studied with ¹⁸F-FDG PET, primarily for oncologic indications.

One intriguing aspect of ¹⁸F-FDG uptake is the strong correlation with biologically aggressive behavior in numerous tumor types. The maximum standardized uptake value has been shown to predict prognosis in lung cancer (10), esophageal cancer (11), and thyroid cancer (12) and to assist in differentiation between indolent and aggressive lymphomas (13).

Rapidly accumulating data indicate that ¹⁸F-FDG PET may be useful in treatment response as well, and this topic is now the focus of intense study. More than 600 articles can be found in PubMed using "¹⁸F-FDG" and "treatment response" as search terms. A few examples illustrate the breadth of application: An early paper by Wahl et al. indicated the potential utility of ¹⁸F-FDG PET in breast cancer (14); a study found that a change in maximum standardized uptake value in esophageal cancer predicted the effectiveness of neoadjuvant therapy (15); a paper proposed the use of ¹⁸F-FDG PET as an outcome measure in advanced prostate cancer (16); and other papers proposed the use of ¹⁸F-FDG PET in lymphoma as a guide to the completeness of response and possible alternative therapies (17,18).

Prentice's Criteria for Surrogate Biomarkers

It is not easy to qualify a particular marker as a surrogate endpoint. The surrogate marker must meet rigid standards, including Prentice's criteria, which state that on a statistical basis, in order to be a true surrogate, the endpoint must be a prognostic factor and explain all the disease-specific mortality (19). Also, it is important to evaluate each specific response parameter on its own merits. For example, in a 919-patient study reported by D'Amico et al., changes in prostate-specific antigen after treatment did not qualify as a surrogate marker, but a doubling time of less than 3 mo for prostate-specific antigen did meet the criteria (20).

In summary, the NCI guidelines provide an excellent starting point for standardization of the use of ¹⁸F-FDG in clinical trials. The guidelines emphasize the technical performance of studies in order to avoid spurious results unrelated to the response of tumors to treatment and to enhance the reliability and reproducibility of the imaging test. Obtaining optimal results from such trials will require that great care be exercised in selecting patients who are in a well-defined clinical state and in timing the imaging such that the secondary effects of treatment, such as inflammation, do not interfere with accurate interpretation of the treatment response of tumors. The worthy intention of the guidelines is to prepare for the widespread testing of ¹⁸F-FDG PET in multicenter, adequately powered, NCI-sponsored clinical trials of treatment response.

Steven M. Larson
Lawrence H. Schwartz
Memorial Sloan-Kettering Cancer Center
New York, New York

REFERENCES

1. Shankar LK, Hoffman JM, Bacharach S, et al. Guidelines for the use of ¹⁸F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute trials. *J Nucl Med.* 2006;47: 1059–1066.
2. Kelloff GJ, Hoffman JM, Johnson B, et al. Progress and promise of FDG-PET imaging for cancer patient management and oncologic drug development. *Clin Cancer Res.* 2005;11:2785–2808.
3. Kelloff GJ, Krohn KA, Larson SM, et al. The progress and promise of molecular imaging probes in oncologic drug development. *Clin Cancer Res.* 2005;11:7967–7985.

4. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer.* 1999;35:1773–1782.

5. Scher HI, Morris MJ, Kelly WK, Schwartz LH, Heller G. Prostate cancer clinical trial end points: "RECIST"ing a step backwards. *Clin Cancer Res.* 2005;11:5223–5232.

6. Mervis J. Pharma goes to work [introduction]. *Science.* 2005;309:721.

7. Husband JE, Schwartz LH, Spencer J, et al. Evaluation of the response to treatment of solid tumours: a consensus statement of the International Cancer Imaging Society. *Br J Cancer.* 2004;90:2256–2260.

8. Zhao B, Schwartz L, Moskowitz C, Ginsberg MS, Rizvi NA, Kris MG. Computerized quantification of tumor response in lung cancer: initial results. *Radiology.* In press.

9. Larson SM, Erdi Y, Akhurst T, et al. Tumor Treatment Response Based on Visual and Quantitative Changes in Global Tumor Glycolysis Using PET-FDG Imaging. The Visual Response Score and the Change in Total Lesion Glycolysis. *Clin Positron Imaging.* 1999;2:159–171.

10. Downey RJ, Akhurst T, Gonen M, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. *J Clin Oncol.* 2004;22:3255–3260.

11. Rizk N, Downey RJ, Akhurst T, et al. Preoperative 18[F]-fluorodeoxyglucose positron emission tomography standardized uptake values predict survival after esophageal adenocarcinoma resection. *Ann Thorac Surg.* 2006;81:1076–1081.

12. Robbins RJ, Wan Q, Grewal RK, et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. *J Clin Endocrinol Metab.* 2006;91:498–505.

13. Schoder H, Noy A, Gonen M, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. *J Clin Oncol.* 2005;23:4643–4651.

14. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. *J Clin Oncol.* 1993;11:2101–2111.

15. Downey RJ, Akhurst T, Ilson D, et al. Whole body 18FDG-PET and the response of esophageal cancer to induction therapy: results of a prospective trial. *J Clin Oncol.* 2003;21:428–432.

16. Morris MJ, Akhurst T, Larson SM, et al. Fluorodeoxyglucose positron emission tomography as an outcome measure for castrate metastatic prostate cancer treated with antimicrotubule chemotherapy. *Clin Cancer Res.* 2005;11:3210–3216.

17. Juweid ME, Wiseman GA, Vose JM, et al. Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. *J Clin Oncol.* 2005;23:4652–4661.

18. Schwaiger M, Wieder H. Role of PET in lymphoma. *Chang Gung Med J.* 2005;28:315–325.

19. Alonso A, Molenberghs G, Geys H, Buyse M, Vangeneugden T. A unifying approach for surrogate marker validation based on Prentice's criteria. *Stat Med.* 2006;25:205–221.

20. D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer specific mortality in patients with non-metastatic hormone refractory prostate cancer. *J Urol.* 2005;173:1572–1576.

Erratum

In the article "Procedure Guideline for Tumor Imaging with 18F-FDG PET/CT 1.0" by Delbeke et al. (*J Nucl Med.* 2006;47:885–895), Table 1 contained an error. The corrected table appears below:

TABLE 1
18F-FDG Radiation Dosimetry for Adults and Children

Patient	Intravenously administered activity	Organ receiving the largest radiation dose, mGy/MBq (rads/mCi)	Effective dose, mSv/MBq (rems/mCi)
Adult	370–740 MBq (10–20 mCi)	Bladder, 0.16* (0.59)	0.019 (0.070)
Child (5 y old)	5.18–7.4 MBq/kg (0.14–0.20 mCi/kg)	Bladder, 0.32† (1.2)	0.050 (0.18)

*Voiding interval, 3.5 h. Changes in bladder wall dose are approximately linear with changes in voiding interval; therefore, for a voiding interval of 2.0 h, dose to bladder wall would change by a factor of 2/3.5.

†Voiding interval, 2.0 h.

Data are from International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals.* St. Louis, MO: Elsevier; 2000:49. ICRP publication 80.

In addition, the affiliation for one of the authors, Scott Holbrook, is listed incorrectly. The correct affiliation is Precision Nuclear, Gray, Tennessee.