INVITED COMMENTARY

Combined ^{18}F-FDG–FDOPA Tumor Imaging for Assessing Response to Therapy

The article on imaging metastatic melanoma with ^{18}F-FDG, 6-fluoro-L-dopa (FDOPA), and ^{15}O-water, by Dimitrakopoulou-Strauss et al. (*1*) in this issue of *The Journal of Nuclear Medicine*, raises several interesting issues likely to be important in the evolution of PET in oncology. These issues are the use of PET to monitor response to therapy, the impact of tumor uptake of alternative substrates on FDG imaging, and the combined use of multiple tracers to assess tumor metabolism.

RESPONSE TO THERAPY

FDG PET is now widely used in the diagnosis and staging of a broad variety of malignancies. Metabolic imaging is an obvious method for assessing tumor response to therapy, because metabolic changes have to precede the more conventionally measured parameter of change in tumor size. Although metabolic imaging is an obvious choice, what is not obvious is how to do the imaging. We do not know which tracers or combinations of tracers should be used, when the imaging should be done after therapy, what the optimal imaging times are, or which data analysis methodology is best. In addition, each tumor–therapy combination may need to be independently optimized and validated. Also, the need for comparison pretreatment studies in assessing posttreatment response is not clear.

Dimitrakopoulou-Strauss et al. (*1*) used PET with FDG, FDOPA, and ^{15}O-water to assess the metabolic status of melanoma metastases after treatment with dacarbazine and α-interferon. This approach, without pretreatment imaging, cannot assess subtle increases or decreases in tumor metabolism. However, the approach should be able to assess whether the response has been complete or whether residual viable tumor is present. This method is appropriate if a reasonable probability exists that a single course of therapy will result in a complete response. We have used ^{67}Ga imaging of lymphoma in this way for years, often without pretreatment imaging. Posttherapy imaging alone will not be adequate if the goal is to assess the extent of partial response, as is likely to occur in the middle of a course of therapy, when the therapist needs to decide whether to continue or change the therapy. In this situation, we will need to perform quantitative imaging before and after therapy. Simple standardized uptake values may be sufficient, but more complex data analysis may have significantly greater predictive accuracy. Overall, this illustrates the need to define a specific imaging protocol and data analysis strategy for each combination of tumor and therapy.

ALTERNATIVE SUBSTRATES

One important assumption, when PET is used in this fashion, is that viable tumor will show increased uptake and nonviable tumor will not. Dimitrakopoulou-Strauss et al. (*1*) show that most, but not all, viable melanoma metastases show increased uptake of FDG. Some tumors show increased FDG uptake, some show increased FDOPA uptake, and some show increased uptake of both tracers. Whether a few tumors do not show significant uptake of either tracer is not clear. The minimal FDG uptake in some viable tumors implies that, for these tumors, glucose is not the primary source of energy metabolism (i.e., generation of adenosine triphosphate, nicotinamide adenine dinucleotide, and nicotinamide adenine dinucleotide phosphate). The ability of tumors to metabolize alternative substrates such as glutamine (*2*,*3*) or lactate (*4*) is well known. This observation by Dimitrakopoulou-Strauss et al. suggests that some tumors, even in a group of a single tumor type (melanoma), do not significantly metabolize glucose. We do not know if this lack of glucose metabolism is in response to the prior therapy. However, a likely possibility is that some tumors not visualized with FDG use alternative substrates, because most studies have found sensitivities for tumor detection of less than 100% with FDG.

Is FDOPA an appropriate tracer for detecting tumors that use alternative substrates? This study used FDOPA because it is a substrate for melanin synthesis and thus should show increased uptake in melanoma cells. However, because the label is lost early in the metabolic sequence, and because metabolism is probably slow compared with the period of imaging, no metabolic trapping was seen with FDOPA.

FDOPA uptake is, then, simply an indicator of large neutral amino acid (LNAA) transport. Other amino acids transported by the same mechanism include methionine, histidine, leucine, isoleucine, valine, tyrosine, phenylalanine, tryptophan, and threonine (*5*). Most studies on amino acid transporters have been of the brain. Presumably, other tissues, including tumors, use the same or similar transporters (*6*).

FDOPA may be a good general-purpose tracer for examining amino acid transport qualitatively. Significant

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difficulties make quantitative imaging with FDOPA problematic. One difficulty is the relatively large, and presumably variable, amount of circulating metabolite. The metabolite, methyl-FDOPA, apparently behaves similarly to FDOPA (*7*,*8*) in that methyl-FDOPA is taken up by the same carrier as is FDOPA, although probably with different affinity. Uptake in tissue will be a mixture of the two labeled ligands. Complex data collection and analysis would be required to derive a reliable, accurate measure of FDOPA transport into tissues. Thus, the FDOPA rate constants, K1 and k2, and volume of distribution, Vb, presented by Dimitrakopoulou-Strauss et al. (*1*) are a mixture of values for FDOPA and for 3-*O*-methyl-FDOPA. Another major difficulty is that FDOPA competes with all the other amino acids carried by the LNAA transporter. This competition has been reported for tyrosine (*9*) and is almost certainly true for other ligands transported by amino acid carriers. Consequently, the dietary status of the patient—fasting versus fed—may affect uptake.

FDOPA is unlikely to be a specific imaging agent for melanoma. FDOPA may be a useful empiric agent for tumor imaging but will be difficult to use quantitatively. If FDOPA were readily available, it could actually find widespread use; however, perhaps other ^{18}F-labeled amino acids such as fluorotyrosine would be equally effective.

How should we deal with the problem of alternative-substrate uptake by tumors? Can we image all such tumors with FDOPA? Does alternative-substrate uptake have implications for the therapist in choosing a specific type of therapy? We clearly do not know the answers to these questions. Studies are needed. An obvious approach is to image patients with tumors using both FDG and FDOPA (or an alternative tracer) on either the same or different days. Such studies will identify what fraction of tumors uses a specific class of alternative substrates and whether any tumors are still not detected. We can also determine if alternative-substrate uptake correlates with response to therapy.

MULTITRACER STUDIES

Sequential injections are unlikely to be clinically practical; however, injection of two tracers such as FDG and FDOPA simultaneously may be possible. This approach is not appealing from the viewpoint of rigorous quantitation of metabolism but may be an effective way to improve the sensitivity of PET for detecting tumor viability. A precedent for simultaneous injection of two tracers exists, ^{18}F-fluoride ion and FDG having been used to define skeletal anatomy along with FDG uptake (*10*).

Multitracer studies are potentially powerful because different parameters can be used to improve the accuracy of parameter estimates or can be combined to create new parameters. Although Dimitrakopoulou-Strauss et al. (*1*) did not do either, their data illustrate the potential for such analyses. For instance, ^{15}O-water K1 can be used as an upper bound for K1 for the other two tracers, because ^{15}O-water K1 is an estimate of blood flow, and delivery of the other tracers cannot exceed blood flow. Volumes of distribution can be constrained to be equal or a fixed ratio. These approaches have proven useful with other tracers and might have been used in this study.

Another technique for multitracer studies is to divide or multiply parameters from one tracer by parameters from another tracer. As Mankoff et al. (*11*) showed for breast cancer, the ratio of flow to FDG uptake is a more robust indicator of tumor status than is either parameter by itself. The combination of FDOPA, FDG, and ^{15}O-water parameters is actually a rich set of data that can be analyzed in several ways. As the authors complete more patient studies, examination of some of these more powerful analysis strategies may be possible.

FDG PET is an effective but imperfect tool that takes advantage of a common defect in tumor metabolism: inefficient and elevated glucose metabolism. However, this metabolic defect is apparently not present in all tumors. We need to identify other tracers that can probe alternative metabolic pathways and minimize the false-negative findings that are a significant problem with FDG imaging. These tracers may also reduce the false-positivity problems with FDG caused by uptake in normal and inflamed tissues (*12*).

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