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EDITORIAL

PET Cancer Evaluations with FDG

A high rate of glycolysis is a biochemical hallmark of many types of aggressive tumors, a phenomenon first described in the now widely cited work of Warburg et al. (*1,2*) and validated by others (*3*). Like many scientific discoveries, some of the practical implications of this observation were to remain undefined for a period of time. The development of the autoradiographic ^{14}C-deoxyglucose technique by Sokoloff and colleagues (*4*) followed by the extension of the method to human studies with 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) and PET (*5–7*) made possible the first in vivo cross-sectional evaluations of glucose utilization in health and disease. One of the first clinical applications of PET FDG imaging was the evaluation of astrocytomas, a field pioneered by Di Chiro and colleagues at the NIH (*8,9*).

Di Chiro et al. (*10,11*) demonstrated that a high glycolytic rate of high-grade astrocytomas effectively differentiates them from low-grade astrocytomas. Diagnostically, preoperative PET FDG studies of brain tumor patients permit accurate histological grading of the lesions and often has implications for surgical and other therapeutic approaches. Postoperatively, PET FDG studies of brain tumor patients are utilized to monitor the progression of residual tumor and to differentiate radiation necrosis from recurrent tumors (*12*). Several investigators have also shown that the relative rate of glucose utilization of brain tumors mapped by PET FDG images also has prognostic significance: length of survival is inversely correlated with FDG uptake in some series (*13*).

It is now widely recognized that PET FDG brain tumor imaging is useful diagnostically for grading lesions noninvasively and is also effective in monitoring disease progression and, potentially, response to therapy.

In addition to PET FDG imaging of brain tumors, other oncologic applications of the PET FDG method have emerged. Primary lesions studied with FDG have included head and neck tumors [evaluated with a specially collimated gamma camera (*14*) and PET (*15*)], lung carcinomas (*16*), lymphoma (*17*), breast carcinomas [PET FDG (*18,19*) and gamma camera FDG studies (*20*)], colorectal carcinomas (*21,22*), thyroid cancer [imaged with a gamma camera and FDG (*23*)], and musculoskeletal tumors (*24*).

The accelerated glycolytic rate of malignant tumors is associated with increased activities of rate-controlling enzymes for glycolysis, including hexokinase, phosphofructokinase and pyruvate dehydrogenase (*1,2*). Investigations have demonstrated a relationship between the magnitude of the increase in the glycolytic rate and the rate of tumor growth (*3*), and the neoplastic transformation of some cell lines is associated with increased membrane glucose transport capability (*25*). Initial studies by Minn et al. (*14,20*) revealed a relationship between glucose metabolism and the proliferative activity of breast, head and neck tumors based on DNA flow cytometry data. Minn also demonstrated decreased FDG uptake in 17 of 19 patients with malignant head and neck tumors who responded to radiation therapy.

In the large majority of reported cases, both untreated primary and metastatic lesions have had high levels of glycolysis reflected by high levels of FDG uptake. These initial studies have established the potential of PET FDG imaging as a tumor localization procedure and have produced interesting insights into the prognostic and therapeutic implications of FDG uptake in tumors.

In this issue of the *Journal*, Haberkorn et al. (*26*) report their experience with PET FDG studies of patients with colorectal carcinomas receiving radiotherapy. Their group previously reported the utility of PET FDG studies in identifying recurrent colorectal carcinomas (*22*). In this work, they investigated the effect of radiation therapy on quantitative indices of FDG uptake in the residual primary lesions. Employing a two-ring PET system that generates three simultaneous transaxial images (two in-plane images and one cross-plane image), they studied a total of 44 patients with recurrent colorectal carcinomas after total resections of the original primary lesions. Patients were treated either with standard radiation therapy (photon source) or a combination of standard radiation therapy and neutron therapy. All patients received baseline PET FDG studies and a smaller group were evaluated up to 2 wk after photon therapy and up to 6 wk after neutron therapy.

Using a quantitative index, they refer to as the "standardized uptake value (SUV)," (defined as tissue concentration of FDG in nCi/g divided by the injected dose in nCi per body weight in g), they found that about

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50% of the lesions revealed decreased FDG uptake following therapy. They postulated that inflammatory reactions incited by the radiation therapy could explain the non-decrease of FDG uptake in some cases. This phenomenon is known to last for up to about 6 mo following radiation therapy treatment (*27*). Additionally, they found no synergistic effect between photon and neutron therapy in terms of further decreasing the SUV. Two possible reasons for this observation included continuation of the inflammatory reaction process, and non-responsiveness to neutron therapy by the tumor. This issue of persistent inflammatory reaction versus tumor non-responsiveness could be clarified by additional longitudinal studies with follow-up times beyond 6 mo, as suggested by the authors.

This work represents an important contribution to PET FDG oncologic studies and demonstrates the potential utility of FDG for monitoring the effects of treatment. While some of the issues raised by Haberkorn et al. will require further studies, their observations concerning both the diagnostic and therapeutic implications of the technique are illustrative of the direction PET oncologic studies are heading.

The utility of FDG as a tumor imaging and treatment monitoring agent in systemic tumors, as well as tumors of the central nervous system, illustrates the significance of the axial field of view of the PET technique. While Haberkorn et al. (*26*) have contributed significantly to the evaluation of colorectal carcinomas, the PET system they employed for that investigation produces only three simultaneous cross-sectional images. Even with more modern PET systems equipped with larger numbers of detector rings, the axial field of view is relatively limited and evaluation of larger body regions is difficult. It is for that reason that we developed a total-body imaging technique with PET that produces longitudinal tomographic and two-dimensional images of the total-body distribution of positron-emitting radiopharmaceuticals (*28–30*). This technique is particularly useful for ^{18}F studies, because the 109 min half-life of ^{18}F permits long enough image acquisition times to generate high quality total-body images. We have used this technique both for PET bone scans using ^{18}F ion and for total-body tumor evaluations with FDG (see Fig. 1). These studies are ordinarily performed following a 30-min uptake period after injection of FDG, and can be preceded by kinetic acquisitions of FDG uptake data over limited regions of the body, the extent determined by the axial field of view of the tomograph.

Figure 1 illustrates several examples of FDG images of tumor patients acquired with the total-body technique. Because of the impracticality of performing total-body transmission scans, we generate these images in a nonattenuation corrected mode, although several methods for developing calculated attenuation corrections to whole-body PET images are under investigation at UCLA. Because the sinographic projection data are stored as the patient is incrementally moved through the gantry, the data can be processed and displayed in a two-dimensional mode (Fig. 1A), in longitudinal tomographic mode (Fig. 1 B,C,E,F,G,H), transaxially (Fig. 1D), or in other image planes (e.g., sagittal). This technique is useful for defining primary and metastatic lesions and, because of the large regions of the body included in the image sets, is particularly useful for comparing with other imaging modalities such as x-ray CT, MRI, and plain films. This multimodality approach produces a view of the anatomic and biochemical status of malignant disease in the entire patient.

Because FDG images reflect glycolytic rates of all structures in the field of view, total body FDG images reveal predictably high contrast between tissues with high glucose utilization rates (e.g., striated muscle) versus those with low glucose utilization rates (e.g., bone). The projection images (Fig. 1A) can be displayed at many angles around the patient and are very helpful for quickly reviewing the overall FDG distribution. The tomographic images add anatomic precision to the

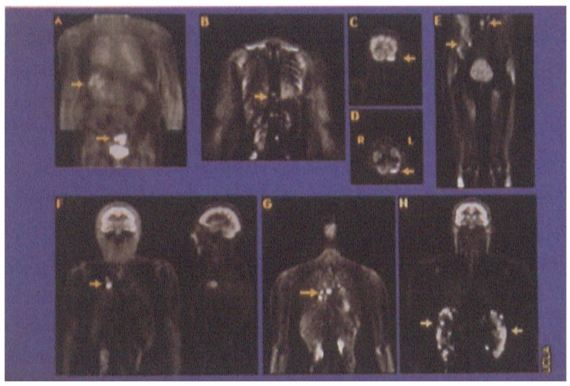

FIGURE 1. All images were acquired on a Siemens 931 tomograph following the injection of 10 mCi FDG (after a 40-min uptake period) using the whole-body acquisition and processing technique (*28*). The images were not corrected for attenuation. (A) Projection image (two-dimensional) of the torso of a patient with primary colorectal carcinoma (lower arrow) with metastases to the liver (upper arrow). The patient was fasting, so therefore very little myocardial uptake is evident. Selected coronal tomographic (B and C) and transaxial (D) images from a breast cancer patient with metastases to the spine (B, multiple lesions at level of arrow and below) and the cerebellum (C and D). (E) Coronal tomographic image illustrating abdominal metastases (arrows) in a patient with ovarian carcinoma. (F) Coronal tomographic image through the torso and head of a patient with a primary bronchogenic carcinoma (arrow). (G) Coronal tomographic image of patient with Hodgkin's disease with multiple thoracic nodal involvement (arrow). (H) Coronal tomographic image of patient with metastatic melanoma to the liver and spleen (arrows).

technique and facilitate lesion detection because of the higher in-plane contrast of focal zones of FDG uptake.

This approach, like other applications of FDG PET tumor imaging, must also be applied in large populations of patients to define its role diagnostically and for monitoring disease. However, whole-body PET images demonstrate the potential of PET in a multiorgan format for multiorgan diseases such as cancer.

In addition to acquiring more clinical studies of cancer patients with PET FDG studies, future investigations will also need to address development of more quantitatively precise methods for characterizing FDG uptake and glucose metabolism in tumors. While complexities surrounding the compartmental model configuration and the numerical values of model parameters, such as the rate constants and lumped constant, remain to be explored, analytical approaches previously employed with neoplasms of the central nervous system (*31*) can also be applied to systemic tumors with appropriate modifications. The SUV of Haberkorn et al. (*26*) should indicate directional changes in FDG uptake in tumors. It does not, however, take into account the dynamic nature of the distribution of FDG between its free and phosphorylated forms (*4–7*) and the impact of differences in the time of image acquisition after injection on the measured image FDG tissue concentration. With major changes in tumor glucose utilization, many quantitative methods, including the SUV, will produce useful quantitative results. To identify more subtle changes in tumor glucose metabolism, however, more rigorous methods are required.

PET also offers the obvious opportunity to evaluate other biochemical characteristics of tumors with other positron-emitting radiopharmaceuticals (*32*). Fundamental processes such as perfusion and oxygen metabolism (*31*), protein synthesis and amino acid uptake in tumors (*34–37*), and DNA replication rates (*36*), all have been evaluated with PET and have great potential in tumor imaging. More targeted radiopharmaceuticals, such as ^{18}F fluoroestradiol for breast cancer (*39*) evaluations, or appropriately labeled chemotherapeutic agents, such as ^{18}F FUdR (*40*), also show promise for tumor imaging, as well as in vivo pharmakokinetic studies.

As PET applications in oncology are further developed and the range of biochemical processes monitored continues to expand, it is likely that FDG will remain the most widely utilized PET cancer imaging agent for some time; it permits us to evaluate the glycolytic characteristics of tumors that, like Warburg's original observations, continue to produce useful, and sometimes surprising, results.

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