INVITED COMMENTARY

Local and Distant Effects of Radiotherapy on FDG Accumulation in Bone Marrow

The use of FDG imaging in oncology is ever increasing, fueled by its demonstrated clinical usefulness that has led to third-party reimbursement, the expanding number of centers with dedicated PET units or coincidence gamma cameras (or both), and the establishment of networks for supply of FDG to centers not having a cyclotron (*1*,*2*). The article by Higashi et al. (*3*) in this issue of *The Journal of Nuclear Medicine* is the latest in a series of fundamental studies of FDG to come out of the University of Michigan, Ann Arbor. Despite the widespread clinical use of FDG imaging in oncology, there remains a need for basic information that can only be obtained in vitro or in animal models.

The greatest strength of nuclear medicine—noninvasive measurement of radiotracer distribution in the body—is also its greatest limitation: There is no direct knowledge of the chemical form of the radiotracer, the type of cell in which it is localized, and the metabolic status of that cell. Within the detected volume of a tumor is an ever-changing mixture that includes viable tumor cells, normal stroma, inflammatory cells, blood vessels with abnormal permeability, and areas of necrosis. Moreover, there may be altered glucose levels, reduced pH, increased interstitial fluid pressure, and decreased oxygen tension. In vitro studies and animal models can tease apart these confounding factors to provide information that will allow correct interpretation of what is seen in the clinic.

Although the usefulness of FDG imaging in diagnosis and staging of certain cancers is well established, the situation is more complicated in the use of FDG to monitor response to radiation or chemotherapy. Several studies of FDG accumulation in tumor models after single-dose or fractionated radiotherapy have been reported (*4*–*6*). The observed pattern of FDG accumulation over time after irradiation is a complex function of the number of viable cancer cells, the extent of energy-requiring repair processes, the number of cells undergoing apoptosis, and the degree of macrophage infiltration.

In the work by Higashi et al. (*3*), a similarly complex pattern is observed in normal bone marrow. The first thing to note is the high level of FDG accumulation in bone marrow—levels similar to those of the spleen and exceeded only by the heart (the brain was not excised in this study) (*3*, Table 1). The irradiated marrow shows a significant increase in FDG accumulation over baseline on day 1, a significant decrease on day 9, and a return to normal on days 18 and 30. The early peak is likely associated with glycolysis in infiltrating neutrophils, whereas the subsequent trough is associated with decreased cellularity (*3*). Accumulation of FDG in neutrophils and macrophages is a well-known cause of false-positive findings in oncologic PET (*7*,*8*) and is now being exploited in the use of FDG for imaging inflammation (*9*).

However, it is the distant effects, seen in the bone marrow of the contralateral, nonirradiated leg and in the spleen and lung, that are perhaps most interesting. Indeed, the extent of these remote effects is remarkable. Whereas the peak accumulation of FDG in the bone marrow of the irradiated leg on day 1 is 40% above the control value, the increases in the bone marrow of the nonirradiated leg, the spleen, and the lung on day 18 are 50%, 67%, and 72%, respectively, above the control value (*3*, calculated from Table 1). As Higashi et al. (*3*) point out, these phenomena in nonirradiated tissues could be mediated by cytokines released in response to radiotherapy. Additionally, this might be potentiated by acute, post-translational upregulation of glucose transport in hematopoietic cells that can also be induced by cytokines (*10*–*12*) and that would not be evident in terms of altered cellularity or by Western or Northern blotting. Indeed, Higachi et al. found that the nonirradiated marrow of the irradiated rats on day 18 was no different from that of the control group in terms of total cellularity or differential counts (*3*, Tables 4 and 5).

The remote effects seen in bone marrow in this preclinical study—if they are reproduced in the clinic after standard fractionated radiotherapy—may represent another limitation to the specificity of FDG imaging in the monitoring of response to radiotherapy (*7*,*8*). It will be important to know the extent and time course of such effects. As Higashi et al. (*3*) point out, such uptake must not be misinterpreted as metastatic spread, and care must be exercised in the use of irradiated-to-nonirradiated activity ratios for semiquantitative analysis.

FDG has been the workhorse of PET in oncology, despite its limited specificity. However, the recent development of ^{18}F-labeled markers of protein and DNA synthesis, previously available only with a ^{11}C label and thus limited to centers with a cyclotron, will allow multiparameter assessment of tumors to become more widely available (*13*,*14*). This holds promise for im-

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proved specificity of PET in oncologic imaging.

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