EDITORIAL

ANNALS OF SURGERY
Vol. 227, No. 3, 324–325

Future of Positron-Emission Tomography in Oncology

The article by Flanagan and associates featured in the "What's New in General Surgery" section of this issue is timely and important.[1] The authors call our attention to one of the areas of medicine that truly enjoys significant progress—the field of imaging science. Medical imaging technology is rapidly expanding, and the role of each modality used in medicine today is constantly being redefined. In clinical oncology, advances in imaging continue to provide some of our greatest progress, especially in early detection and staging of disease. The constantly increasing power of imaging is dramatically enhancing the capacity to screen for early stage disease to define accurately the true extent of the cancer and to locate early metastatic recurrences more precisely. These advances have significantly impacted the ability to plan appropriate surgeries and to make crucial nonsurgical therapeutic decisions.

Whereas conventional imaging modalities—including dynamic (helical) computerized axial tomography and magnetic resonance imaging—have provided ever increasing sensitivity and specificity in defining the extent of the tumor, they both depend on anatomic alterations to detect disease. Nuclear imaging techniques, positron emission tomography (PET), and monoclonal antibody (mAb) scintigraphy, in contrast to computed tomography (CT) and magnetic resonance imaging (MRI), have the ability to detect cancer based on physiologic and biochemical processes within the tumor tissues.[2–5] Positron emission tomography uses radioactive chemicals made with a positron-emitting isotope. When the isotope decays, a positron is emitted, collides with an electron, and causes both particles to be annihilated. The result is a release of two 511-keV photons that radiate outward in opposite directions, 180° from each other.[6] The scanner is designed to detect these photons and to determine their point of origin. Determining the point of origin creates a CT-like image. For example, PET images generated with the glucose analogue 2[18F] fluoro-2-deoxy-D-glucose (FDG) allows direct assessment of cellular glucose metabolism.[7] FDG enters the cell's metabolic cycle as glucose does, but because FDG lacks a hydroxyl group in the 2-position, its first metabolite FDG-6-PO_4 cannot undergo further metabolism and it becomes trapped in the tissue as 18FDG phosphate without further breakdown.[8] Viable and rapidly dividing tumor cells have a greater rate of glucose metabolism than normal tissues and an obviously greater rate than adjacent tumor cells undergoing necrosis or programmed cell death. The increased rate of glycolysis associated with malignancy was first described by Warburg[9,10] in the 1930s and is caused, in part, by a greater level of intracellular phosphokinases and glucose transport proteins. FDG—PET has been shown to detect a variety of tumor foci, including cancers of the colon and rectum, breast, lung, head and neck, and musculoskeletal tissues.

FDG has distinct advantages when compared with other positron-emitting radiopharmaceuticals, which accounts for its current popularity. It can be prepared in quantities that allow study of a number of patients during its half-life; as noted above, the fact that it is trapped in the cell greatly simplifies its use as an imaging agent and the longer half-life of 110 minutes provides an opportunity for off-site preparation avoiding the need for an on-site cyclotron.[11] Although FDG is currently the most used radiopharmaceutical for clinical PET in the study of patients with cancer, ^{11}C-methionine and fluorine-18 labeled tyrosine are used for experimental studies of amino acid transport and protein synthesis, and ^{11}C-thymidine is used for determining tumor cell proliferation.

Positron emission tomography is not a recent discovery. It has been the subject of investigation since the early 1960s. Only recently, however, has PET imaging begun to evolve from a research tool used to provide detailed quantitative assessment of cerebral and myocardial metabolism to a promising modality for early detection and decision making in the management of patients with malignant tumors.[2,5] The development of PET scanners capable of acquiring whole-body images in reasonable time frames, combined with full three-dimensional image construction and the simultaneous acquisition of both emission and transmission data, are responsible for this renewed interest.[11,12] As a result, in clinical oncology, PET imaging is evolving to the point where it has a number of specific potential applications that are summarized below.

1. Characterizing tumor lesions using receptor-binding small peptides (^{111}In-Octreotide) and determining tumor grade (brain tumors), thus establishing a noninvasive diagnosis;

2. Differentiating recurrent tumors from surgical scar, altered postsurgical anatomy, and radiation-damaged tissue;
3. Determining the extent and location of the tumor when undetectable by other imaging modalities;
4. Monitoring the response of tumor to therapy by quantitating viable remaining tumor;
5. Measuring tissue localization, concentration and metabolic activity of specific anticancer agents as a rapid method of determining efficacy.[13]

There are two important advantages to functional tumor imaging over anatomic imaging. They include the ability to provide both rapid whole-body images and metabolic or functional information regarding the tumor tissue. The field of functional imaging is growing rapidly with the development of tumor-specific and nonspecific radiopharmaceuticals and new highly sophisticated imagery systems. An example of the latter is the development of new detection systems that combine single photon-emission CT (SPECT) with PET as a hybrid camera system that allows coincidence detection and photon detection by electronic collimation from positron emitting agents such as FDG.

Although the results by Flanagan and colleagues suggest an important role for FDG—PET in evaluating patients with colorectal cancer who have elevated CEA and normal CT–MRI scans, some caution is warranted.[1] First, the number of patients studied (22) is small with the inherent biases of retrospective analysis. Second, using only a 6-month cut off for requiring CT–MRI evidence of tumor presence before determining FDG-PET to be falsely positive is probably insufficient based on what is known regarding the natural history of recurrent colorectal cancer. Third, although not specifically stated by the authors, it appears that the method used to analyze FDG accumulation in tumors was a less rigorous method—one that has come under some criticism. In the less rigorous method, a standard uptake value (SUV) is calculated by simply dividing the concentration of FDG in the region of interest at 45 to 60 minutes after injection by the dose injected normalized to body weight.[11] This is, at best, semiquantitative and depends heavily on time of measurement. This method makes one assume that the blood-to-tissue time–activity curves measured by PET do not vary from patient to patient. A more rigorous calculation based on determining the actual glucose metabolic rate remains the preferred method.[11,14,15] Even so, the authors have reported excellent rates of detection. There appear to be reasonable explanations for false-positive FDG-PET scans, and the authors show a respectable 89% positive-predictive value and a 100% negative-predictive value. Although it is unclear what constitutes the minimal amount of tumor that can be reliably detected by FDG–PET, the results of studies such as the one reported by Flanagan et al. will certainly continue the debate with investigators who tout the efficacy of radioimmunoscintigraphy.[1] A direct comparison is clearly warranted as investigators work to define the role of functional imaging in clinical oncology.

John E. Niederhuber, MD
Director, Comprehensive Cancer Center
University of Wisconsin—Madison

References

1. Flanagan FL, Dehdashti F, Ogunbiyi OA, Kodner IJ, Siegel BA. Utility of FDG-PET for investigating unexplained plasma CEA elevation in patients with colorectal cancer. Ann Surg 1998;227:319–323.
2. Moh CK, Schiepers C, Seltzer MA, et al. PET in oncology: will it replace the other modalities? Semin Nucl Med 1997;27:94–106.
3. Tempero M, Brand R, Holdeman K, Matamoros A. New imaging techniques in colorectal cancer. Semin Oncol 1995;22:448–471.
4. Thoeni RF. Colorectal cancer. Radiologic staging. Radiol Clin North Am 1997;35:457-485.
5. Gupta N, Bradfield H. Role of positron emission tomography scanning in evaluating gastrointestinal neoplasms. Semin Nucl Med 1996;26: 65–73.
6. Phelps ME, Mazziotta JC, Schelbert HR. Positron emission tomography and autoradiography: principles and applications for the brain and heart. New York: Raven Press, 1986.
7. Phelps ME, Huang SC, Hoffman EJ, et al. Tomographic measurements of local cerebral glucose metabolism in humans with (F-18)-2-fluoro-2-deoxy-D-glucose: validation of method. Ann Neurol 1979;6:371–388.
8. Gallagher BM, Fowler JS, Gutterson NI, et al. Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of [18F]-2-deoxy-2-fluoro-D-glucose. J Nucl Med 1978;19:1154–1161.
9. Warburg O, Wind F, Neglers E. On the metabolism of tumors in the body. In, Warburg O (ed): Metabolism of Tumors. London, England. Constable, 1930 pp 254–270.
10. Warburg O. The metabolism of tumors. New York: Smith RR, 1931 pp. 129–169.
11. Fischman AJ. Positron Emission Tomography in the clinical evalution of metastatic cancer. J Clin Oncol 1996;14:691–696.
12. Park CH. The role of radioisotopes in radiation oncology. Semin Oncol 1997;24:639–654.
13. Kissel J, Brix G, Bellemann ME, et al. Pharmacokinetic analysis of 5-[^{18}F]fluorouracil tissue concentrations measured with positron emission tomography in patients with live metastases from colorectal adenocarcinoma. Cancer Res 1997;57:3415–3423.
14. Sokoloff L, Reirich M, Kennedy C, et al. The ^{14}C-deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure and normal values in the conscious and anesthetized albino rat. J Neurochem 1997;28:897–916.
15. Phelps ME, Huang SC, Hoffman EJ, et al. Tomographic measurements of local cerebral glucose metabolism in humans with (F-18)-2-fluoro-2-deoxy-D-glucose: validation of method. Ann Neurol 1979;6:371–388.