EDITORIAL

Commentary on "The Applications of PET in Clinical Oncology"

Positron emission tomography (PET) of the brain has been available for over a decade, and its role is gradually being defined. The recent improvement in whole-body PET scanning technology has resulted in a large number of studies, of which one of the most interesting is in the field of oncology. Since PET scanning can produce both qualitative and quantitative spatial and metabolic information, it can assume a complementary role to routine x-ray computed tomography (CT) and magnetic resonance imaging (MRI). However, the high cost of PET scanners and the cyclotron necessary to generate the positron-emitting radionuclide, as well as the relatively poor resolution compared with CT scans, have to date limited PET's clinical usefulness. Drs. L. G. Strauss and P. S. Conti have summarized the data currently available on the role of whole-body PET scanning in the field of oncology, and have added a significant amount of information that has not yet been available.

Whole-body PET studies with metabolically active tracers have focused on qualitative imaging of primary or recurrent tumors, lymph nodes, and distant metastases. Quantitative studies measuring uptake of metabolically active tracers such as ^{18}F-fluorodeoxyglucose (FDG) have addressed the issue of tumor "grade" and response of the tumor to chemotherapy and radiotherapy. Other quantitative studies using radiolabeled chemotherapeutic agents such as ^{18}F-fluorouracil have addressed the issue of tumor drug uptake and predicting response to chemotherapy.

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IMAGING STUDIES

CT, MRI, and endoluminal ultrasound imaging provide relatively good information about the primary tumor, the presence of metastatic lesions, and, rarely, the involvement of lymph nodes. PET scanning offers little to the patient in the evaluation of the primary tumor. The only study addressing the T-staging of a tumor was made by Conti and Strauss. They studied 20 patients with malignant lung tumors and found that the PET scan correctly changed the T-staging of the primary tumor in 8 of the 20 patients, while in 12 patients CT staging had been accurate and was confirmed on PET scanning. PET scans also were able to differentiate benign from malignant lesions, although no data are presented. Unfortunately, the limited range of their study precluded the examination of lymph nodes.

PET scanning will likely play a larger role in defining recurrent or metastatic disease. In rectal cancer, despite the increasing use of adjuvant radiation therapy and chemotherapy, local pelvic recurrence remains a significant problem. For patients with pelvic pain or a rising CEA after a low anterior resection or abdominal-perineal resection, it can be very difficult to distinguish between scar and recurrence. Conti and Strauss studied 33 patients who had previously undergone surgery for rectal cancer; 23 had biopsy-proven recurrence and 10 had scar tissue. Before the PET scan, a CT scan with ^{18}[F]FDG was necessary to delineate the pelvic mass.

It is important to note that the PET scan alone does not give adequate morphologic information to define the area of suspected recurrence. Twenty-two of the 23 patients with recurrence were correctly identified by high uptake of FDG on PET scan as representing recurrent disease. All patients with scar tissue had low FDG uptake. A similar study with [^{15}0]H_2O (a measure of tumor blood flow) failed to differentiate between scar and tumor. Inflammatory tissue can also take up higher than normal quantities of [^{18}F]FDG, which can result in false-positive tests. This is increasingly important as the role of adjuvant radiation for rectal cancer becomes more prominent. In addition, a significant amount of tracer is excreted in the urine, thus limiting the usefulness of this technique in the pelvis. Despite these limitations, the problem of pelvic recurrence is such a significant issue, not only for rectal cancer, but for gynecologic, urologic, and soft-tissue tumors, that further studies in the role of PET scanning in this area will be awaited with interest by many oncologists.

Several studies have addressed the issue of imaging metastatic cancer. Carbon-11-thymidine has been used for imaging lymphoma, ^{11}C-alpha-aminoisobutyric acid and [^{18}F]FDG for imaging metastatic melanoma, and [^{18}F]FDG for imaging metastatic breast cancer. All studies report some success, but frequently not all metastases were visualized. Many studies have been remiss in assessing and reporting the extent of disease in the patient who has a positive PET scan. Clearly, if all sites of disease could be demonstrated by one PET scan, this would be a clinically useful tool for staging a large variety of tumors.

Preoperative staging of a tumor is very useful in this age of neoadjuvant therapy. It is often preferable to treat a patient with advanced local cancer with preoperative radiation or chemotherapy. Whereas CT, MRI, and endoluminal ultrasound have allowed us to define accurately the T-stage in many tumors, N-staging has proved more difficult. Whereas enlarged nodes seen on CT, MRI, or ultrasound are frequently malignant, up to 50% of positive lymph nodes in colorectal cancer are not enlarged. Any methodology that would improve our

ability to nonoperatively stage patients eligible for preoperative adjuvant therapy would be useful. Unfortunately, the resolution of the PET scanners at this time may not be adequate to assess nonenlarged lymph nodes.

TUMOR GRADE

Some of the most provocative studies described by Drs. Strauss and Conti examine the hypothesis that FDG uptake is an indicator of proliferative activity or ploidy of the tumor. While these studies are predominantly based on animal experiments, the usefulness of this information is clear. For example, if high- and low-grade sarcomas could be distinguished preoperatively, it would be possible to tailor neoadjuvant protocols appropriately. These data are limited but rapidly being accumulated, and the results promise to be very interesting.

TUMOR DRUG UPTAKE

An application that may be useful in predicting response and tailoring treatment is the ability to measure tumor drug uptake with PET scanning using radiolabeled chemotherapeutic agents. The drug that has been most thoroughly examined is ^{18}F-5-FU. In using PET scanning over time, it is possible to measure drug uptake (a function of blood flow, transport into the cell, and retention by the cell). The PET scanner measures only the amount of ^{18}F label in the region of interest, whether normal tissue or tumor. In most reports, drug uptake correlates with blood flow; in other words, good blood flow is a prerequisite of good tumor drug uptake. However, many tumors with good blood flow do not have high tumor drug levels because transit into the cell is poor or egress from the cell is good.

Most reported studies have not measured tissue drug levels over time, thus, it has not been confirmed that measurement of ^{18}F content at a single point in time is an accurate assessment of active drug or metabolites in the cell. The metabolism of 5-FU is complex and involves metabolism into inert compounds and active compounds, such as F-dUMP, which inhibits thymidylate synthetase and affects both the DNA and RNA systems. It is a generalization to assume that most or all of the ^{18}F label represents active material. In order to assess this complex problem and to understand exactly what is being measured on PET scanning, it will be necessary to measure drug and metabolite levels over time in patients undergoing PET scanning for tumors. Studies show that if no drug is in the tumor, these patients do not respond to therapy. Unfortunately, while ^{18}F-5-FU has been given to many patients, and uptake measured, few studies have correlated such findings with patient response to chemotherapy, which is, of course, the gold standard by which to judge the results of the scan. If it could be confirmed that the scan successfully predicts response, then it would be very interesting to study a variety of modifying agents in order to improve response. It is intriguing to think that a patient's chemotherapy could be individually planned to maximize the blood flow and transport into the cell, while minimizing the transport out of the cell. PET scanning offers the opportunity to look at all three components of drug uptake by using multiple-tracer dilution techniques.

RESPONSE TO THERAPY

The role of the PET scanner in identifying early response to chemotherapy and radiotherapy is controversial. FDG as an analog of glucose is transported into cells and phosphorylated. Radiation therapy and chemotherapy will alter the glucose metabolism of the tumor cell. Clearly, if the cell is dead, there will be no uptake of glucose. However, if the therapy slows the metabolism permanently or temporarily, the FDG uptake will be decreased. Whether a temporary change in glucose metabolism following therapy is an accurate predictor of response is the critical question in these studies. The authors describe patients whose FDG content decreased during treatment but whose tumor did not respond by CT or MRI criteria. Conversely, some patients who did respond to treatment had little change in their FDG content on PET scanning. Furthermore, changes in FDG uptake after therapy were dependent on the site of the tumor; primary tumors changed more than metastatic tumors. Further studies are necessary to understand how changes in FDG content during therapy are to be interpreted.

CONCLUSION

PET scanning offers many research opportunities to explore in the field of oncology. However, it remains a very expensive, labor-intensive modality. It is likely that in the near future its applications will be limited and that its major role will be in the field of research. Its role will always be complementary to morphologic scans such as CT and MRI. However, it provides a unique view of the physiology of tumor biology, which no other methods can provide. Its role in studying in vivo tumor biology makes it an exciting tool of the future.

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