Positron-Emission Tomographic Imaging of Cancer: Glucose Metabolism and Beyond

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Positron emission tomography (PET) has become an important diagnostic tool in oncology. We briefly review the physics of PET, instrumentation for imaging, and approaches to radiopharmaceutical production. The principles underlying the use of [¹⁸F]-fluorodeoxy-glucose (FDG) are described, and the clinical experience with FDG pertinent to radiation oncology is reviewed.

ndividualized treatment planning in oncology L relies on detailed information on cancer stage and tumor grade. Tumor grade is determined by histopathologic analysis of biopsy material and indicates tumor aggressiveness and the likelihood of responding to a particular therapy. Tumor stage is determined by a combination of imaging and biopsy to indicate the local and distant spread of disease. Metabolic imaging methods capable of providing regional information on tumor biochemistry, such as positron emission tomography (PET), offer the oncologist a unique combination of information on both tumor biology and extent and, in addition, on the regional heterogeneity of biologic properties.¹⁻⁴ In this way, PET imaging provides functional capabilities that add to the existing set of diagnostic tools. Metabolic imaging provides a method of tumor staging that is complementary to anatomically based imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI). Tumor sites that are not anatomically different from normal tissue may be biochemically distinct, and because PET imaging is inherently quantitative, it can quantify the regional change in tumor physiology over the course of therapy.

In this article, we review the underlying principles of PET and discuss approaches to imaging

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instrumentation and tracer production. We review physiologic aspects of the most widely used PET tracer for clinical imaging, [¹⁸F]-fluorodeoxyglucose (FDG), and highlight clinical applications of FDG-PET that are relevant to radiation oncology. Finally, we discuss preliminary results using alternate PET tracers to explore aspects of tumor physiology other than glucose metabolism, including tumor receptor expression and cellular proliferation. This will serve as an introduction to the current and future capabilities of PET, a diagnostic tool that will become an integral part of the practice of radiation oncology.

PET Principles and Instrumentation

The Physics of PET

Positron-electron annihilation after positron emission leads to 2 opposing 511-keV photons. The detection of this "coincidence" pair defines a line along which positron emission has occurred. PET tomographs are designed to detect photon pairs along all possible projection lines through the body to reconstruct quantitative maps of tracer concentration. Tomographs primarily collect annihilation photon counts from the patient (emission scans); however; they also use transmission or attenuation scanning to correct for the body's absorption of photon pairs (Fig 1). This is accomplished, in analogy to transmission CT, by rotating a source around the patient to measure the fraction of photons absorbed along any coincidence line.⁵ This allows for precise correction of body attenuation and an estimation of the absolute regional concentration of tracer in the body.⁶

PET Tomographs

Commercially available, dedicated PET tomographs achieve high sensitivity to annihilation

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Figure 1. Scanning modes for PET: Emission scanning (left) captures annihilation photons from positronemitting tracers in the patient. Transmission scanning (right) uses a source external to the patient to measure photon attenuation.

photon pairs using a ring of detectors surrounding the patient. Fundamental physical processes limit the ultimate spatial resolution of PET in patient imaging to 3 to 4 mm, depending on the positron emitting isotope.⁷ Further practical considerations, including cost and tracer radiation dose considerations, limit practical spatial resolution to 5 to 10 mm.^{6,8} Current systems use detectors that are blocks of small crystals⁹ or large continuous crystals.¹⁰ Dedicated PET tomographs using either approach can achieve limiting spatial resolution of approximately 5 mm and provide excellent image quality for clinical FDG-PET imaging, achieving high quality imaging of the torso in 45 to 60 minutes.

Because many smaller facilities do not have sufficient volume to warrant a dedicated PET device, much work has gone into the adaptation of conventional nuclear medicine cameras to image positron-emitting radiotracers, in particular, FDG. The use of high-energy collimators to permit single-photon emission computed tomography (SPECT) imaging of positron tracers yields spatial resolution that is not acceptable for most clinical FDG oncology applications.¹¹ More recently, SPECT cameras with 2 opposing detector heads have been adapted to "coincidence imaging," capable of detecting annihilation photon pairs.¹² These devices have higher spatial resolution than collimated SPECT; however, because they are forced to make compromises in design to accommodate both coincidence and single-photon imaging, the overall performance of the hybrids as PET scanners is inferior to dedicated PET tomographs.^{11,13} PET-SPECT hybrid cameras can provide adequate image quality for limited applications that need to cover only a portion

of the body.¹⁴ Ongoing work in the use of PET-SPECT hybrids may broaden the applicability of these systems; however, institutions with a sufficient practice in oncology are likely to benefit from the use of a dedicated PET tomograph.

Isotope Production

The positron-emitters most commonly used in oncologic PET are ¹⁸F, ¹¹C, and ¹⁵O.¹⁵ These have half-lives of 110, 20, and 2 minutes, respectively, and therefore require local production. Of these, only ¹⁸F is used commonly in routine clinical applications (in the form of [¹⁸F]-FDG). With a nearly 2-hour half-life, FDG can be produced in regional tracer production facilities and shipped to sites that are within a 1 to 2 hour flight of the production facilities have been constructed and serve some of the large metropolitan areas in the United States and Europe.

Positron-emitting isotopes are typically produced by a medical cyclotron. Small, self-shielding cyclotrons capable of fitting in a modest-sized room with minimal additional shielding have been developed and are ideal for hospitals or regional production facilities.¹⁶ These devices can provide high beam current for production of 18 F, ¹¹C, and ¹⁵O, and come equipped with automated targetry and "black boxes" for radiochemistry of more routine radiopharmaceuticals like FDG. Other longer-lived positron-emitting isotopes such as ¹²⁴I, ^{94m}Tc, and ⁶⁴Cu have shown promise for applications that require imaging periods of several hours to days.¹⁷ These isotopes require more versatile cyclotrons for production and, therefore, typically come from centralized production facilities. Their longer half-life means they can be shipped widely, as with isotopes such as ²⁰¹Tl and ¹¹¹In.

FDG Biochemistry and Physiology

Tracer Biochemistry

FDG was originally designed as a tracer of brain glucose metabolism¹⁸⁻²⁰ and arose from work using [¹⁴C]-deoxyglucose and an autoradiographic method to quantify regional brain glucose metabolism in animals.²¹ Its biochemical behavior is illustrated in Fig 2. FDG is transported into cells and phosphorylated in parallel to glucose; however, unlike glucose, it is not a substrate for



Figure 2. FDG biochemistry: (A) Chemical structure of FDG in comparison with glucose. (B) Diagram of FDG metabolism in comparison with glucose. FDG phosphorylated by hexokinase is "metabolically trapped" and therefore has increased uptake and retention in metabolically active tissue.

enzymatic reactions beyond phosphorylation. Furthermore, it is not readily dephosphorylated in most tissues, including tumors, and the phosphorylated compound cannot cross cell membranes. Therefore, phosphorylated FDG is "metabolically trapped" in the cell as FDG-6P.

The rate of FDG uptake and trapping is a quantitative indicator of glucose metabolism. The term "lumped constant" refers to a proportionality constant describing the ratio of FDG metabolism to glucose metabolism, and its value has been determined in normal brain to be in the range of 0.4 to 0.8.19,20,22 The most accurate method of determining the rate of FDG metabolism requires dynamic PET imaging and blood sampling and uses kinetic analysis to estimate the flux of FDG from the blood to tissue where it is trapped as FDG-6P. Static measures of FDG uptake normalized to the injected dose, frequently referred to as the standard uptake value (SUV), provide an approximate indicator which correlates with FDG metabolism,23

$$SUV = \frac{A}{ID/w}$$

where A is the tissue tracer content (μ Ci/g), ID is injected dose (mCi), and w is patient weight (kg). Although less precise than kinetic determinations, SUV is conveniently implemented in a routine clinical setting. Several alternatives to the SUV with slightly better correlation with kinetic estimates of FDG metabolic rate have also been proposed.^{24,25}

Elevated FDG Uptake in Tumors

The studies of Warburg in the 1930s²⁶ established that glucose metabolism is elevated in tumors in comparison with normal tissues. The observation that FDG accumulates in most untreated tumors led to the concept that increased FDG uptake reflects increased glucose metabolism in tumors. While this is undoubtedly an important cause of uptake in tumors, some recent work has suggested that other factors may be important. Spence et al²² compared FDG and 1-[¹¹C]-glucose metabolism and found a consistent relationship between glucose and FDG metabolism in normal brain, in agreement with prior work. However, the relationship between FDG and glucose metabolism varied considerably in brain tumors, which tended to have higher levels of FDG metabolism relative to glucose metabolism when compared with normal brain. In other words, the handling of FDG relative to glucose is different in tumors versus normal tissue in a way that may increase the prominence of FDG uptake in tumors. The reasons for these differences may be related to phosphorylation, transport, or other factors, and the detailed biochemistry of FDG in tumors is the subject of investigations in many laboratories (see, for example, Aloj et al²⁷). These ongoing studies seek to elucidate the nature of FDG uptake in tumors and will provide further insights into the biologic significance of increased FDG uptake in tumors.

Clinical Applications of FDG-PET

The role of FDG-PET in clinical radiation oncology has vastly expanded in recent years. PET has helped improve initial patient staging, assess response to treatment, and in a more investigational setting, predict tumor aggressiveness and patient outcome. This review serves to highlight the relevance of PET to the practicing radiation oncologist, emphasizing its application to current and future oncologic management. The reader is referred to other excellent reviews for more detailed discussions of individual disease sites.^{2,28}



Figure 3. Example of FDG-PET for cancer staging. A 35-year-old woman with a history of invasive ductal right breast cancer at age 30. She underwent mastectomy with 2 of 17 axillary lymph nodes positive for metastatic breast cancer and was treated with adjuvant chemotherapy. She presented 5 years later with sternal pain and cough. (A) CT showed suspicious right hilar (white arrow) and mediastinal (black arrow) lymph nodes, but no clear sternal involvement. (B) Selected FDG-PET coronal images are shown in B, C, and D (front to back) and demonstrate 2 internal mammary lymph node metastases (arrow in B), extension to the sternum (arrow in C), bilateral hilar (arrows in D), and mediastinal involvement (not shown). Normal cardiac uptake is also seen (dotted arrow in D). Mediastinal lymph node biopsy confirmed metastatic breast cancer. This case shows the ability of FDG-PET to delineate all sites of active disease.

Staging

Accurate cancer staging is crucial to both correctly predicting prognosis and tailoring treatment strategies to each individual patient. PET imaging has been used as an adjunct to traditional anatomic modalities to more accurately assess local and regional disease extent and to detect early sites of metastasis (Fig 3). Preoperative FDG-PET evaluation of regional metastases has been tested in a number of disease sites, including the axilla^{29,30} in breast cancer, the neck

 Table 1. Accuracy of FDG-PET for Mediastinal

 Staging of NSCLC from Selected Studies

Study	No. of Patients	Sensitivity	Specificity
Berlangieri ³⁶	50	80%	97%
Saunders ³⁵	97	71%	97%
Vansteenkiste ³⁷ (PET + CT)	68	93%	95%
Dwamena ³⁸ (meta-analysis)	514	79%	91%

in squamous cell carcinomas of the head and neck,^{31,32} and the liver in colorectal carcinoma.^{33,34}

FDG-PET has been most extensively studied in non-small cell lung cancer (NSCLC), where surgical assessment of the mediastinal lymph nodes is typically performed before definitive resection (Table 1). Nodal involvement radically alters the prognosis, and often results in a decision not to attempt what would have otherwise been considered a potentially curative surgical resection. The largest of these studies, reported from Guy's and St. Thomas' Hospitals in London³⁵ involved 97 patients with NSCLC. All patients underwent both FDG-PET and conventional CT imaging before planned surgical resection. Imaging results were compared with surgical biopsy. FDG-PET, compared with CT, was found to be more sensitive (71% v 20%) and more specific (97% v 90%) for mediastinal involvement. Berlangieri et al³⁶ similarly compared the predictive value of FDG-PET against the surgical standard mediastinoscopy in evaluating the



Figure 4. Example of FDG-PET to follow lymphoma response to therapy. A 21-year-old patient with Hodgkin's disease treated with chemotherapy (A) Pretherapy transverse CT scan and (C) pretherapy coronal FDG-PET scan show large right subclavicular/supraclavicular mass (thick arrows). The maximum SUV of this mass was 9.8. FDG-PET also shows right hilar disease (thin arrow), which was not seen on CT (not shown). (D) Post-therapy FDG-PET image shows resolution of all abnormal foci except a superior supraclavicular focus (thick arrow), also seen on (B) post-therapy CT. Maximum SUV of this lesion was 5.2, suggesting a response to therapy, but residual viable tumor. Dotted arrow indicates normal cardiac uptake in pretherapy and post-therapy FDG PET scans.

mediastinum. Fifty patients with NSCLC underwent CT, FDG-PET, and subsequent surgical staging. FDG-PET involvement was assessed by a physician blinded to the rest of the staging evaluation. CT was considered positive when any lymph node (long axis) measured greater than 1 cm. FDG-PET was found to have a sensitivity of 80% (65% for CT), a specificity of 97% (90% for CT) and an overall accuracy of 95%. Vansteenkiste et al³⁷ achieved excellent results in predicting pathologic mediastinal involvement when CT was used in conjunction with FDG-PET. The combination resulted in a sensitivity of 93% and a specificity of 95%. It is apparent that these 2 diagnostic modalities function in a complementary rather than exclusionary fashion, with FDG-PET offering biologic information and CT anatomic detail. A recent meta-analysis by Dwamena et al at the University of Michigan³⁸ confirmed these results in 514 patients collected from 14 studies undergoing preoperative FDG-PET, and 2,226 patients in 29 studies with preoperative CT evaluation of the mediastinum. Both sensitivity and specificity of FDG-PET (79% and 91%, respectively) were greater than that of CT (60% and 77%, respectively). However, it is not clear that FDG-PET can replace mediastinoscopy in patients being considered for surgical cure. Clearly, FDG-PET is less sensitive than histopathologic evaluation for identifying small-volume diseases. Nonetheless, more limited and directed surgical staging is often possible.

FDG-PET is also useful in the noninvasive evaluation of distant metastatic disease in lung cancer. Erasmus et al, at Duke University,³⁹ studied 27 patients with known NSCLC and an adrenal mass shown on conventional imaging (mean size, 3 cm). FDG-PET identified metastatic disease in 25 of 33 lesions, 23 of which were confirmed positive by biopsy. All lesions negative by PET were also negative histologically (sensitivity, 100%). In a cohort of 94 patients at the University Hospital, Zurich, prospectively evaluated by FDG-PET imaging for mediastinal involvement,⁴⁰ 14% were found to have distant metastatic disease that was not shown by conventional CT.

Response and Residual Disease

In addition to providing a sensitive and noninvasive tool for oncologic staging, FDG-PET has also shown utility in assessing response to treatment (Fig 4). This is particularly helpful in lymphoma, where post-treatment fibrosis can obscure detection of residual disease.^{41,42} In a study of 44 patients with abdominal presentations of Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL),⁴³ FDG-PET proved superior to anatomic imaging in determining post-treatment tumor viability. Thirtyseven of the 44 patients had residual CT abnormality following chemotherapy with or without radiation therapy. Thirteen patients were also shown to be positive by FDG-PET, and all of these patients eventually relapsed. Only 1 patient, negative by FDG-PET but positive by CT, relapsed. The relapse-free survival rate was 0% for those patients positive by FDG-PET, and 95% for those negative by FDG-PET at 2 years. Clearly, patients shown to have residual disease by FDG-PET should be considered for additional treatment. Similarly, Cremerius et al44 studied the diagnostic power of FDG-PET in 27 patients following treatment for lymphoma. FDG-PET was positive in 15 patients with residual disease (confirmed by biopsy or subsequent relapse). Of 12 patients who remained disease free, 11 were negative by FDG-PET. The single false-positive finding was thought to be secondary to inflammation resulting from radiation pneumonitis.

FDG-PET can also serve as a sensitive means to monitor therapy in progress, with an eye to changing ineffectual treatments in midcourse. A provocative study from Germany used early response to FDG-PET to predict outcome. The treatment course of 11 patients with NHL was monitored by Romer et al.45 All patients underwent FDG-PET imaging before treatment, at 1 week, and again at 6 weeks. The mean decrease in SUV at day 42 was 79%. Interestingly, the tumor SUV levels at week 1 were significantly lower in the group of 6 patients remaining in remission after 16 months follow-up, than in the group of patients eventually relapsing. Patients showing no response by FDG-PET at 1 week might be candidates for more aggressive/altered treatment regimens. Others have used FDG-PET in a similar fashion to monitor response to neoadjuvant chemotherapy in patients with locally advanced breast cancer.46,47

FDG-PET can also aid in determining response to organ preservation treatment in head and neck cancer, where true disease status after radiation is often obscured by fibrosis. Greven et al⁴⁸ reviewed the utility of FDG-PET in 31 patients suspected of persistent disease after definitive radiation therapy for carcinoma of the larynx. The overall sensitivity of FDG-PET was 80% and the specificity was 81%. The authors concluded that potentially morbid post-treatment biopsy can/be postponed in FDG-PET-negative patients, /despite clinical evidence of persistent disease. Similarly, Farber et al⁴⁹ reviewed their experience with 28 patients with head and neck cancers treated with definitive radiation therapy, all suspected of harboring recurrent/persistent disease. Twelve of 13 patients with FDG-positive scans had biopsy-proven active disease; 2 of 15 patients with negative PET imaging did have residual disease, yielding an overall accuracy of 89%. Others have also observed high sensitivity and specificity values for FDG-PET in a similar setting of suspected residual/recurrent disease after definitive treatment.^{50,51} Thus the results of FDG-PET imaging can guide early intervention following treatment, potentially at a stage when surgical salvage is still possible.

Care should be taken not to generalize these results to all tumor sites. At least 2 recent studies that examined the utility of FDG-PET in assessing residual tumor viability following chemotherapy for testicular carcinoma found discrepancies. Ganjoo et al⁵² performed a prospective evaluation of 29 patients with residual abnormalities on CT after chemotherapy for testicular seminoma. All patients imaged after primary chemotherapy had negative FDG-PET imaging, and stable or resolving masses with mean follow-up of 11.5 months. However, in a second group that received salvage chemotherapy, only 1 patient had positive FDG-PET imaging. The increased uptake in this case was in a posterior mediastinal mass that, at resection, showed only fibrosis. Five additional patients subsequently relapsed, all with negative postchemotherapy FDG-PET. Nuutinen et al53 also found poor specificity of FDG-PET after chemotherapy for patients with testicular germ cell tumors (both seminoma and nonseminoma). Three of 9 patients with positive FDG-PET scans were found to have only inflammatory changes on biopsy testing. When comparing median SUV values in tumors that did and did not prove to contain active disease, they found considerable overlap between groups (cancer: median SUV 2.7, range 1.6 to 9.5; noncancer: median SUV 1.7, range 0.7 to 5.5). It may be that some malignancies have lower FDG uptake or are associated with greater levels of inflammatory change after treatment that obscures their detection by PET.

Prognosis

The most exciting prospects for oncologic PET imaging lie not just in improved staging and

assessment of response to treatment, but in the ability to characterize individual tumor biology more precisely and thus predict treatment efficacy. Preliminary examples have shown the ability of FDG-PET to predict tumor aggressiveness at a multitude of disease sites. Patronas et al⁵⁴ have found that increased FDG uptake compared with normal white matter predicted poor outcome in patients with grade III and IV gliomas. Patients with tumors with high FDG uptake had a mean survival of 5 months compared with 19 months for tumors with low uptake. Barker et al⁵⁵ also showed that the level of FDG uptake in patients suspected of having recurrent brain tumor predicted survival. Stelzer et al⁵⁶ found in preliminary studies of glioblastoma patients that the total volume of abnormal FDG-PET uptake was a statistically significant predictor of diseasefree survival. De Witte et al⁵⁷ found FDG to be a useful predictor of clinical outcome in patients with low-grade glioma. Twenty-eight patients with low-grade gliomas underwent FDG-PET imaging. Of 9 patients with increased FDG uptake, 6 died and 2 were alive with recurrent disease (1 had radionecrosis); all patients with normal FDG imaging were alive, although 1 patient's tumor did undergo histologic upgrading. FDG-PET appeared to be able to detect areas of high-grade disease that were not initially apparent and predicted for a more aggressive disease course.

Ahuja et al⁵⁸ have looked at the predictive value of FDG-PET in 155 patients with NSCLC. On multivariate analysis, a standardized uptake ratio (SUR) of greater than 10 predicted for poorer median survival (5.7 v 11.4 months). Vansteenkiste et al³⁷ also assessed the potential prognostic value of SUV in 125 patients with NSCLC. Multivariate analysis identified stage, performance status and SUV as predictive of prognosis. In preoperative assessment of soft tissue sarcomas, Eary et al⁵⁹ found a strong correlation between FDG-PET-determined tumor metabolic rate and pathologically assessed tumor grade. Similarly, Higashi et al⁶⁰ found a statistically significant correlation between SUV levels and the proliferating cell nuclear antigen labeling index in NSCLC. Providing a noninvasive means of determining tumor grade allows for tailoring of treatment to the specific biology of each individual tumor, and also overcomes the sampling error inherent in biopsy.

In addition to enhancing staging, predicting biologic tumor characteristics and aiding in posttreatment management decisions, PET may also be a valuable tool in radiation treatment planning. Two provocative recent reports suggest a potential role of FDG-PET in lung cancer treatment planning. Nestle et al⁶¹ compared FDG-PET-based treatment planning with standard CT-based portals in a blinded series of 34 patients. In 12 cases, the field size or shape was changed, and in 10 cases it was reduced (median area of 182 cm² v 167 cm²). The investigators suggest that PET was able to distinguish atelectasis from tumor more accurately than CT, and that with more sensitive imaging, radiation portals could be more precisely tailored to the volume of lung involved with tumor. Similarly, Kiffer et al⁶² retrospectively looked at treatment fields in NSCLC with both CT and FDG-PET, and found that in 27% of patients, PET would have facilitated a change in treatment volume.

Beyond Glucose Metabolism: Other Tracers of Tumor Biology

While the success of FDG-PET in oncology has been widely documented, the utility of PET in the management of cancer is not limited to FDG. Other PET tracers have been developed and are targeted to areas of tumor biology that include cellular proliferation,63,64 protein and membrane biosynthesis,65,66 tissue hypoxia,67 and tumor receptor and/or gene product expression.68 In this section, we briefly summarize preliminary work with tracers for imaging cellular proliferation, amino acid transport and metabolism, and tumor receptor imaging. Although these tracers have not yet reached routine clinical implementation, they are likely to be important in oncologic PET imaging in the future. The reader is referred to a recent review for more detailed discussion of PET radiopharmaceuticals for cancer imaging.¹⁵

Cellular Proliferation

The DNA synthetic pathway requires 4 nucleoside triphosphates (TTP, ATP, CTP, and GTP) to synthesize DNA. Because thymidine is the only base that is not also incorporated into RNA, it is the logical choice for cell growth measurements.⁶⁹ Therefore, most of the work on PET cellular proliferation imaging has focused on labeled thymidine or thymidine analogs. Most pa-

23

Figure 5. [¹¹C]-thymidine to measure tumor proliferation: (A) Diagram of the exogenous or "salvage" pathway for thymidine. [¹¹C]thymidine traces the incorporation pathway into DNA shown on the diagram. It competes with thymidine degradation (not shown on diagram), which releases labeled metabolites. (B) Serial coronal images of a patient undergiong combined radiation therapy and chemotherapy for NSCLC. Both FDG (left) and $[^{11}C]$ thymidine (right) summed images show a decline in uptake in the primary tumor (large arrow) and a hilar metastasis (small arrow) over the course of treatment. Thymidine imaging shows evidence of a response earlier in the course of therapy, indicating the ability of cell proliferation imaging to measure early response to treatment.



tient studies of cellular proliferation imaging have used $[^{11}C]$ -thymidine, labeled in the methyl or ring-2 position.^{70,71} Thymidine PET imaging determines the rate of cellular proliferation by measuring the labeled thymidine that is phosphorylated and incorporated in DNA and is therefore trapped in tumor tissue (Fig 5).72,73 Studies in patients with NHL, head and neck cancer, small-cell lung cancer, high-grade sarcoma, and brain tumors have found high uptake of [11C]-thymidine, and some studies have shown correlations between the level of uptake and indicators of tumor aggressiveness.74-77 Recent preliminary studies in brain tumors suggested that thymidine PET imaging can detect viable tumor and add new information when compared with other imaging modalities, including FDG-PET.77 Because a decline in cellular proliferation is an early event in response to therapy, [¹¹C]-thymidine imaging may be particularly well suited to

measuring early response to chemotherapy. A preliminary study in patients with small-cell lung cancer or high-grade sarcoma treated with chemotherapy suggested that [¹¹C]-thymidine PET showed large declines in uptake as early as 1 week after successful chemotherapy and that declines in uptake were greater for [¹¹C]-thymidine than for FDG.⁷⁵

While studies of [¹¹C]-thymidine have been promising, the short half-life of ¹¹C (20 minutes) and the presence of labeled metabolites make [¹¹C]-thymidine impractical for routine clinical use. Several labeled thymidine analogs with longer half-lives and/or less metabolism have been developed and are undergoing testing with promising initial results.^{17,78,79}

Amino Acid Transport and Metabolism

With the idea that proliferating tumors must utilize amino acids to synthesize proteins for

growth, a number of groups have investigated labeled amino acids as oncologic PET tracers. An array of labeled compounds has been investigated, mostly using ¹¹C labels.⁶⁵ The most widely investigated has been [11C]-methionine, which has been applied to a variety of tumors, including head and neck, breast, brain, and lung cancers.⁸⁰⁻⁸² Some studies have shown improved specificity over FDG and advantages in measuring response to therapy.^{80,81} Despite these findings, [¹¹C]-methionine has not reached routine clinical implementation because of the short halflife of ¹¹C and the difficulty of interpreting the biologic significance of methionine uptake, which reflects amino acid transport and nonprotein metabolism, not simply protein synthesis.65 The search for an optimal labeled amino acid continues, along with research into alternate tracers of biosynthesis, such as $[^{11}C]$ -choline, which has shown promise as an indicator of membrane biosynthesis in tumors.66

Tumor Receptors

Work in breast cancer and prostate cancer has shown that determination of the expression of tumor receptors such as androgen receptors (AR), estrogen receptors (ER), and progesterone receptors (PR) can predict tumor behavior and response to hormonally directed therapy.^{83,84} The determination of receptor status is performed through analysis of biopsy material using radioligand binding methods or immunocytochemistry.85 The development of positron-emitter-labeled sex-steroid analogs provides the capability of quantifying receptor expression noninvasively.86 This has particular advantages in advanced disease, where large tumors and/or multiple sites of disease make it impractical to determine the regional variability in receptor expression, which can be significant.87

While preliminary work has been done with AR- and PR-based receptors,^{88,89} the tumor receptor with the largest body of experience in PET imaging is ER, for which a variety of PET radiopharmaceuticals has been developed.⁸⁶ The most promising of these has been [¹⁸F]-fluorestradiol (FES). Preliminary studies have shown that the quantitative level of FES uptake correlates with the level of ER expression,⁹⁰ that changes in FES uptake reflect receptor blockade in patients treated with tamoxifen,^{91,92} and that FES imaging demonstrates site-to-site variability in ER expression in advanced breast cancer.⁹³ A recent trial of FES imaging in patients with locally advanced breast cancer undergoing primary tamoxifen therapy showed that the quantitative level of FES uptake in the tumor before therapy was predictive of response.⁹¹ Work on the metabolism and transport of FES has elucidated some of the factors that may be important in the uptake of this tracer into ER-containing breast tumors.⁹⁴⁻⁹⁷ This work may lead to an improved ability to quantify ER expression using FES or other radiopharmaceuticals tailored to ER imaging.

Conclusion

PET imaging has demonstrated its value in oncologic decision making.^{2,4} Most clinical oncology studies to date have used FDG and have focused on issues related to tumor staging. This work has shown the capability of metabolic imaging to direct individualized patient treatment; however, it has barely scratched the surface of the potential of PET in oncology. By investigating an array of clinical problems and by using a range of radiopharmaceuticals to image multiple aspects of tumor biology, PET will play an increasing role in the practice of oncology over the foreseeable future. Rather than being viewed as a competitor to anatomically based imaging methods such as CT and MRI, PET should be viewed as a complementary imaging modality that can provide additional biologic information. Preliminary studies combining PET with CT or MRI at our institution have shown that the combination of anatomic and functional imaging can be a powerful tool in cancer treatment planning.56,98,99 As instrumentation and clinical experience progress, PET imaging will be used to provide increasingly sophisticated and individualized treatment planning for cancer.

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