

Implications of PET Based Molecular Imaging on the Current and Future Practice of Medicine

Abass Alavi, Justin W. Kung, and Hongming Zhuang

The last quarter century has witnessed the introduction of a variety of powerful techniques that have allowed visualization of organ structure and function with exquisite detail. This in turn has brought about a true revolution in the day-to-day practice of medicine. Structural imaging with x-ray computerized tomography and magnetic resonance imaging has added tremendously to many areas of medicine, including preoperative evaluation of patients. Many surgical procedures have been replaced by minimally invasive techniques, which have become a reality only because of the availability of modern imaging modalities. However, despite such accomplishments, structural imaging is quite insensitive for detecting early disease in which there often are no gross structural alterations in organ anatomy. Therefore, these modalities should be complemented by methodologies that can detect abnormalities at the molecular and cellular levels. The introduction of [¹⁸F]-

fluorodeoxyglucose positron emission tomography (FDG-PET) in 1976 as a molecular imaging technique clearly has shown the power of this approach for treating a multitude of serious disorders. The impact of FDG-PET has been particularly impressive in patients with cancer diagnosis, for whom it has become important in staging, monitoring response to treatment, and detecting recurrence. In this review, we emphasize the role of FDG-PET in the assessment of central nervous system maladies, malignant neoplastic processes, infectious and inflammatory diseases, and cardiovascular disorders. New radiotracers are being developed and promise to expand further the list of indications for PET. These include novel tracers for cancer diagnosis and treatment capable of detecting hypoxia and angiogenesis. Prospects for developing new tracers for imaging other organ diseases also appear very promising.

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THE INTRODUCTION by Röntgen of the x-ray as a means to visualize anatomic structures in a living body was one of the most striking discoveries in medicine. The role of x-ray radiography in the day-to-day practice of medicine was further enhanced when computerized tomography (CT) was used to generate images as tomographic slices, which substantially improved the sensitivity and specificity of the technique.¹⁻³ The addition of magnetic resonance imaging (MRI) has added a major dimension to the investigation of soft tissue abnormalities that are associated with a multitude of organ disorders.⁴⁻⁷ The impact of this technology was further recognized this year by the Nobel Prize committee. Despite the exquisite resolution of CT and MRI, which allows visualization of normal and diseased tissues with great detail, many disorders may go undetected for an extended period, and some may never manifest as detectable abnormalities using these modalities. This major shortcoming of gross structural imaging techniques

is due to the initiation of the disease process at the molecular and cellular levels. Thus, early stages of disease may not be detected if there are no associated structural abnormalities present. Only as the disease progresses and gross structural abnormalities become evident can anatomic imaging techniques be successful. Obviously, some disorders may never manifest as structural abnormalities throughout the course of the disease. Therefore, by the time that certain pathologies are detected by these techniques, they may be in advanced stages and cannot be treated optimally with therapeutic interventions.

In addition, the assessment of response to such treatments may not be feasible for a period of time, which further complicates the appropriate treatment strategies for these patients. This is particularly important when therapeutic regimens are associated with significant side effects and are delivered periodically over an extended period. In such circumstances, not only will there be no benefit from the continued administration of the treatment, but there may be side effects that could render a patient ineligible for other therapeutic options. Therefore, imaging techniques that allow the assessment of disease activity accurately at examination are necessary for the optimal treatment of patients. Functional imaging techniques can complement the structural modalities and overcome some of the deficiencies enumerated previously.

In general, functional imaging is based on the

From the Division of Nuclear Medicine, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA.

Address reprint requests to Abass Alavi, MD, Division of Nuclear Medicine, Department of Radiology, Hospital of the University of Pennsylvania, 110 Donner Bldg., 3400 Spruce St., Philadelphia, PA 19104.

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use of 1 or more of the following 3 approaches (1) imaging of physiologic processes, such as blood flow to an organ or diseased tissue; (2) visualizing ongoing biochemical and metabolic activities of normal and abnormal tissues; and (3) using established pharmacologic methods to assess disease processes and develop new drugs. Most early techniques in nuclear medicine were designed to mimic physiologic processes, which allowed for the successful treatment of a multitude of diseases. Despite their superior sensitivity over structural imaging modalities in assessing disease activity, they lacked the required specificity and precision that can be achieved by techniques based on biochemical and pharmacologic principles.

Biochemical disorders are initiated at the molecular and organelle levels, and may remain localized at their origin for an extended period. Therefore, early dysfunction in the metabolic and biochemical pathways may not immediately translate into physiologic abnormalities such as disrupted blood flow to the diseased tissue. Thus, reliance on changes in physiologic processes may result in overlooking early disease activity, changes that may follow therapeutic intervention, and detection of recurrence despite original response. In addition to conventional nuclear medicine techniques, certain radiologic approaches, such as contrast enhanced CT and MRI, rely on physiologic parameters in the interpretation of either organ function or pathologic states. For the reasons described previously, radiologic techniques that provide functional information also are insensitive and nonspecific in assessing disease activity. Therefore, the information provided by physiologic or structural techniques should be combined with molecular imaging methodologies for the effective treatment of patients with serious disorders.

During the last 2 decades, imaging at the molecular and cellular levels has proven to be extremely sensitive, and quite specific in assessing a variety of diseases and disorders.⁸ Molecular imaging in a broad sense implies visualizing disease processes using either biochemical or pharmacologic tools, regardless of the type of approach used. This would indicate that nuclear medicine methodologies that are based on the assessment of non-physiologic functions and that use tracer kinetics can be categorized as molecular probes for the purposes of molecular imaging.

It is our belief that conventional planar imaging

with single gamma emitting radionuclides will be used less frequently in the day-to-day practice of medicine by the end of this decade. Similarly, the role of single photon emission computed tomography (SPECT) as a powerful molecular imaging technique is also questionable at this time. This prediction is based on considering several shortcomings that are associated with this approach. Preparation of biologically important radiopharmaceuticals with single emitting radionuclides has proven to be a difficult task compared with those synthesized using positron emitting elements. In addition, conventional and SPECT images have limited spatial resolution. High-resolution images of small objects can be achieved using pinhole collimation. However, this limits its use to small organs or animals. Screening the whole body for cancer and other disorders also is impractical with the current SPECT machines. Finally, quantitative measurements with SPECT are inaccurate, which further diminishes enthusiasm for this modality for routine use in clinical practice and in research applications.

Functional MRI is primarily intended for the assessment of physiologic phenomena, such as changes in cerebral blood flow and perfusion to an organ or diseased tissue.^{9,10} As with other physiologic imaging techniques, the sensitivity and specificity of this approach are limited. Therefore, the term molecular imaging may not be applicable to functional MRI as we have defined in this article. Nuclear magnetic resonance spectroscopy is a molecular probe but has not been adopted as an effective and important modality in the day-to-day practice of medicine. Therefore, its use has been limited despite its widespread availability in every center with access to a modern MRI instrument. Optical imaging is a very powerful molecular imaging probe.¹¹ However, it does not lend itself well to examining biologic processes in human beings. Traditionally, this approach has had physical limitations in visualizing deep structures. New advances may enhance its use for these purposes.¹² However, optical imaging is and will continue to be used as an important molecular technique in small animal research projects.

Positron emission tomography (PET) as a unique imaging technique has overcome many of the shortcomings that are associated with the competing modalities. The potential for labeling nu-

merous, biologically important compounds with positron emitting radionuclides such as carbon 11 (^{11}C) and fluorine 18 (^{18}F) is enormous. In addition, positron emitting metallic radionuclides, such as technetium 94 (^{94}Tc) and copper 64 (^{64}Cu), are being used for diagnostic purposes that may expand the domain of PET further as a substitute for the functional studies currently provided by single emitting radiotracers.¹³ Modern PET instruments provide outstanding images with superb spatial resolution and have enhanced the role of this technique as an efficient modality for examining the entire body in a reasonably short period. Among functional imaging techniques, PET can provide the most accurate quantitative results, and as a result will play a critical role in clinical and research applications.

The introduction of fluorodeoxyglucose in 1976 has been an effective molecular probe in the investigation of a variety of serious disorders.¹⁴ This radiotracer was used originally to determine regional brain function in normal physiologic states and in neuropsychiatric disorders.¹⁵ However, over the last decade, we have noted an expansion of its applications to many other diseases. The impact of [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) and certain other tracers on the treatment of a number of disorders has been well established. However, there are several novel radiopharmaceuticals that have the promise of being adopted for routine application in the near future.

In this review, we provide our perspective on the use of PET for molecular imaging, and describe how this modality has and will continue to have important clinical applications. The impact of FDG-PET has been enormous and will be reviewed in depth. The use of other novel radionuclides that hold great promise of being routinely adapted in the future will be addressed. Because our aim in preparing this review was to describe molecular imaging techniques, which are well established or have the potential to become clinically relevant in the near future, we have intentionally omitted discussion of some very exciting areas of research. These include imaging gene expression¹⁶ and using molecular targeting techniques to develop new drugs.^{17,18} Application of these methodologies to the day-to-day practice of medicine is speculative at this time.

CENTRAL NERVOUS SYSTEM DISORDERS

Epilepsy

The use of FDG-PET in localizing seizure foci in the temporal lobe for surgical interventions is well established.¹⁹ It has been clearly shown that FDG-PET is quite sensitive in detecting such sites, with 85% to 90% accuracy using modern techniques.¹⁹ Hypometabolism at the seizure focus is noted when there is clinical evidence for epilepsy while anatomic images remain normal for an extended period.²⁰⁻²² However, as more experience has been gained with these imaging techniques, we have realized that longstanding seizure episodes eventually lead to significant atrophy, which can be detected by MRI.^{23,24} Therefore, combined MRI and FDG-PET may provide the best results for accurate localization of the epileptogenic foci. It is our hypothesis that longstanding metabolic and molecular abnormalities eventually will result in significant atrophy in most chronic disorders of the brain. Nuclear magnetic resonance spectroscopy as a functional method for localization of seizure disorders in temporal lobe epilepsy is experimental at this time.²⁵ Further work is required to determine its applicability to this setting.

Alzheimer Disease and Related Disorders

Currently, several drugs are on the market for the treatment of Alzheimer's disease, which are intended to increase acetylcholine levels in the brain.²⁶⁻³⁰ These drugs would be most efficacious if prescribed early during the disease course. Thus, detection of abnormalities soon after the onset of disease is crucial. As with seizure disorders, early Alzheimer's disease would be detectable only by metabolic imaging techniques.³¹⁻³⁵ FDG-PET may become the critical test for selecting the appropriate patients for treatment when the disease process is at the molecular level and before structural alterations have taken place.^{19,36,37} However, similar to patients with seizure disorders, as the disease progresses, metabolic changes may translate into significant cortical atrophy, which can be detected by anatomic techniques like MRI. Obviously, therapeutic interventions with existing drugs may not be as effective when such structural alterations have taken place in the brain.

Movement Disorders

Although research regarding the applications of neuroreceptor and/or neurotransmitter compounds

to the central nervous system (CNS) has yielded extraordinary scientific results,³⁸⁻⁴⁰ such techniques have remained mostly as research tools, and their clinical use remains unknown at this time. Among the compounds that have been explored, those that visualize the dopaminergic system have the highest potential for the assessment of movement disorders and, therefore, have the promise of becoming useful in the daily practice of the neurologic disciplines. In particular, Parkinson's disease can be effectively diagnosed with radiopharmaceuticals, such as fluorine-18-6-fluoro-L-dopa, or radiotracers that bind to the dopamine transporter sites and, therefore, allow assessment of the integrity of the presynaptic dopaminergic neurons.³⁸⁻⁴⁰ We expect that these agents, specifically fluorine-18-6-fluoro-L-dopa, will be extensively used in the early and accurate diagnosis of Parkinson's disease. Some additional information can be gained by using presynaptic radiotracers along with postsynaptic radiotracers, but the routine use of the latter agents may not be justifiable at this time.

Other CNS Disorders

At this stage, the role of FDG-PET in other CNS abnormalities is not as well characterized as in seizure disorders or in Alzheimer's disease. However, severe dysfunction in head injury,^{41,42} frontal lobe dementia,^{43,44} and Huntington disease⁴⁵⁻⁴⁷ can be assessed with the FDG-PET technique with high accuracy.

MALIGNANT NEOPLASTIC DISEASE

Clearly, the introduction of molecular imaging techniques has revolutionized the field of oncology, which in turn has substantially contributed to the growth of the field of nuclear medicine.⁴⁸ In particular, FDG-PET has definitely become necessary for the treatment of a variety of malignancies.⁴⁸⁻⁵¹ Although FDG-PET plays an important role in staging various malignancies, its role in the diagnosis of cancer is limited at this time because most malignancies are diagnosed before FDG-PET is considered. Exceptions to this include PET's role in the diagnosis of cancer in patients with lung nodules.⁵²⁻⁵⁴ It also may play a role in the early diagnosis of primary breast and colon cancers, and has been used for these purposes.^{55,56} As whole body imaging for diagnosing cancer gains momentum, it is our belief that FDG-PET may have more

potential than either whole body CT or MRI for this purpose. The high contrast resolution provided by this technique allows detection of lesions that are not detectable by CT or other radiologic techniques due to their small size or the lack of contrast compared with surrounding structures. Also, the high specificity of FDG-PET for cancer offers a major advantage over structural imaging modalities. This will have serious implications when imaging techniques are used for screening a large population in which a test with a low false-positive rate may prevent unnecessary invasive and noninvasive procedures. Currently, in patients with a high clinical suspicion of cancer of an unknown primary, PET is a study of choice for localizing the abnormal site.⁵⁷⁻⁶¹ Finally, PET will play an important role in the evaluation of response to therapy and detection of recurrence following initial response to treatment.

We believe that as FDG-PET becomes widely available and can be performed at reduced costs, it may become important for the staging of a multitude of malignancies. Its role in staging certain cancers has led to substantial changes in the cost-effective treatment of a large number of patients. Staging primary lung cancer continues to be an important indication for PET and has paved the way for the staging of other malignancies with this modality. FDG-PET can accurately stage head and neck tumors and, therefore, may be used routinely in the future for the treatment of this disease.^{57,62,63} This approach also may be of value in the early staging of colon cancer. The use of FDG-PET for staging lymphoma has been well established, and we project that this technique may completely replace CT and other structural imaging techniques in the staging of this very common malignancy. The sensitivity and specificity of FDG-PET is substantially higher than that of the anatomic imaging techniques in patients with lymphoma.⁶⁴ The accurate diagnosis of disease stage is of utmost significance for the treatment strategies used in these patients. There are many effective treatment regimens for this disease, but most carry significant risk to the patient. Therefore, an imaging technique that provides the most accurate results would contribute to the optimal treatment of such patients. We predict that FDG-PET may become the test of choice in the staging, assessment of response to treatment, and detection of recurrence in both Hodgkin and non-Hodgkin lym-

phoma. Based on the data that we are accumulating in our center, the routine use of CT may be redundant and at times may prove to be misleading.

FDG-PET has become an invaluable examination in the evaluation of patients with suspected recurrent colorectal cancer based on increased tumor marker levels in the blood, such as carcinoembryonic antigen and negative CT, and other radiologic studies.⁶⁵⁻⁶⁹ Carcinoembryonic antigen has a sensitivity of 59% and specificity of 84% for detecting recurrence and, furthermore, cannot localize lesions.⁷⁰ CT is conventionally used to localize lesions but misses hepatic metastases in approximately 7% of patients.⁷¹ The yield from FDG-PET is quite impressive in this very difficult clinical setting, and, eventually, it may become the test of choice when recurrent colon cancer is suspected. Delayed imaging may improve the sensitivity of FDG-PET for detecting recurrence in this and other malignancies.

FDG-PET may play an important role in the monitoring of treatment response in hematologic and solid neoplasms. This is illustrated by its use in evaluation of treatment of lymphoma and gastrointestinal stromal tumors. The best model is exemplified in patients with lymphoma in whom the efficacy of treatment can be assessed accurately with PET and offers many advantages over CT.⁷²⁻⁷⁴ Detection of the effects of treatment with CT totally relies on changes in the size of the lymph nodes, which is a slow process and may not be conclusive in the early phases of favorable response. Furthermore, CT is unable to distinguish between active disease and residual scar tissue after therapy.⁷⁴ Because chemotherapeutic regimens for lymphomas are administered periodically (ie, every 3 weeks) over several months and are associated with significant morbidity and serious side effects, determining their efficacy is imperative soon after this type of treatment is initiated. The use of PET may overcome the shortcomings of structural techniques for assessing response to treatment of this malignancy.

Monitoring response to treatment with PET is increasingly being adopted for some solid tumors.⁷⁵⁻⁷⁷ However, the paucity of effective treatment for most solid tumors has resulted in limited data regarding the role of PET and other diagnostic imaging techniques for this purpose. However, recent investigations of the efficacy of imatinib

mesylate (Gleevec, Novartis Pharmaceuticals Corp., East Hanover, NJ) for the treatment of advanced gastrointestinal stromal tumors showed a promising role for PET in the evaluation of this specific malignancy.⁷⁷ All patients responding to Gleevec had markedly decreased FDG uptake from baseline as early as one day after therapy. All patients with disease progression had increased FDG uptake showing that PET was a sensitive and reliable indicator of response or resistance to Gleevec. As new therapy for solid tumors are evaluated, PET may show its efficacy in evaluating early response.

Finally, the role of PET for detecting the recurrence of tumor following the initial response has become the hallmark of this technique in almost every malignancy. Structural changes following surgery and/or radiation/chemotherapy render radiologic techniques inconclusive in such settings. FDG-PET currently plays an important role in patients with suspected recurrent brain tumors and inconclusive, contrast enhanced MRI or CT examinations. Because radiation induced necrosis and recurrent tumors appear enhanced on these scans, metabolic imaging with FDG, which reflects disease activity at the cellular level, is invaluable in this setting. Application of FDG-PET for detecting recurrent disease has added a major dimension to the day-to-day practice of oncology that, due to its sensitivity and noninvasiveness, may prove to be an invaluable tool in following patients with cancer.

INFECTIOUS AND INFLAMMATORY PROCESSES

FDG has proven to be an excellent tracer to detect inflammation in the setting of either infectious or noninfectious processes.⁷⁸ Based on laboratory, animal, and human studies, activated inflammatory cells appear to have increased rates of glycolysis and, as such, accumulate this tracer with high concentration.⁷⁹ Therefore, FDG-PET can be effectively used to detect sites of infection and inflammation. Orthopedic infections, particularly those related to implanted prostheses⁷⁹⁻⁸¹ and osteomyelitis,^{82,83} can be detected successfully by FDG-PET, and appear to be the study of choice in such complicated and difficult clinical settings. Increasingly, this technique is being used for detecting infection in soft tissues anywhere in the body, including the sources of fever of unknown

origin.⁸⁴⁻⁸⁶ The potential of FDG-PET for detecting inflammatory processes in disorders such as regional ileitis,⁸⁷ sarcoidosis,⁸⁸⁻⁹¹ rheumatologic disease,⁹² and vasculitis⁹³⁻⁹⁵ and any other disorders, is also vast. Detection of infection and inflammation may become the second most common clinical application of FDG-PET, furthering its role as an indispensable clinical modality.

CARDIOVASCULAR DISORDERS

Myocardial Viability

The use of FDG-PET to determine myocardial viability remains a very important technique and is considered the gold standard for this purpose. However, because of the extraordinary successes of SPECT techniques in the investigation of coronary artery disease, FDG-PET is infrequently used for this purpose. This will remain the typical pattern of practice until "All PET" based nuclear medicine becomes a reality during the next decade.

The use of nitrogen-13-ammonia as a viable option for evaluation of myocardial perfusion and viability is questionable because of the short half-life of this radiotracer. However, the use of rubidium-82 (⁸²Rb) generators as a source of radiotracers for blood flow imaging may result in the routine use of PET for this purpose. The ability of ⁸²Rb to detect changes in myocardial perfusion has been evaluated and shows promise.^{96,97} Obviously, the cost-effectiveness of using ⁸²Rb generators as the method of choice will heavily depend on the number of patients who are examined on a daily basis.

Atherosclerosis

It is becoming increasingly apparent that FDG is taken up in the atherosclerotic vessels.⁹⁸ This process is quite noticeable in the aorta in its entirety and other major arteries. There is evidence that the uptake is mainly located in the intima and likely represents high metabolic activity in macrophages, which are in abundance in the atherosclerotic plaques.⁹⁹ It is also likely that the smooth muscles in the arterial wall are visualized due to high glucose use by this tissue. We have speculated that uptake in the peripheral vessels, such as the popliteal and the lower femoral arteries, is mostly located in the smooth muscle rather than in the intima, while FDG is mainly localized in the atherosclerotic plaques in the aorta, and its tributaries in the trunk, neck, and upper thighs.

OSSEOUS DISORDERS

We expect that in the near future, conventional bone imaging with ^{99m}technetium labeled methylene diphosphonate (or similar compounds) using non-tomographic scanning techniques will be replaced with PET using [¹⁸F]-fluoride as the radiotracer of choice for detecting osseous abnormalities. The molecular basis for the uptake of fluoride lies in its ability to incorporate into the hydroxyapatite crystals laid in the osseous structures. Although their mechanisms of incorporation differ at the molecular levels, the images generated from both types of radiotracers reveal very similar gross distributions in physiologic and pathologic states. Both techniques show increased incorporation of the injected compound at the sites of new bone formation.¹⁰⁰ This is commonly seen in active benign and malignant disorders. Tomographic images provided by PET have substantially higher resolution and, therefore, provide superior sensitivity and specificity compared with conventional planar and even SPECT techniques.

The question remains whether in patients with cancer, bone scanning with either [¹⁸F]-fluoride or single emitting preparations can provide additional information for the purposes of staging, determining response to treatment, and detecting recurrence beyond that which can be discovered with FDG and other biologically important tracers. FDG and other relevant tracers directly target malignant cells anywhere in the body, including the marrow space, and, therefore, are able to visualize disease activity directly at all anatomic sites. However, bone imaging displays indirect evidence for the presence of disease. It is still debatable whether bone imaging is sensitive enough to detect early disease activity and is specific enough to determine response to treatment. Some aggressive malignancies such as lung cancers may not result in an adequate degree of new bone formation to be detectable by bone scanning. However, they can be visualized directly by FDG-PET in the marrow space. Furthermore, reactive new bone formation may remain active for an extended period despite response to treatment. This may result in the mistreatment of patients because of assumed disease activity. Validation of the role of bone imaging as an addition to FDG-PET examination in the assessment of patients with suspected malignancy will require further investigation. It may be reason-

able to propose the sequential use of FDG and ^{18}F -fluoride (ie, fluoride followed by FDG) as a means for a complete appraisal of the disease process until further data become available for defining the role of bone imaging in patients with cancer. It is our belief that a relatively slow disappearance of reactive bone formation despite response to treatment may make bone imaging of limited value for following the course of metastatic bone marrow disease.

PROSPECTS FOR NEW TRACERS

Cell Proliferation Agents

Because there is upregulation of thymidine transport into malignant cells due to accelerated deoxyribonucleic acid synthesis, either $^{11}\text{C}^{101,102}$ or ^{18}F -labeled $^{103-105}$ thymidine radiotracers can be used to determine cellular proliferation. Several of these compounds have been synthesized, but only 3'-deoxy-3'-[^{18}F]-fluorothymidine (FLT) appears most promising for this purpose.¹⁰⁶ Theoretically, FLT has the potential to be used as a specific agent for assessing disease activity in various stages of different malignancies. Particularly, FLT appears to be of high value for determining response to therapy because cytotoxic chemotherapeutic agents affect cell division earlier and more prominently than glucose metabolism. Therefore, FLT may prove to be superior to FDG for assessing response to treatment. Also, following favorable treatment response, an inflammatory reaction may confound the use of FDG but will not affect the use of FLT in this setting.

Tumor Hypoxia

Hypoxia in tumor tissue appears to be an important prognostic indicator of response to either chemotherapy or radiation therapy. Therefore, detection of hypoxia in advance of such interventions is of utmost importance in optimizing the use and outcome of different therapeutic modalities. This assessment is of value before, during, and following treatment. Several compounds have been synthesized for these purposes. These compounds diffuse into normally oxygenated and hypoxic cells but are retained substantially in higher concentrations in the latter tissues, which can be detected by external imaging techniques. A number of reports have appeared describing the use of the following compounds in animal and human studies: [^{18}F]-

fluoromisonidazole (FMISO),^{107,108} Cu-60 diacetyl-bis(N^4 -methylthiosemicarbazone) (^{60}Cu -ATSM),¹⁰⁹ 2-(2-nitroimidazol-1-[H]-yl)-N-(3-[^{18}F]fluoropropyl)acetamide ([^{18}F]-EF1),¹¹⁰ and [2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide] ([^{18}F]-EF5).¹¹¹ FMISO, an analogue of 2-nitroimidazole, appears suboptimal for assessing hypoxia because its uptake is low in hypoxic cells, and it also clears slowly from the normal tissues.¹⁰⁸ In contrast, Cu-ATSM appears to overcome these difficulties and may prove to be an effective agent for this purpose.¹⁰⁹ Finally, the [^{18}F]-EF compounds have performed well in animal studies and may also prove to be effective for noninvasive imaging of tumor hypoxia.¹¹⁰ These preparations have been introduced by investigators at the University of Pennsylvania and will be tested in human malignancies in the near future. Because detection of hypoxia appears to be of high importance for the treatment of patients with cancer, the use and development of hypoxic agents may expand in the coming years. In fact, hypoxia agents may become the next generation of compounds that will be used in the treatment of patients with certain malignancies.

Along these lines, we must point out that detection of cell death (apoptosis) by imaging is an area of interest for assessing malignant and benign disorders.¹¹² The use of $^{99\text{m}}\text{Tc}$ -labeled annexin V has led the way for this purpose. This agent binds to phosphatidylserine, which is externalized in the cell membrane following apoptosis. Because apoptosis mediates tumor cell and angiogenic vascular endothelial cell regression, annexin V imaging may provide insight into therapeutic response to cancer therapy. Labeling annexin V with ^{18}F may further increase the use of this promising method. Imaging of angiogenesis, a common phenomenon noted in cancer and most malignant processes, may also provide important information. One promising approach involves the assessment of the integrins, a family of heterodimeric endothelial cell membrane proteins, which are receptors for extracellular matrix proteins containing the amino acid sequence arginine, glycine, and aspartate (RGD). One integrin, $\alpha_{\text{V}}\beta_3$, is expressed at high levels in tumor capillaries and some tumor cells.^{113,114} Peptides containing the RGD sequence with affinity to $\alpha_{\text{V}}\beta_3$ have been designed and radiolabeled with ^{18}F .^{115,116} These tracers may find a role in the clinical treatment of patients with cancer.

Antibodies and Peptides (Tumor Receptors and Antigens)

The use of antibodies as diagnostic agents has proven of limited value because of the clearance from the circulation and low concentration at intended targets. Therefore, the potential for using antibodies as diagnostic agents is very limited at this time despite the theoretically high specificity that may be achieved with these compounds. However, some therapeutic successes achieved with either ^{131}I or ^{90}Y -labeled anti-CD-20 and CD-22 antibodies against B cell non-Hodgkin lymphomas have revitalized interest in this approach over the last decade.^{117,118} The demonstration of antibody targeting to the diseased tissue is important for predicting outcome from these treatments. We expect that future diagnostic agents proposed for pretreatment targeting purposes will be synthesized using positron emitting radionuclides such as ^{124}I (as a surrogate for ^{131}I) and ^{86}Y (as a surrogate for ^{90}Y) for optimal visualization of the targeting sites. Using positron emitting labeled antibodies will significantly improve our ability to select patients who are optimal candidates for treatments with β -emitting antibodies or peptides labeled with therapeutic radionuclides. Comparison between images acquired with more specific tracers, such as FDG, that reveal disease activity without regard to a specific antigen in the cells and scans which are generated with radiolabeled antibody for diagnostic purposes, may identify patients who are appropriate candidates for treatment with radiolabeled therapeutic antibodies.

Similarly, peptides such as octreotide labeled with positron emitting radionuclides will be preferably used for imaging neuroendocrine tumors and other malignancies. These include ^{64}Cu -labeled octreotide and ^{68}Ga -labeled octreotide analogues.^{119,120} Both have been shown to provide substantially superior image quality compared with either planar or SPECT images with indium-111 labeled compounds.¹¹⁹⁻¹²¹

Labeled Amino Acids

Much experience has been gained in using positron labeled amino acids for assessing disease activity in brain tumors. The uptake of such tracers is very minimal in the normal brain structure.¹²² This allows for a clear separation of the sites of active disease from the surrounding background. Therefore, malignant tumors can be distinctly vi-

visualized with high contrast. L-[methyl- ^{11}C]-methionine has been studied extensively and has shown excellent sensitivity in patients with high-grade tumors.¹²¹ However, it is our belief that FDG still is the agent of choice in such settings if the images generated are interpreted carefully. We must emphasize that FDG-PET is requested only after anatomic studies have revealed abnormal findings suggestive of active disease (mostly as a suspected recurrent process). FDG-PET images must be carefully compared with these scans to define the true location of the FDG uptake in the normal and abnormal tissues. This process allows determination of whether the contrast enhancement identified based on radiologic criteria represents either radiation necrosis or recurrent tumors. By following this scheme, we have been able to guide the referring physician in selecting the optimal option for treating these very difficult cases.

The ^{11}C or ^{18}F amino acids, such as choline, appear to be of value for assessing slow growing tumors like prostate cancer.¹²³⁻¹²⁵ Although negative FDG-PET in these cancers may purely reflect the slow growing nature of the malignancy and, therefore, forecast favorable prognosis, labeled amino acids may allow optimal staging because of their higher sensitivity in these settings. More data will be needed to justify the use of these tracers in assessing the extent and the presence of malignancy in patients with prostate cancer. ^{11}C labeled acetate also appears to be of value for examining patients with prostate cancer.^{126,127} However, the 20-minute half-life of this preparation may limit its practical application in centers that are not within the proximity of the preparation site. In our opinion, the routine use of amino acids, which may pose certain logistical issues in most centers, may not be justified until more data is accumulated to prove the superiority of these compounds over FDG.

Labeled Hormones

The use of labeled hormones, such as ^{18}F -labeled estrogen analogues, for assessing breast cancer response to hormone therapy with tamoxifen has been studied^{128,129} but is experimental at this time, and further work is required to determine the efficacy of this approach. Similar statements can be made regarding the efficacy of ^{18}F -labeled male hormone imaging for the assessment of hormone therapy in prostate cancer.¹³⁰

SPECIFICITY OF FDG

Among the large number of positron imaging radiopharmaceuticals that have been synthesized to date, FDG stands out as the most effective preparation for research and clinical applications. This preparation will remain the agent of choice for many years to come. More than 95% of PET procedures performed around the world use FDG as the imaging agent. The list of potential applications for FDG is large and is growing. In addition to its clearly proven efficacy for the assessment of CNS diseases, malignant disorders, and myocardial viability, FDG is increasingly being used for the detection of infection and inflammation in a variety of clinical settings. As previously noted, FDG may play a role in the detection of a number of inflammatory and infectious processes.^{79-81,87-95} There is also evidence that thrombosis and atherosclerosis are associated with increased glucose use, which can be detected with FDG-PET.^{98,131,132} Finally, there is a potential for using FDG-PET for the assessment of muscle spasm and motility disorders. This application could also prove of extraordinary importance in voluntary and smooth muscle related disorders.

Clearly, the rapidly expanding list of indications for the use of FDG-PET highlights its nonspecificity. This issue becomes a particularly serious challenge when this modality is used for diagnosing cancer. Because inflammation is a common phenomenon and often can be visualized with FDG-PET, theoretically, a distinction between cancer and inflammatory processes can be a difficult task. We and other groups have made an attempt to improve the specificity of this tracer by imaging the sites of abnormality at dual times following its administration.^{62,133,134} While uptake of FDG continues to increase at malignant sites for several hours, as can be shown by an incremental increase of the standardized uptake values (SUV), inflammatory lesions peak at approximately 60 minutes, and their SUV either stabilize or decline thereafter. This difference in the behavior of FDG in malignant versus inflammatory cells can be explained best by the varying levels of enzymes that degrade deoxyglucose-6-phosphate in the respective cells. Glucose-6-phosphatase dephosphorylates intracellular FDG-6-phosphate, allowing it to leave the cell. It has been shown that most tumor cells have low levels of this enzyme, while its expression is high in the mononuclear cells.¹³⁵⁻¹³⁷

For this reason, imaging at 2 time points after administration of FDG may prove to be important in differentiating between these 2 common disorders. Further refinement of this approach may result in improvement in its efficacy, particularly in patients with known or suspected malignancy. Recent unpublished work performed by our group has shown that delayed imaging up to several hours in the evaluation of patients with nonsmall cell lung cancer improves the sensitivity of the technique. This finding will have important implications for both the diagnosis and staging of this and possibly other malignancies.

ROLE OF PET-CT CO-REGISTRATION

Integrated PET and x-ray CT units are manufactured by all major vendors in the field and are currently being refined further.^{138,139} However, their efficacy in the routine day-to-day practice of nuclear medicine needs to be validated before they can be adopted and used by the medical community on a large scale as advocated by the industry and some PET-CT proponents. It is quite attractive to be able to show the accurate anatomic location of the normal and pathologic sites visualized by PET tracers by adopting a system that provides this additional piece of information. This clearly is of interest and may facilitate interpretation of certain PET studies.¹⁴⁰⁻¹⁴² A recent study showed that co-registered images by integrated PET-CT resulted in higher diagnostic accuracy in the staging of nonsmall cell lung cancer than that achievable by visual alignment alone.¹⁴² This study highlights the potential for these integrated units when adopted in the appropriate settings. However, we believe that PET-CT units may not be incorporated in day-to-day practice for practical reasons. We will discuss 2 major factors that form the basis for this speculation.

The interpretation of the majority of FDG-PET performed for clinical purposes may not substantially be influenced by performing sequential PET and CT. Whole-body PET is most commonly used for the evaluation of lymphomas and lung nodules (66-70% of test cases in some centers). This pattern of practice may continue in the foreseeable future. In most circumstances, determining the mere presence or absence of disease allows the referring physician to make a treatment decision. Therefore, although lesion by lesion co-registration offers more information, it may not alter the

treatment plan. This is illustrated in the treatment of lymphoma where the precise anatomic localization of the structures involved may not contribute to or alter the treatment of these patients. Likewise, in patients with well defined nodules shown on chest x-ray or CT, co-registration of findings between CT and PET will not substantially influence the outcome.

Incorporation of integrated PET-CT units also may be difficult because the space requirements for these instruments are significant. Installing several of these units in an active nuclear medicine service could be a major challenge to the existing facilities. If the routine use of PET-CT units can be validated and justified, modern nuclear medicine facilities will have to be designed with serious consideration given to this shift in resource allocation.

Considering that the majority of nuclear medicine procedures in the coming decade will be performed by PET rather than by conventional planar and/or SPECT techniques, it is highly unlikely that PET-CT instruments could be adopted as the sole modality for this purpose. It is our belief that stand-alone PET instruments may provide the best option for performing the majority of the current procedures. This will include examining a fairly large number of disorders (in addition to lymphoma and lung nodules) in which exact anatomic localization of the abnormality (abnormalities) may not be essential for the appropriate treatment of patients. Therefore, the routine use of integrated PET-CT may not be practical in day-to-day practice when the issues enumerated previously are taken into consideration.

Finally, by using the existing and readily available software, it is quite feasible to co-register PET and CT images that have been acquired independently by free-standing machines. Justification for this approach can be further strengthened by considering the basic differences that exist between the time needed to acquire PET and CT images. While CT images are acquired over a very short period with minimal patient motion (breath hold-

ing), PET images are generated over several minutes. Constant physiologic movement of the organs and/or lesions in the field of view shifts the source of signals received. Therefore, it is difficult to conceive that integrated PET-CT units allow precise co-registration of lesions, and that this cannot be achieved with the electronic and interactive approach using images that are provided by PET and CT machines independently. Obviously, further work is required to define the merits of free-standing versus combined PET/CT machines as PET becomes the mainstay of our specialty.

The impact of FDG-PET for assessing physiologic and pathologic states has been truly overwhelming. In fact, we predict that in the not so distant future, FDG-PET imaging alone could become the most common procedure provided by nuclear medicine laboratories, and may represent the main source of recognition and financial support for the field. The power of molecular imaging lies in the vast domain of cell biology and the high potential that exists for extending its application to a large number of pathologic states, which are well characterized using biochemical and pharmacologic probes. It is quite conceivable that molecular imaging based on tracer kinetics with positron emitting radiopharmaceuticals could become the main source of information for the treatment of individual patients. As such, nuclear medicine procedures may become the most common imaging studies performed in the practice of medicine. This is not a farfetched speculation when one realizes the enormous amount of excitement and change that one, single, biologically important compound (ie, FDG) has brought about to the medical arena. The major challenge that we face is attracting highly qualified individuals and securing resources that are required to harness the opportunities that await us in the ever exciting specialty of molecular imaging. Ever increasing applications of PET appear to have begun to attract more talented individuals to consider a career in nuclear medicine.

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