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A shifting landscape: What will be next FDG in PET oncology?

Tomio INOUE,* Noboru ORIUCHI,** Katsumi TOMIYOSHI*** and Keigo ENDO**

*Department of Radiology, Yokohama City University School of Medicine
**Department of Nuclear Medicine, Gunma University School of Medicine
***Radiopharmaceutical Division, Nishidai Clinic Diagnostic Imaging Center

The tumor-seeking agent most widely used in positron emission tomography (PET) is 2-^{18}F-fluoro-deoxy-D-glucose (FDG). The clinical usefulness of FDG PET has already been proved in detecting, staging and restaging various kinds of malignant tumors, but nuclear medicine physicians suffer from a "diagnostic dilemma," in which a relatively high false positive ratio of FDG PET in diagnosing malignant tumors prevails. To increase more specific tumor uptake or more specific tumor characterization, numerous PET radiopharmaceuticals have been developed, and some of them are being tested in clinical trials. This review will briefly survey the tumor uptake mechanism and clinical significance of representative non-FDG PET radiopharmaceuticals used in clinical trials for patients with cancers.

Key words: FDG, PET, PET oncology

INTRODUCTION

THE MOST WIDELY used tumor-seeking agent with positron emission tomography (PET) is 2-^{18}F-fluoro-deoxy-D-glucose (FDG), which is transported, phosphorylated and metabolically trapped in tumor cells as a glucose substitute.[1] The clinical usefulness of FDG PET has already been proved in detecting, staging and restaging various kinds of malignant tumors, most notably lung cancer,[2–6] malignant lymphoma,[7–11] colorectal cancer,[12–16] esophageal cancer,[17–21] malignant melanoma[22–26] and head/neck cancer.[27–30] FDG PET for these six malignant tumors is now approved for reimbursement by public insurance in the United States of America. In relation to the reimbursement by public insurance, the clinical use of FDG PET has been sharply increased since 1998, but the Japanese Ministry of Health and Welfare has yet to approve FDG PET for coverage by public medical insurance.

Nuclear medicine physicians suffer from a "diagnostic dilemma," in which a relatively high false positive ratio of FDG PET in diagnosing malignant tumors prevails. This is based on the physiologic uptake of FDG in normal tissue[31] and non-specific FDG uptake in macrophage and reactive inflammatory cells surrounding the tumor cells.[32–34] To increase more specific tumor uptake or more specific tumor characterization, numerous PET radiopharmaceuticals have been developed, and some of them are being tested in clinical trials.

This review will briefly survey the tumor uptake mechanism and clinical significance of representative non-FDG PET radiopharmaceuticals used in clinical trials for patients with cancers.

TUMOR DETECTION BY PET WITH RADIOLABELED AMINO ACIDS

Methionine

As applications of metabolic imaging expand, radiolabeled amino acids may gain increased clinical interest. Among various radiolabeled amino acids for PET study, ^{11}C methionine has been most used clinically, although its scale is much smaller than that of FDG.

^{11}C methionine is a natural essential amino acid and enters tumor cells via the L-amino acid transporter according to the accelerated protein and RNA synthesis in malignant tumors. An experimental study demonstrated that FDG accumulates in macrophages and granulation

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For reprint contact: Tomio Inoue, M.D., Department of Radiology, Yokohama City University School of Medicine, 3–9 Fukuura, Kanazawa-ku, Yokohama 236–0004, JAPAN.

tissue, which caused false positive results in diagnosing cancers.[34] Conversely, ^{11}C methionine accumulates more specifically in viable cancer cells[35] and it reduces false positive results in diagnosing malignant tumors. Radiolabeled methionine is more sensitive to cytotoxic treatment, such as chemotherapy or radiotherapy, than FDG.[36] It is also more receptive to changes in glucose metabolism in tumors after treatment is delayed compared to methionine metabolism.[36]

^{11}C methionine can detect brain tumors,[37] lung cancer[38] and head/neck cancer.[39] A comparative study of FDG and ^{11}C methionine revealed that tumor uptake of FDG was significantly higher than that of ^{11}C methionine.[40] Nevertheless, the tumor uptake of ^{11}C methionine correlated well with that of FDG, and the diagnostic sensitivity of ^{11}C methionine for malignant tumors was similar to that of FDG.[40] In a comparison of normal biodistribution of ^{11}C methionine and FDG in human subjects, ^{11}C methionine uptake in the brain is less than that of FDG. Myocardial tracer uptake of FDG is visualized even when patients fast before the FDG injection, and it hampers tumor visualization near the heart. Lower uptake of ^{11}C methionine in the brain and heart is an advantageous characteristic in detecting brain tumors and lung cancer localized near the heart.[40] On the other hand, ^{11}C methionine has intense physiological uptake in the lachrymal glands, salivary glands, and, most significantly, in the bone marrow. Because a high serum glucose level may reduce tumor FDG uptake, ^{11}C methionine is the better choice in patients with uncontrolled diabetes mellitus. FDG yields better results in detecting tumors near the bone marrow or pancreas.

Radiolabeled tyrosine

Tyrosine, another type of amino acid tracer, tends to be incorporated in the process of cellular proliferation and protein biosynthesis. ^{11}C tyrosine PET makes it possible to visualize malignant tumors and quantify the protein synthesis rate of tumors, which correlated well with tumor SUV.[41] By the clinical use of ^{11}C tyrosine remains limited to only a few institutes.[42–45]

^{11}C labeled compound as ^{11}C methionine and ^{11}C tyrosine has the disadvantage of a short physical half-life (20 min). It may limit the number of patients in a day and make it difficult to obtain a whole-body PET image for the detection of distant metastasis. Alternative ^{18}F labeled compound with a relatively longer half-life to improve patient throughput have been required. As a result, researchers developed ^{18}F tyrosine, which is clinically useful in detecting and delineating brain tumors.[46] ^{18}F tyrosine is metabolized and incorporated into protein[47] and its metabolites appear in the blood at 60 minutes post-injection, but its low radiochemical yield prevents its widespread use in clinical PET.

Our institute designed clinical trials on PET with ^{18}F α-methyl tyrosine after successful European clinical trials of ^{123}I α-methyl tyrosine in patients with brain tumors.[48] The radiochemical yield of ^{18}F α-methyl tyrosine is higher than that of other ^{18}F labeled amino acids such as ^{18}F tyrosine and ^{18}F phenylalanine.[49] Approximately 800 MBq of ^{18}F α-methyl tyrosine can be obtained in one radiosynthesis. Basic experiments with tumor-bearing mice showed tumor uptake of ^{18}F α-methyl tyrosine and its prolonged retention in tumor cells.[50] The competition with L-alanine on ^{18}F α-methyl tyrosine tumor uptake suggested the accumulation of ^{18}F α-methyl tyrosine in tumor cells via an amino acid transport system. Approximately 90% of ^{18}F α-methyl tyrosine was not metabolized and remained in the tumor cells. Unlike natural amino acid, most of ^{18}F α-methyl tyrosine in the tumor cells was not incorporated into the protein like ^{123}I α-methyl tyrosine (Fig. 1).[50]

Clinical experience with ^{18}F α-methyl tyrosine PET

We have conducted clinical trials of ^{18}F α-methyl tyrosine PET in patients with malignant tumors.[51–53] Most notably, ^{18}F α-methyl tyrosine was proven to be useful in diagnosing brain tumors in comparison with FDG. In astrocytic tumors, ^{18}F α-methyl tyrosine accumulated in both low grade and high grade glioma. PET with ^{18}F α-methyl tyrosine yielded better results in tumor delineation than FDG (Fig. 2). A gliomatosis cerebri, diffusely disseminated glioma, is difficult to identify by MRI or CT, but PET with ^{18}F α-methyl tyrosine successfully revealed this pathological condition. It is not perfect but ^{18}F α-methyl tyrosine is useful for differential diagnosis of neoplasms and other etiologies in the brain.

We also conducted clinical trials in detecting musculoskeletal tumors in comparison with FDG. The diagnostic sensitivities and specificities for malignancy were 72.7% and 84.9%, respectively, with using ^{18}F α-methyl tyrosine with cut-off standardized uptake values (SUV) of 1.2, and 72.7% and 66.0%, respectively, and FDG with a cut-off SUV of 1.9. The accuracy with ^{18}F α-methyl tyrosine was 81.3%, higher than that for FDG (68.0%), and the difference with respect to specificity was significant. On the other hand, although a significant correlation was found between malignant tumor grade and SUV with both ^{18}F α-methyl tyrosine- and FDG-PET, only FDG demonstrated a significant differences among grades I, II and III. ^{18}F α-methyl tyrosine and FDG for PET appear equally effective at detecting musculoskeletal tumors. In evaluating musculoskeletal tumors, ^{18}F α-methyl tyrosine may be superior to FDG in the differentiation between benign and malignant tumors, whereas FDG may be the better choice for non-invasive malignancy grading. In a patient with a slow growing mass in the thigh, ^{18}F α-methyl tyrosine PET showed abnormal accumulation in the calcified mass lesion but FDG PET showed no abnormal accumulation (Fig. 3). Our pathological diagnosis found osteosarcoma and the diagnosis with ^{18}F α-methyl tyrosine was accurate.

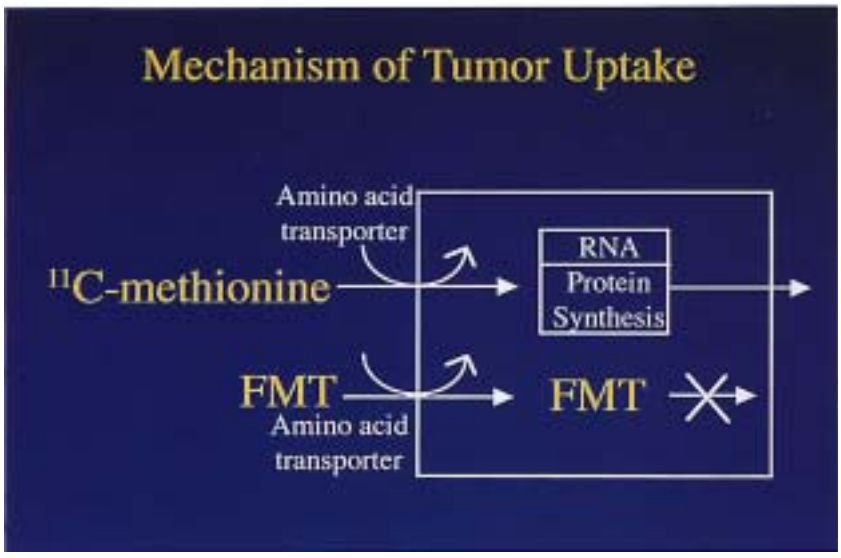

Fig. 1 Mechanism of tumor uptake of ^{11}C methionine and ^{18}F α-methyl tyrosine. Both ^{11}C methionine and ^{18}F α-methyl tyrosine accumulate in the tumor cell via an amino acid transporter system. ^{11}C methionine enters the metabolic process of RNA and protein synthesis, but most ^{18}F α-methyl tyrosine in the tumor cell was not incorporated into the protein/RNA synthetic process like ^{123}I α-methyl tyrosine.

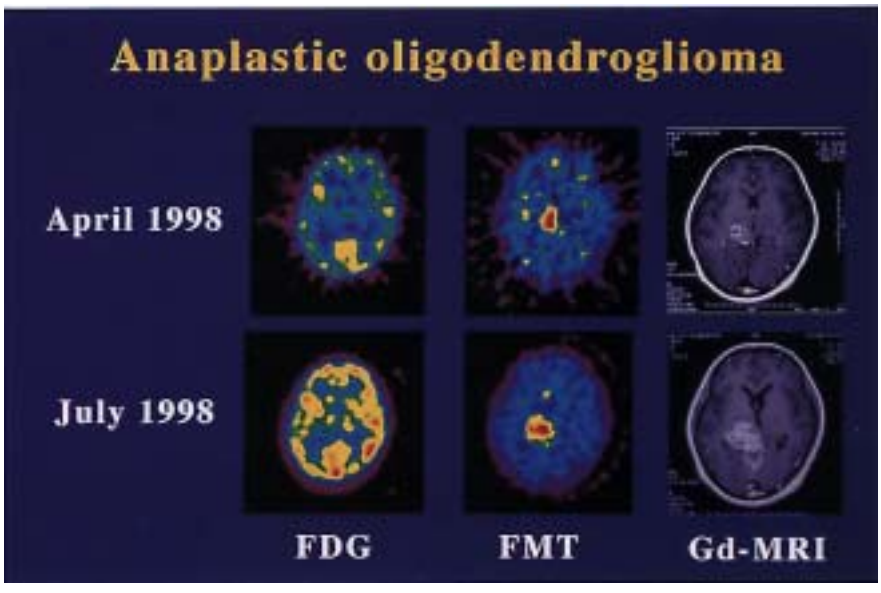

Fig. 2 A case of an aplastic oligodendroglioma. ^{18}F α-methyl tyrosine (FMT) PET (*middle*) could delineate the brain tumor, which was visualized as a ring-like enhanced lesion on the T1 weighted MR image (*right*). But FDG PET (*left*) failed to visualize the tumor even if the tumor had increased in size more than 3 months later (lower images obtained in July 1998).

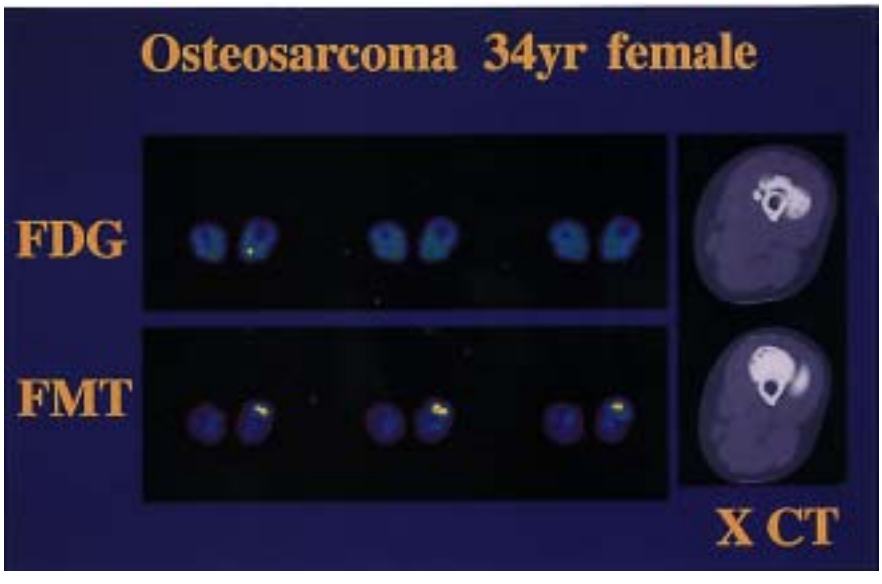

Fig. 3 A 34-yr-old female with an osteosarcoma. She suffered from a slow growing mass in the thigh. ^{18}F α-methyl tyrosine PET showed abnormal accumulation in the calcified mass lesion but FDG PET showed no abnormal accumulation.

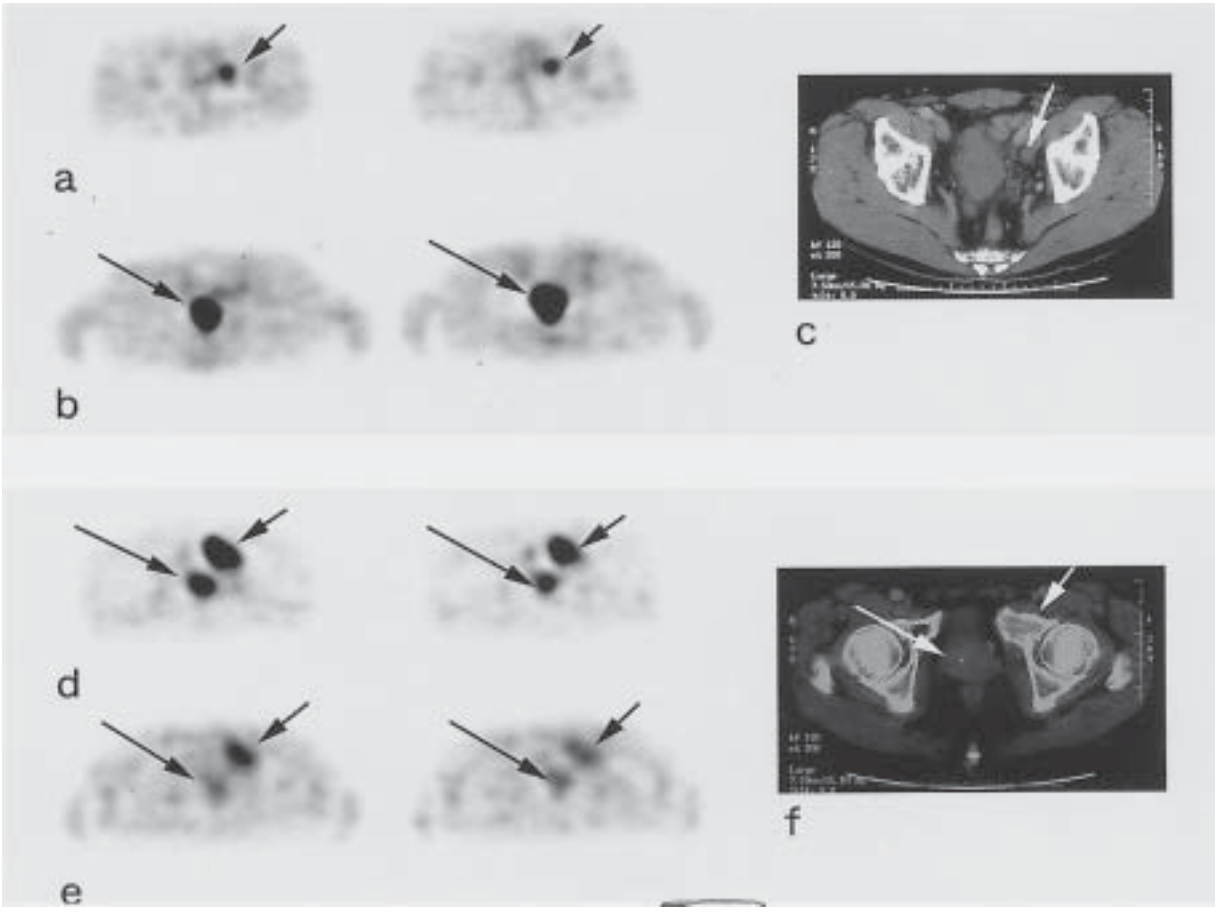

Fig. 4 A 57-yr-old male with prostate cancer. At the slice level of 37.5 mm above the prostate, ^{11}C-choline PET (a) showed a regional lymph node metastasis (*short arrow*) and no radioactivity in the urinary bladder. FDG PET (b) revealed noticeably high radioactivity in the urinary bladder (*long arrow*) but no significant uptake in the lymph node metastasis (false positive result), which was confirmed on the CT image (c) (*arrow*). At the slice level of the prostate, both ^{11}C-choline PET (d) and FDG PET (e) revealed a primary lesion (*long arrow*) and a metastatic lesion of the pubic bone (*short arrow*) shown on the CT image (f).

The theoretic and preclinical background of amino acid imaging is sound and supports clinical applications. The fact that amino acid imaging is less influenced by inflammation may be advantageous in comparison with FDG PET imaging, but its tumor specificity is not absolute.[54] In brain tumor imaging, the use of radiolabeled amino acids is established, since the diagnostic accuracy of amino acid imaging seems to be adequate. The general feasibility of amino acid imaging in various tumor types has been sufficiently shown, but more research such as multicenter trials is required in a larger patient series and in a well-defined clinical setting.

Tumor detection with $^{11}C/^{18}F$ choline and ^{11}C acetate

More recently, [methyl-^{11}C]choline (^{11}C-choline) was introduced as another novel tumor seeking agent for detecting brain tumors.[55,56] prostate cancer,[57] lymph node metastasis of esophageal cancer[58] and mediastinal lymph node metastasis of lung cancer.[59] ^{11}C-choline is incorporated into the kidneys and liver, and converted to ^{11}C-betaine.[60] ^{11}C-choline, but is phosphorylated within the tumor cells, and is integrated into phosphatidylcholine (lecithin) of a component of cell membrane phospholipids. Once ^{11}C-choline is incorporated into cell membrane phospholipids, it remains there, as opposed to the "chemical trapping" characteristic of FDG. Since malignant tumor cells proliferate rapidly, the biosynthesis of cell membrane is facilitated, and it may yield an increasing tumor uptake of ^{11}C-choline. These different mechanisms of FDG and ^{11}C-choline may play complementary roles in clinical PET in detecting various malignant tumors exhibiting different metabolic or biologic behavior.

^{11}C-choline PET can be started just 5 min after the intravenous injection of the tracer, and it may produce a rapid diagnosis for suspected malignant tumors in comparison with FDG PET, which can be started at the earliest 40 min after the tracer injection. In the case of some cancers, tumor detectability of ^{11}C-choline PET seemed

to be slightly superior to that of FDG PET, especially in patients suffering from prostate cancer (Fig. 4). The absence of radioactivity in the urinary bladder on the ^{11}C-choline PET image makes it possible to improve tumor detectability of intrapelvic lesions such as primary prostate cancer and its metastasis (Fig. 4). On the other hand, ^{11}C-choline is unsuitable for PET scan in patients with tumors in the upper abdomen such as pancreas cancer or hepatic cell carcinoma, since physiologically intense uptake of ^{11}C-choline in the liver and kidney may interfere with the tumor visualization on PET images. Kobori et al. reported that physiologically intense liver uptake of ^{11}C-choline prevents imaging metastatic lymph nodes in the upper abdomen.[58]

Both ^{11}C-choline and FDG accumulated in malignant tumors more than in non-malignant lesions (Fig. 5). Except for lung cancer, ^{11}C-choline uptakes were higher than FDG uptakes, and ^{11}C-choline PET was expected to provide a clearer tumor image than FDG PET. Image quality may depend on the difference in the tumor uptake mechanism. FDG is incorporated actively in limited tumor cells that are in a hypoxic condition and obtain most of their energy from glycolysis. In cases of relatively small tumors with a sufficient blood supply, FDG will unlikely be incorporated actively. In contrast, ^{11}C-choline uptake may be simply proportional to the rate of cell membrane synthesis related to cell proliferation, irrespective of the oxygen supply or glycolysis-related energy metabolism in tumor cells.[59,60]

Tumor detectability of ^{11}C-choline PET seemed to be slightly superior to that of FDG PET. ^{11}C-choline is labeled with ^{11}C of a shorter physical half-life of radioactivity (20 minutes), which is less suitable for whole body imaging than FDG, labeled with ^{18}F, having a relatively longer physical half-life of radioactivity (109 minutes). This is one of the major shortcomings of ^{11}C-choline PET. But even if we take into consideration the drawbacks of ^{11}C-choline PET, such as its unsuitability for upper abdominal imaging and whole body imaging, the combined use of ^{11}C-choline PET and FDG PET is ideal for diagnosing cancer patients. ^{11}C-choline PET is indeed an excellent diagnostic tool for detecting malignant tumors. Furthermore, ^{18}F choline has also been developed and its clinical usefulness is being investigated.[61,62]

^{11}C acetate as a metabolic substrate of beta-oxidation, precursor of amino acid, and fatty acid, is useful in detecting various malignancies. Liu et al. assessed the feasibility of clinical application of [^{11}C]acetate in oncology.[63] They conducted ^{11}C acetate PET studies in 513 patients with various malignancies. ^{11}C acetate PET is more accurate in detecting meningioma (accuracy 97%), glioma (91%), nasopharyngeal cancer (93%), lymphoma (85%), non-small cell cancer (81%), colon cancer (78%), renal cell cancer (80%) and ovarian cancer (76%), than in detecting small-cell cancer of the lungs, thyroid cancer and pancreas cancer. The advantages of ^{11}C acetate PET

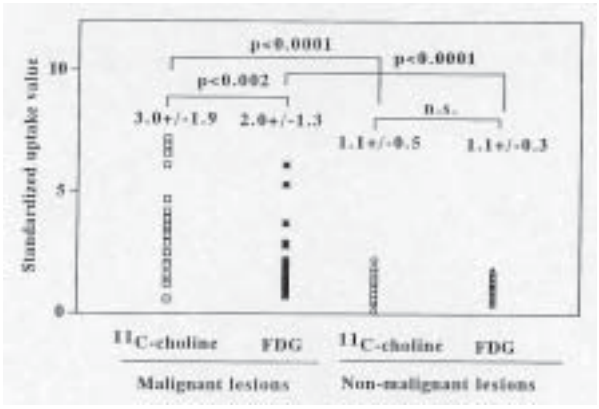

Fig. 5 Standardized uptake (SUV) of ^{11}C choline and FDG in malignant lesions and non-malignant lesions. Differences between ^{11}C-choline and FDG in SUVs were significant in lesions ($p < 0.002$), but not significant in non-malignant lesions. Both ^{11}C-choline and FDG PET revealed significantly higher SUV in malignant lesions than in non-malignant lesions ($p < 0.0001$, respectively).

were less time consuming (the entire procedure was completed within 45 minutes after injection), no hyperglycemic effect and few urinary excretions. The disadvantages are the increased uptake in salivary glands and pancreas, and sometimes the bowels, which may cause either false positive or false negative results, and the on-site-cyclotron dependency. Both advantages and disadvantages of ^{11}C acetate are quite similar to those of ^{11}C choline. ^{11}C acetate is clinically useful in detecting various malignant tumors and may play a complementary role to FDG.

TUMOR CHARACTERIZATION BY EVALUATING DNA SYNTHESIS

Oncologists are developing a number of new potential therapeutic methods, including gene targeting. To evaluate tumor cell response to gene targeting therapy at a preclinical level, a non-invasive method for evaluating tumor cell proliferation is highly desirable in the clinical context. The growth fraction can be estimated by the incorporation of radiolabeled thymidine into the DNA of S-phase cells. ^{11}C tymidine PET shows an earlier chemotherapeutic response for lung cancer than FDG PET and X ray CT as a morphologic evaluation.[64] The thymidine analogue bromodeoxyuridine (BrUdR) labeled with ^{76}Br was also developed for PET imaging and employed in a PET scanner in patients with melanoma by Boni et al.[65] Their study showed that the accumulation of [^{76}Br]BrUdR in PET correlated significantly with the immunohistochemical assessment of S-phase and cycling cells.

Shields et al. developed and tested ^{18}F 3′-deoxy-3′-fluorothymidine [FLT].[66] FLT is resistant to degradation and is retained in proliferating tissues by the action of

thymidine kinase 1 (TK). They presented high-contrast images of normal marrow and tumors in a patient with lung cancer.[66] Recent clinical trials of FLT PET in patients with non-small cell lung cancer and breast cancer seem to indicate its clinical usefulness in cancer diagnosis.[67,68]

TUMOR CHARACTERIZATION BY EVALUATING HYPOXIC TUMOR CELLS

Since tumor hypoxia is associated with increased resistance to radiotherapy or chemotherapy, development of a method for measuring tumor hypoxia is important in making an optimal decision on cancer treatment. Misonidazole behaves uniquely in a low oxygen environment, in other words, misonidazole remains in the tumor cell under hypoxic conditions. ^{18}F fluoromisonidazole was employed for the evaluation of tumor hypoxia in patients with nasopharyngeal cancer and its cervical lymph node metastases.[69]

Koh et al. investigated tumor re-oxygenation of lung cancer during fractionated radiation therapy by means of PET with ^{18}F fluoromisonidazole. They found that there was a general tendency toward improved oxygenation in human tumors during fractionated radiotherapy but these changes were unpredictable.[70] PET findings with ^{18}F fluoromisonidazole may be insufficient in extent and timing to overcome the negative effects of existing pretreatment hypoxia. The selection of patients with radioresistant hypoxic cancers can be appropriately achieved through single pretreatment evaluations of tumor hypoxia using PET with ^{18}F fluoromisonidazole.

THERAPEUTIC DRUG MONITORING AND OPTIMIZATION FOR CANCER TREATMENT WITH PET AND RADIOLABELED DRUGS

Assessing *in vivo* pharmacokinetics of therapeutic drugs in each patient is needed to gain the efficient outcome of drug treatment or the best choice of drugs. The conventional way of therapeutic drug monitoring and optimization is to measure the serum drug concentration, which does not provide *in vivo* biodistribution of the therapeutic drug. PET technology enables us to measure the drug behavior in each patient once the positron emitter can be attached to the drug, but there are some difficulties in the wide spread use in clinical practice of this PET technology. For example, once we label a radionuclide with a drug, the metabolism of the radiolabeled drug may change, and the difference between the metabolic fate of the original drug and the radiolabeled drug must be acceptable at the clinical level.

Moehler et al. employed ^{18}F 5FU PET in colorectal cancer with metastases to the liver treated with 5FU.[71] In scatter plot analysis, they found a statistically significant correlation between the SUV of ^{18}F 5FU and survival time. Patients with high ^{18}F-FU uptake values were more likely to achieve at least stabilization of the disease with planned chemotherapy. ^{18}F-5FU PET may be a valuable new tool for determining, prior to 5-FU-based chemotherapy, which patients are likely to have a good response and prolonged survival.

Strauss et al. employed ^{15}O labeled water and ^{18}F 5FU in patients with liver metastases from colorectal carcinoma, and assessed the intrahepatic distribution of 5FU after intraarterial and intravenous injection.[72] Then they found the very high and rapid elimination of the cytostatic agent out of the tumor cells to be the main factor limiting a therapy response. Furthermore, they found that the injection route is also an important factor in determining the *in vivo* drug distribution and the response to therapy.

Tamoxifen, the transisomer of a substituted triphenylethylene, is a nonsteroidal antiestrogenic drug that is widely used for endocrine therapy in patients with breast cancer. Tamoxifen binds to the cytoplasmic estrogen receptor (ER) within the ER-positive tumor cell. ER assays of excised tumor tissue provide information about whether endocrine therapy is effective in each patient, but only 60% of patients who have ER-positive breast cancer have an objective response to endocrine therapy.[73,74] The development of a supplemental technique to predict the responsiveness of breast cancer to adjuvant endocrine therapy for individual patients would therefore be helpful.

Radiolabeled estrogen and progesterone have been developed for use in PET to detect primary or metastatic lesions and to predict the responsiveness of breast cancer to endocrine therapy. The positron-emitting estrogenic steroid 16 alpha-[^{18}F]fluoro-17 beta-estradiol (FES) has been shown to exhibit selective uptake in primary breast carcinomas; the uptake of tracer by positron emission tomography (PET) is strongly correlated with the tumor estrogen-receptor concentration. FES PET revealed ER positive primary and metastatic lesions in breast cancer patients.[75–78]

The functional status of tumor ERs can be characterized *in vivo* by FES PET. The results of PET are predictive of responsiveness to tamoxifen therapy in patients with advanced ER(+) breast cancer.[77,78] Because tamoxifen has several anti-tumor activities except for an ER-mediated mechanism, radiolabeled tamoxifen may provide more accurate information about anti-estrogen therapy than does radiolabeled estradiol. Although a further large-scale study is needed to confirm the clinical utility of PET with ^{18}F fluorotamoxifen, a preliminary study reveals that PET with ^{18}F fluorotamoxifen provided useful information in predicting the effect of tamoxifen therapy in patients with ER-positive breast cancer.[79]

In this review, we described PET radiopharmaceuticals for cancer diagnosis and therapeutic management that are already employed in clinical trials. There are many PET radiopharmaceuticals that we could not include in this review. Recent research in the field of PET oncology is

undertaking the extremely difficult task of imaging the gene expression in tumor cells or monitoring the gene targeting cancer therapy.[80,81] As shown in this review, we are watching a continually changing landscape in the field of PET oncology. Through trial and error, a field of candidates have emerged in their efforts to develop "the next FDG." Technological advances in the field of PET oncology provide optimism that the next technological breakthrough will open up a new era in nuclear medicine.

REFERENCES

1. Gallagher BM, Fowler JS, Gutterson NI, MacGregor RR, Wan C-N, Wolf AP. Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of [^{18}F]2-deoxy-2-fluoro-D-glucose. *J Nucl Med* 1978; 19: 1154–1161.
2. Sazon DA, Santiago SM, Soo Hoo GW, et al. Fluorodeoxyglucose-positron emission tomography in the detection and staging of lung cancer. *Am J Respir Crit Care Med* 1996; 153: 417–421.
3. Pieterman RM, van Putten JWG, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron emission tomography. *N Engl J Med* 2000; 343: 254–261.
4. Kubota K, Matsuzawa T, Fujiwara T, et al. Differential diagnosis of lung tumor with positron emission tomography. A prospective study. *J Nucl Med* 1993; 31: 1927–1933.
5. Inoue T, Kim EE, Komaki R, et al. Detecting recurrent or residual lung cancer with FDG-PET. *J Nucl Med* 1995; 36: 788–793.
6. Sasaki M, Ichiya Y, Kuwabara Y, et al. The usefulness of FDG positron emission tomography for the detection of mediastinal lymph node metastases in patients with non-small cell lung cancer: a comparative study with X-ray computed tomography. *Eur J Nucl Med* 1996; 23: 741–747.
7. Bar-Shalom R, Mor M, Yefremov N, Goldsmith SJ. The value of Ga-67 scintigraphy and F-18 fluorodeoxyglucose positron emission tomography in staging and monitoring the response of lymphoma to treatment. *Semin Nucl Med* 2001; 31: 177–190.
8. Buchmann I, Reinhardt M, Elsner K, et al. 2-(fluorine-18)fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma. A bicenter trial. *Cancer* 2001; 91: 889–899.
9. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [^{18}F]FDG-PET a valid alternative to conventional diagnostic methods? *J Clin Oncol* 2001; 19: 414–419.
10. Hueltenschmidt B, Sautter-Bihl ML, Lang O, et al. Whole body positron emission tomography in the treatment of Hodgkin disease. *Cancer* 2001; 91: 302–310.
11. Kostakoglu L, Goldsmith SJ. Fluorine-18 fluorodeoxyglucose positron emission tomography in the staging and follow-up of lymphoma: is it time to shift gears? *Eur J Nucl Med* 2000; 27: 1564–1578.
12. Hung GU, Shiau YC, Tsai SC, Chao TH, Ho YJ, Kao CH. Value of ^{18}F-fluoro-2-deoxyglucose positron emission tomography in the evaluation of recurrent colorectal cancer. *Anticancer Res* 2001; 21: 1375–1378.
13. Flamen P, Hoekstra OS, Homans F, et al. Unexplained rising carcinoembryonic antigen (CEA) in the postoperative surveillance of colorectal cancer: the utility of positron emission tomography (PET). *Eur J Cancer* 2001; 37: 862–869.
14. Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. *Semin Nucl Med* 2000; 30: 150–185.
15. Flamen P, Stroobants S, Van Cutsem E, et al. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. *J Clin Oncol* 1999; 17: 894–901.
16. Abdel-Nabi H, Doerr RJ, Lamonica DM, et al. Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. *Radiology* 1998; 206: 755–760.
17. Weber WA, Ott K, Becker K, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol* 2001; 19: 3058–3065.
18. Lerut T, Flamen P, Ectors N, et al. Histopathologic validation of lymph node staging with FDG-PET scan in cancer of the esophagus and gastroesophageal junction: A prospective study based on primary surgery with extensive lymphadenectomy. *Ann Surg* 2000; 232: 743–752.
19. Flamen P, Lerut A, Van Cutsem E, et al. The utility of positron emission tomography for the diagnosis and staging of recurrent esophageal cancer. *J Thorac Cardiovasc Surg* 2000; 120: 1085–1092.
20. Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. *J Clin Oncol* 2000; 18: 3202–3210.
21. Skehan SJ, Brown AL, Thompson M, et al. Imaging features of primary and recurrent esophageal cancer at FDG PET. *Radiographics* 2000; 20: 713–723.
22. Crippa F, Leutner M, Belli F, et al. Which kinds of lymph node metastases can FDG PET detect? A clinical study in melanoma. *J Nucl Med* 2000; 41: 1491–1494.
23. Tyler DS, Onaitis M, Kherani A, et al. Positron emission tomography scanning in malignant melanoma. *Cancer* 2000; 89: 1019–1025.
24. Eigtved A, Andersson AP, Dahlstrom K, et al. Use of fluorine-18 fluorodeoxyglucose positron emission tomography in the detection of silent metastases from malignant melanoma. *Eur J Nucl Med* 2000; 27: 70–75.
25. Dietlein M, Krug B, Groth W, et al. Positron emission tomography using ^{18}F-fluorodeoxyglucose in advanced stages of malignant melanoma: a comparison of ultrasonographic and radiological methods of diagnosis. *Nucl Med Commun* 1999; 20: 255–261.
26. Steinert HC, Huch Boni RA, Buck A, et al. Malignant melanoma: staging with whole-body positron emission tomography and 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1995; 195: 705–709.
27. Lonneux M, Lawson G, Ide C, Bausart R, Remacle M, Pauwels S. Positron emission tomography with fluorodeoxyglucose for suspected head and neck tumor recurrence in the symptomatic patient. *Laryngoscope* 2000; 110: 1493–1497.
28. Jungehulsing M, Scheidhauer K, Damm M, et al. 2[F]-

fluoro-2-deoxy-D-glucose positron emission tomography is a sensitive tool for the detection of occult primary cancer (carcinoma of unknown primary syndrome) with head and neck lymph node manifestation. *Otolaryngol Head Neck Surg* 2000; 123: 294–301.
29. Lowe VJ, Boyd JH, Dunphy FR, et al. Surveillance for recurrent head and neck cancer using positron emission tomography. *J Clin Oncol* 2000; 18: 651–658.
30. Anzai Y, Minoshima S, Wolf GT, Wahl RL. Head and neck cancer: detection of recurrence with three-dimensional principal components analysis at dynamic FDG PET. *Radiology* 1999; 212: 285–290.
31. Engel H, Steinert H, Buck A, Berthold T, Huch Boni RA, von Schulthess GK. Whole-body PET: physiological and artifactual fluorodeoxyglucose accumulations. *J Nucl Med* 1996; 37: 441–446.
32. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose *in vivo*: high accumulation in macrophages and granulation tissues studied by microautoradiography. *J Nucl Med* 1992; 33: 1972–1980.
33. Kubota R, Kubota K, Yamada S, Tada M, Ido T, Tamahashi N. Active and passive mechanisms of [fluorine-18]fluorodeoxyglucose uptake by proliferating and prenecrotic cancer cells *in vivo*: a microautoradiographic study. *J Nucl Med* 1994; 35: 1067–1075.
34. Kubota R, Kubota K, Yamada S, Tada M, Ido T, Tamahashi N. Microautoradiographic study for the differentiation of intratumoral macrophages, granulation tissues and cancer cells by the dynamics of fluorine-18-fluorodeoxyglucose uptake. *J Nucl Med* 1994; 35: 104–112.
35. Kubota R, Kubota K, Yamada S, Tada M, Takahashi T, Iwata R, Tamahashi N. Methionine uptake by tumor tissue: a microautoradiographic comparison with FDG. *J Nucl Med* 1995; 36: 484–492.
36. Kubota K, Ishiwata K, Kubota R, Yamada S, Tada M, Sato T, Ido T. Tracer feasibility for monitoring tumor radiotherapy: a quadruple tracer study with fluorine-18-fluorodeoxyglucose or fluorine-18-fluorodeoxyuridine, L-[methyl-^{14}C]methionine, [6-^{3}H]thymidine, and gallium-67. *J Nucl Med* 1991; 32: 2118–2123.
37. Ogawa T, Shishido F, Kanno I, et al. Related Articles Cerebral glioma: evaluation with methionine PET. *Radiology* 1993; 186: 45–53.
38. Kubota K, Matsuzawa T, Fujiwara T, et al. Differential diagnosis of lung tumor with positron emission tomography: a prospective study. *J Nucl Med* 1990; 31: 1927–1932.
39. Lindholm P, Leskinen S, Lapela M. Carbon-11-methionine uptake in squamous cell head and neck cancer. *J Nucl Med* 1998; 39: 1393–1397.
40. Inoue T, Kim EE, Wong FC, et al. Comparison of fluorine-18-fluorodeoxyglucose and carbon-11-methionine PET in detection of malignant tumors. *J Nucl Med* 1996; 37: 1472–1476.
41. Kole AC, Pruim J, Nieweg OE, et al. PET with L-[1-carbon-11]-tyrosine to visualize tumors and measure protein synthesis rates. *J Nucl Med* 1997; 38: 191–195.
42. Kole AC, Plaat BE, Hoekstra HJ, Vaalburg W, Molenaar WM. FDG and L-[1-^{11}C]-tyrosine imaging of soft-tissue tumors before and after therapy. *J Nucl Med* 1999; 40: 381–386.
43. van Ginkel RJ, Kole AC, Nieweg OE, et al. L-[1-^{11}C]-tyrosine PET to evaluate response to hyperthermic isolated limb perfusion for locally advanced soft-tissue sarcoma and skin cancer. *J Nucl Med* 1999; 40: 262–267.
44. Braams JW, Pruim J, Nikkels PG, Roodenburg JL, Vaalburg W, Vermey A. Nodal spread of squamous cell carcinoma of the oral cavity detected with PET-tyrosine, MRI and CT. *J Nucl Med* 1996; 37: 897–901.
45. Go KG, Keuter EJ, Kamman RL, et al. Contribution of magnetic resonance spectroscopic imaging and L-[1-^{11}C]tyrosine positron emission tomography to localization of cerebral gliomas for biopsy. *Neurosurgery* 1994; 34: 994–1002.
46. Wienhard K, Herholz K, Coenen HH, et al. Increased amino acid transport into brain tumors measured by PET of L-(2-^{18}F)fluorotyrosine. *J Nucl Med* 1991; 32: 1338–1346.
47. Coenen HH, Kling P, Stocklin G. Cerebral metabolism of L-[2-^{18}F]fluorotyrosine, a new PET tracer of protein synthesis. *J Nucl Med* 1989; 30: 1367–1372.
48. Biersack HJ, Coenen HH, Stocklin G, et al. Imaging of brain tumors with L-3-[^{123}I]iodo-alpha-methyl tyrosine and SPECT. *J Nucl Med* 1989; 30: 110–112.
49. Tomiyoshi K, Amed K, Muhammad S, et al. Synthesis of isomers of ^{18}F-labelled amino acid radiopharmaceutical: position 2- and 3-L-^{18}F-alpha-methyltyrosine using a separation and purification system. *Nucl Med Commun* 1997; 18: 169–175.
50. Inoue T, Tomiyoshi K, Higuchi T, et al. Biodistribution studies on L-3-[fluorine-18]fluoro-α-methyl tyrosine: A potential tumor-detecting agent. *J Nucl Med* 1998; 39: 663–667.
51. Inoue T, Shibasaki T, Oriuchi N, et al. ^{18}F alpha-methyl tyrosine PET studies in patients with brain tumors. *J Nucl Med* 1999; 40: 399–405.
52. Inoue T, Koyama K, Oriuchi N, et al. Detection of malignant tumors: whole-body PET with fluorine 18 alpha-methyl tyrosine versus FDG—preliminary study. *Radiology* 2001; 220: 54–62.
53. Watanabe H, Inoue T, Shinozaki T, et al. PET imaging of musculoskeletal tumours with fluorine-18 alpha-methyl-tyrosine: comparison with fluorine-18 fluorodeoxyglucose PET. *Eur J Nucl Med* 2000; 27: 1509–1517.
54. Jager PL, Vaalburg W, Pruim J, de Vries EG, Langen KJ, Piers DA. Radiolabeled amino acids: basic aspects and clinical applications in oncology. *J Nucl Med* 2001; 42: 432–445.
55. Shinoura N, Nishijima M, Hara T, et al. Brain tumors: detection with C-11 choline PET. *Radiology* 1997; 202: 497–503.
56. Hara T, Kosaka N, Shinoura N, Kondo T. PET imaging of brain tumor with [methyl-^{11}C]choline. *J Nucl Med* 1997; 38: 842–847.
57. Hara T, Kosaka N, Kishi H. PET imaging of prostate cancer using carbon-11-choline. *J Nucl Med* 1998; 39: 990–995.
58. Kobori O, Kirihara Y, Kosaka N, Hara T. Positron emission tomography of esophageal carcinoma using ^{11}C-choline and ^{18}F-fluorodeoxyglucose: a novel method of preoperative lymph node staging. *Cancer* 1999; 86: 1638–1648.
59. Hara T, Inagaki K, Kosaka N, Morita T. Sensitive detection of mediastinal lymph node metastasis of lung cancer with ^{11}C-choline PET. *J Nucl Med* 2000; 41: 1507–1513.

60. Roivainen A, Forsback S, Gronroos T, et al. Blood metabolism of [methyl-^{11}C]choline; implications for *in vivo* imaging with positron emission tomography. *Eur J Nucl Med* 2000; 27: 25–32.
61. DeGrado TR, Coleman RE, Wang S, et al. Synthesis and evaluation of ^{18}F-labeled choline as an oncologic tracer for positron emission tomography: initial findings in prostate cancer. *Cancer Res* 2001; 61: 110–117.
62. Kishi H, Hirano Y, Kosaka N, Hara T. Clinical utility of ^{18}F-fluoroethylcholine in prostate cancer imaging. (abstract) *J Nucl Med* 2001; 42: 120P.
63. Liu RS. Clinical Application of ^{11}C acetate. *Clin Positron Imaging* 2000; 3: 185.
64. Shields AF, Mankoff DA, Link JM, et al. Carbon-11-thymidine and FDG to measure therapy response. *J Nucl Med* 1998; 39: 1757–1762.
65. Boni R, Blauenstein P, Dummer R, von Schulthess GK, Schubiger PA, Steinert HC. Non-invasive assessment of tumour cell proliferation with positron emission tomography and [^{76}Br]bromodeoxyuridine. *Melanoma Res* 1999; 9: 569–573.
66. Shields AF, Grierson JR, Dohmen BM, et al. Imaging proliferation *in vivo* with [F-18]FLT and positron emission tomography. *Nat Med* 1998; 4: 1334–1336.
67. Vesselle H, Grierson J, Muzi M, et al. ^{18}F-fluorothymidine PET imaging of non small cell lung cancer (NCLC): comparison to ^{67}Ki proliferation index. (abstract) *J Nucl Med* 2001; 42: 29P.
68. Dohmen BM, Shields AF, Dittman H, et al. Use of ^{18}F-FLT for breast cancer imaging. (abstract) *J Nucl Med* 2001; 42: 29P.
69. Yeh SH, Liu RS, Wu LC, et al. Fluorine-18 fluoromisonidazole tumour to muscle retention ratio for the detection of hypoxia in nasopharyngeal carcinoma. *Eur J Nucl Med* 1996; 23: 1378–1383.
70. Koh WJ, Bergman KS, Rasey JS, et al. Evaluation of oxygenation status during fractionated radiotherapy in human nonsmall cell lung cancers using [F-18]fluoromisonidazole positron emission tomography. *Int J Radiat Oncol Biol Phys* 1995; 33: 391–398.
71. Moehler M, Dimitrakopoulou-Strauss A, Gutzler F, Raeth U, Strauss LG, Stremmel W. ^{18}F-labeled fluorouracil positron emission tomography and the prognoses of colorectal carcinoma patients with metastases to the liver treated with 5-fluorouracil. *Cancer* 1998; 83: 245–253.
72. Dimitrakopoulou-Strauss A, Strauss LG, Schlag P, et al. Intravenous and intra-arterial oxygen-15-labeled water and fluorine-18-labeled fluorouracil in patients with liver metastases from colorectal carcinoma. *J Nucl Med* 1998; 39: 465–473.
73. Wittliff JL. Steroid-hormone receptors in breast cancer. *Cancer* 1984; 53: 630–643.
74. Jordan VC. The role of tamoxifen in the treatment and prevention of breast cancer. *Current Problems in Cancer* 1992; 16: 129–176.
75. McGuire AH, Dehdashti F, Siegel BA, et al. Positron tomographic assessment of 16 alpha-[^{18}F]fluoro-17 beta-estradiol uptake in metastatic breast carcinoma *J Nucl Med* 1991; 32: 1526–1531.
76. Dehdashti F, Mortimer JE, Siegel BA, et al. Positron tomographic assessment of estrogen receptors in breast cancer: comparison with FDG-PET and *in vitro* receptor assays. *J Nucl Med* 1995; 36: 1766–1774.
77. Mortimer JE, Dehdashti F, Siegel BA, Trinkaus K, Katzenellenbogen JA, Welch MJ. Metabolic flare: indicator of hormone responsiveness in advanced breast cancer. *J Clin Oncol* 2001; 19: 2797–2803.
78. Mortimer JE, Dehdashti F, Siegel BA, Katzenellenbogen JA, Fracasso P, Welch MJ. Clin Positron emission tomography with 2-[^{18}F]fluoro-2-deoxy-D-glucose and 16 alpha-[^{18}F]fluoro-17 beta-estradiol in breast cancer: correlation with estrogen receptor status and response to systemic therapy. *Clin Cancer Res* 1996; 2: 933–939.
79. Inoue T, Kim EE, Wallace S, Yang DJ, Wong FCL, Bassa P, et al. Positron emission tomography using [^{18}F]fluorotamoxifen to evaluate therapeutic responses in patients with breast cancer: preliminary study. *Cancer Biotherapy & Radiopharmaceuticals* 1996; 11: 235–245.
80. Gambhir SS, Barrio JR, Wu L, et al. Imaging of adenoviral-directed herpes simplex virus type 1 thymidine kinase reporter gene expression in mice with radiolabeled ganciclovir. *J Nucl Med* 1998; 39: 2003–2011.
81. Phelps ME. PET: the merging of biology and imaging into molecular imaging. *J Nucl Med* 2000; 41: 661–681.