Review Article

Present role and future prospects of positron emission tomography in clinical oncology

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Positron emission tomography (PET) has emerged as a significant molecular imaging technique in clinical oncology and cancer research. PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) demonstrates elevated glucose consumption by tumor cells, and is used clinically for the accurate staging and restaging of cancer, planning of radiotherapy, and predicting response or lack of response in the early stages of treatment. Combined PET and computed tomography (PET-CT) provides both functional and morphological information of the disease to allow accurate diagnosis of cancer. PET with new radiotracers such as protein synthesis markers and proliferation markers, as well as hypoxia and receptor-binding agents, will offer patient-specific images in order to yield tailored diagnostic and prognostic information. (*Cancer Sci* 2006; 97: 1291–1297)

Positron emission tomography (PET) is a non-invasive imaging technique that uses various radiolabeled compounds. PET was developed almost three decades ago and was used initially for evaluating cerebral blood flow and metabolism under physiological conditions and also for assessing pharmacological or neuropsychological intervention.

In the past decade, the clinical applications of PET have expanded with the improvement of PET detectors used for whole-body imaging, and the development of PET in combination with computed tomography (PET-CT). PET-CT offers advantages in accurate diagnosis based on both morphological and metabolic images.

Use of PET has spread particularly in clinical oncology using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) as a tracer. ^{18}F-FDG is the only PET radiotracer for cancer approved by Japanese governmental health insurance. The number of PET cameras installed has increased by geometric progression in developed countries worldwide, including Japan, and the number of ^{18}F-FDG PET studies has increased in proportion to the prevalence of machines.

The increased use of ^{18}F-FDG PET has also been facilitated by administrative and economic decisions. In 2002, the Ministry of Health, Labor and Welfare approved reimbursement for lung, colorectal, breast, head and neck, brain and pancreas cancers, as well as metastatic liver tumor, lymphoma, melanoma, and cancer of unknown primary; recently, esophageal, uterine, and ovarian cancers were also approved. In the USA, the Centers for Medicare and Medicaid Services announced Medicare coverage for PET in January 2005 for all cancers not currently covered, under the condition that patients are enrolled in prospective clinical studies that meet the requirements of the Food and Drug Administration and are designed to collect additional information in patient management. Their policy will contribute to the development of evidence of the clinical usefulness of ^{18}F-FDG PET even in uncommon malignancies.

Positron emission tomography with ^{18}F-FDG has emerged as a significant diagnostic imaging technique in clinical medicine.

PET will aid in the provision of accurate diagnosis, treatment and prognosis in individual patients with cancer. Because the uptake of ^{18}F-FDG depends on the cellular metabolism of glucose, ^{18}F-FDG PET can assess tumor malignancy, therapeutic response and recurrence more accurately than conventional morphology-based imaging methods. PET-CT will aid in the evolution of accurate assessment based on morphological and functional images, and new PET imaging agents other than ^{18}F-FDG will allow for patient-specific evaluation based on molecular and genetic markers of disease.

^{18}F-FDG PET in oncology

^{18}F-fluorodeoxyglucose PET is used for the assessment of various types of cancer before therapy for staging and planning treatment. It is also used after therapy for restaging and evaluating treatment response as well as detecting recurrence of tumors. Tumor uptake of ^{18}F-FDG depends on the expression of glucose transporters and hexokinase of tumor cells.[1] Although ^{18}F-FDG is transported into the cytoplasm and phosphorylated to become ^{18}F-FDG-6-phosphate, it is not metabolized further and stays inside cells, which allows the imaging. The physical half-life of ^{18}F is 110 min and ^{18}F-FDG is excreted into the urine.

The uptake of ^{18}F-FDG is increased in most types of cancer. However, the diagnostic value of ^{18}F-FDG PET is limited because the uptake is variable in some types of cancer. These include thyroid, hepatocellular and renal cell cancers. Tumors that are well-differentiated, hypo-cellular and mucin producing, such as bronchioloalveolar cancer and intraductal papillary mucinous tumor, demonstrate low uptake of ^{18}F-FDG. Tumors in the kidneys and bladder are also difficult to detect because of the physiological excretion of ^{18}F-FDG into the urine.

Moreover, although ^{18}F-FDG PET is useful for the evaluation of neoplasms, the uptake of ^{18}F-FDG is not tumor-specific and a variety of normal organs show increased ^{18}F-FDG uptake. Brain shows high ^{18}F-FDG uptake because the brain exclusively uses glucose for energy metabolism. Myocardium is demonstrated occasionally on ^{18}F-FDG PET in hyperglycemia, shortly after a meal, and in altered myocardial metabolism due mainly to ischemia. Physiological ^{18}F-FDG uptake is seen in tonsil, salivary glands, vocal cord, reactive lymph nodes, liver, gastrointestinal tract and testis, as well as muscles.[2] The extent of uptake in these organs varies depending on physiological state and individual variability. Although the uptake of ^{18}F-FDG is increased in most types of cancer in comparison to the uptake in most normal organs, tumors in the aforementioned areas are sometimes incorrectly interpreted.

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Table 1. Representative radiotracers for positron emission tomography in oncology

| Clinical application and tracer	Analog	Mechanism of uptake
Diagnosis of tumor		
[18]F-fluorodeoxyglucose	Glucose	Glucose transport, phosphorylation
[11]C-methionine[3]	Methionine	A-amino acid transport, protein synthesis
[11]C-tyrosine[4]	Tyrosine	L-amino acid transport
[18]F-fluoro-L-tyrosine[5]	Tyrosine	L-amino acid transport
[18]F-fluoroethyltyrosine[6]	Tyrosine	L-amino acid transport
[18]F-fluoro-α-methyltyrosine[19]	Tyrosine	L-amino acid transport
[18]F-fluorothymidine[20]	Thymidine	Nucleoside transport, phosphorylation
[11]C-choline[9]	Choline	Synthesis of phosphatidylcholine
[18]F-fluorocholine[10]	Choline	Synthesis of phosphatidylcholine
Detection of tumor hypoxia		
[18]F-fluoromisonidazole[11]	Misonidazole	Reduction by low oxygen concentration
[60]Cu-, ^{64}Cu-ATSM[26]		
Detection of estrogen receptor		
[18]F-fluoro-17β-estradiol[12]	Estradiol	Estrogen receptor binding
Therapeutic drug monitoring		
[18]F-fluorouracil[13]	Uracil	Similar to accumulation of 5-fluorouracil
[18]F-paclitaxel[15]	Paclitaxel	Similar to accumulation of paclitaxel
Detection of apoptosis		
[18]F-annexin V[23]	Annexin V	Binding to apoptotic cells
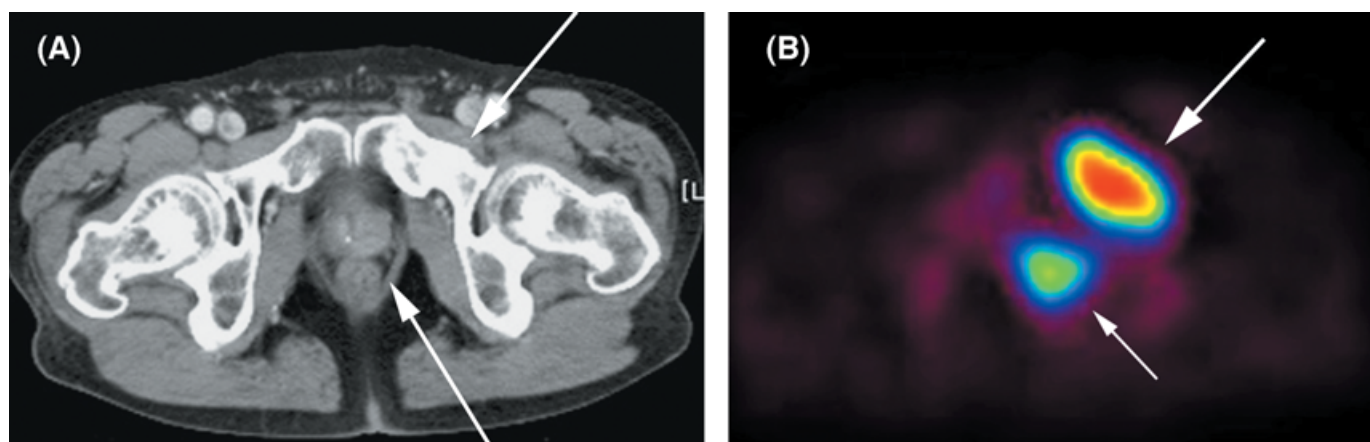
Fig. 1. Detection of prostate cancer by positron emission tomography (PET) with ^{11}C-choline. A man with prostate cancer and bone metastasis underwent PET with ^{11}C-choline. (A) Computed tomography (CT) shows swelling of the left lobe (arrow) and osteoblastic appearance of the left pubic bone (arrow). (B) PET shows markedly increased uptake of ^{11}C-choline in both the primary prostate cancer lesion and bone metastasis (arrows). As PET with ^{18}F-FDG is not suitable for the diagnosis of prostate cancer due to excretion of the [8]F-FDG into urine, PET with ^{11}C-choline is thought to be useful for the detection of tumors adjacent to the urinary tract.

In addition, many pathological processes other than malignant neoplasms show increased ^{18}F-FDG uptake. Benign tumors in the head and neck and colonic adenoma often show levels of ^{18}F-FDG uptake as high as malignant tumors. Infiltrating cells in inflammatory processes or granuloma, and proliferating cells in hyperplastic tissue also demonstrate enhanced uptake of ^{18}F-FDG.

Other PET tracers

As the uptake of ^{18}F-FDG is not tumor-specific, several other radiotracers have been used for the imaging of cancer. Table 1 shows the representative PET tracers in oncology, most of which are more tumor-specific than ^{18}F-FDG. PET is now considered to be one of the standard means of molecular imaging using these tracers as probes for cellular metabolism, proliferation, hypoxia, receptor and apoptosis, among others.[3–15]

One of the PET radiotracers that we have used is ^{11}C-choline (Fig. 1). ^{11}C-choline penetrates the cell membrane and is phosphorylated within the cell, so it remains in the tumor. Cellular uptake of ^{11}C-choline is thought to be proportional to the rate of tumor duplication, because biosynthesis of cell membranes is fast. Clinical studies found that ^{11}C-choline has higher contrast than ^{18}F-FDG in visualizing various types of cancer and is useful for the differentiation between malignant and benign tumors.[16,17]

With further knowledge of the characteristics and clinical effectiveness of these tracers, it will become clear which tracer or combination of tracers is most appropriate for optimal cancer diagnosis.

Protein synthesis markers

A variety of amino acids labeled with radionuclides are used for PET imaging. They are a marker of protein synthesis in a broad
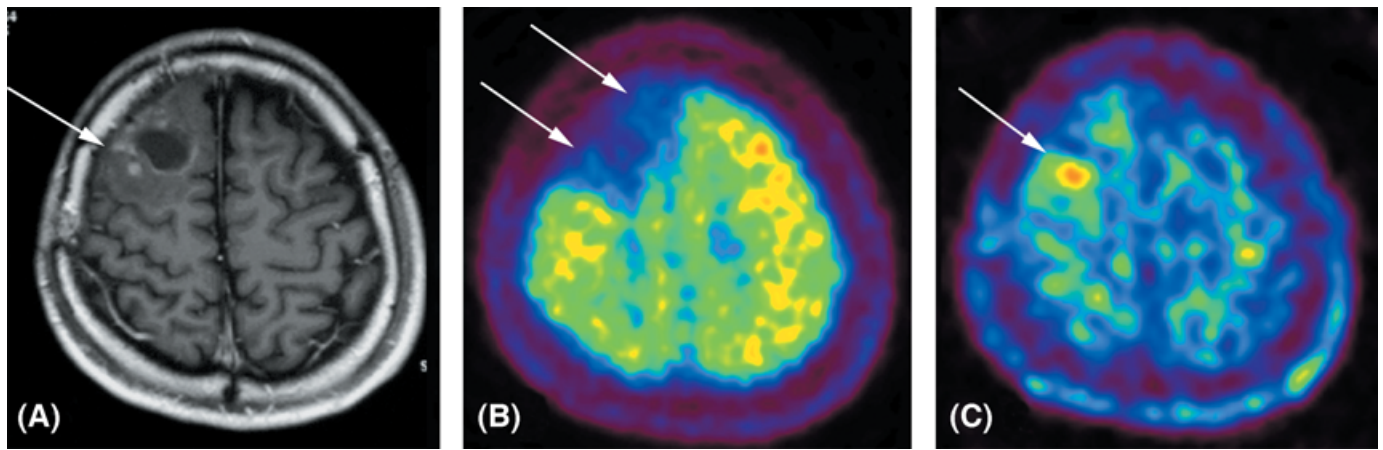
Fig. 2. Detection of recurrent glioblastoma by positron emission tomography (PET) with ^{18}F-fluoro-α-methyltyrosine (FAMT). A woman with glioblastoma in the right frontal lobe underwent resection of tumor and adjuvant chemoradiation. (A) After 8 months, magnetic resonance imaging showed gadolinium-enhancement around the area of resection (arrow). (B) PET with ^{18}F-FDG showed decreased uptake of ^{18}F-FDG in the area as compared with normal brain parenchyma (arrows). (C) PET with FAMT shows increased uptake at the posterolateral portion (arrow) indicating recurrence of glioblastoma.

sense. Some of them are transported by the specific amino-acid transporter and metabolized for protein synthesis in the cytoplasm. Others are transported into the cells without further metabolism.

^{11}C-labeled methionine (MET) has been investigated in the imaging of various types of cancer.[18,19] MET is better for imaging neoplasms than FDG due to higher specificity resulting in improved differentiation between cancer and benign processes. MET is transported into cells and is used for protein synthesis. PET with MET shows relatively intense tracer accumulation in the pancreas, liver, bone marrow, and salivary glands as compared with FDG and other amino-acid tracers not involved in protein synthesis. Therefore, cancers in these organs may be overlooked. The short physical half-life of ^{11}C is another drawback for the clinical use of MET.

^{18}Fluorine has a longer half-life than ^{11}C and is advantageous for chemical synthesis and imaging. Several ^{18}F-based PET tracers have been developed, such as ^{18}F-fluoro-L-tyrosine, ^{18}F-fluoroethyltyrosine, and ^{18}F-fluoro-α-methyltyrosine (FAMT). We have investigated the clinical utility of FAMT in several tumors including brain tumor, lung cancer, head and neck cancer, and lymphoma.[20] FAMT is transported via L-type amino-acid transporter 1 (LAT-1), which is specific to cancer cells. FAMT is not metabolized inside the cell[21] as FAMT is methylated at its α-position. Because it does not show intense accumulation in the pancreas and liver, diagnosis of pancreas cancer and liver tumor may be possible. FAMT can provide clear delineation of the tumor in patients with glioma that is not clearly demonstrated on FDG PET, because FDG accumulation in a recurrent tumor is sometimes equivalent to normal gray matter (Fig. 2).

Cellular proliferation markers

As cellular proliferation has a key role in the advancement of cancer, a variety of cellular proliferation markers such as nucleic acids have been radiolabeled as PET tracers. One example is ^{18}F-fluoro-3′-deoxy-3′-L-thymidine (FLT).[22] FLT is phosphorylated by thymidine kinase and enters the salvage pathway without incorporation into the DNA molecule. A stable accumulation of FLT in the cell happens by so-called metabolic trapping, which is similar to FDG. An early study with FLT demonstrated that the uptake of FLT correlated with the proliferation of cancer cells, as indicated by immunohistological analysis with

Ki-67.[23] Another study indicated its potential use for monitoring tumor response to chemotherapy.[24] Results of previous studies revealed that FLT is more tumor-specific than FDG, and it is thought to be useful for differential diagnosis and for monitoring tumor response in a wide range of cancers. As FLT accumulates in the bone marrow and the liver, tumors in these organs are not suited for PET diagnosis with FLT. Other agents such as FIAU, FBAU and FMAU are markers of DNA synthesis that reflects cellular proliferation.[25,26]

Tissue hypoxia markers

Oxygen content in a tumor is lower than in normal tissue. Therefore, hypoxia itself could be a target for tumor imaging. Moreover, localization of tumor hypoxia has radiobiological significance regarding the planning of treatment, because hypoxic cells are resistant to radiation therapy as well as to chemotherapy. Spatial distribution and the extent of hypoxia are crucial data for performing effective radiotherapy.

The uptake level of a tissue hypoxia marker should ideally be proportional to tumor hypoxia. Two compounds, ^{18}F-fluoromisonidazole (MISO) and ^{60}Cu or ^{64}Cu-diacetyl-bis (N-(4)-methylthiosemicarbazone) (ATSM), are the principal PET tracers clinically available.[27,28] MISO is an analog of a radiosensitizer that has been used for some time. ATSM has a small molecular weight and high membrane permeability, thus it can diffuse; it is retained in hypoxic cells and reduced in viable cells under low cellular oxygen levels.[29] Results of one study showed a significant relationship between ATSM uptake and response to therapy.[30] One or a combination of these agents with FDG will aid in the development of PET-guided radiotherapy.

Receptor-binding agents

Quantitative *in vivo* receptor assay is another advantageous technique using PET. Radiolabeled receptor ligands for imaging neurotransmitters, enzymes, and transporters with high radiochemical purity have been produced for these purposes. For the imaging of tumors with estrogen receptors, 16α-[^{18}F]-fluoroestradiol (FES) has been evaluated using PET imaging of breast cancer.[12] FES PET shows functioning estrogen receptors *in vivo*, and could predict response to anti-estrogen therapy.[31] Functional imaging allows direct
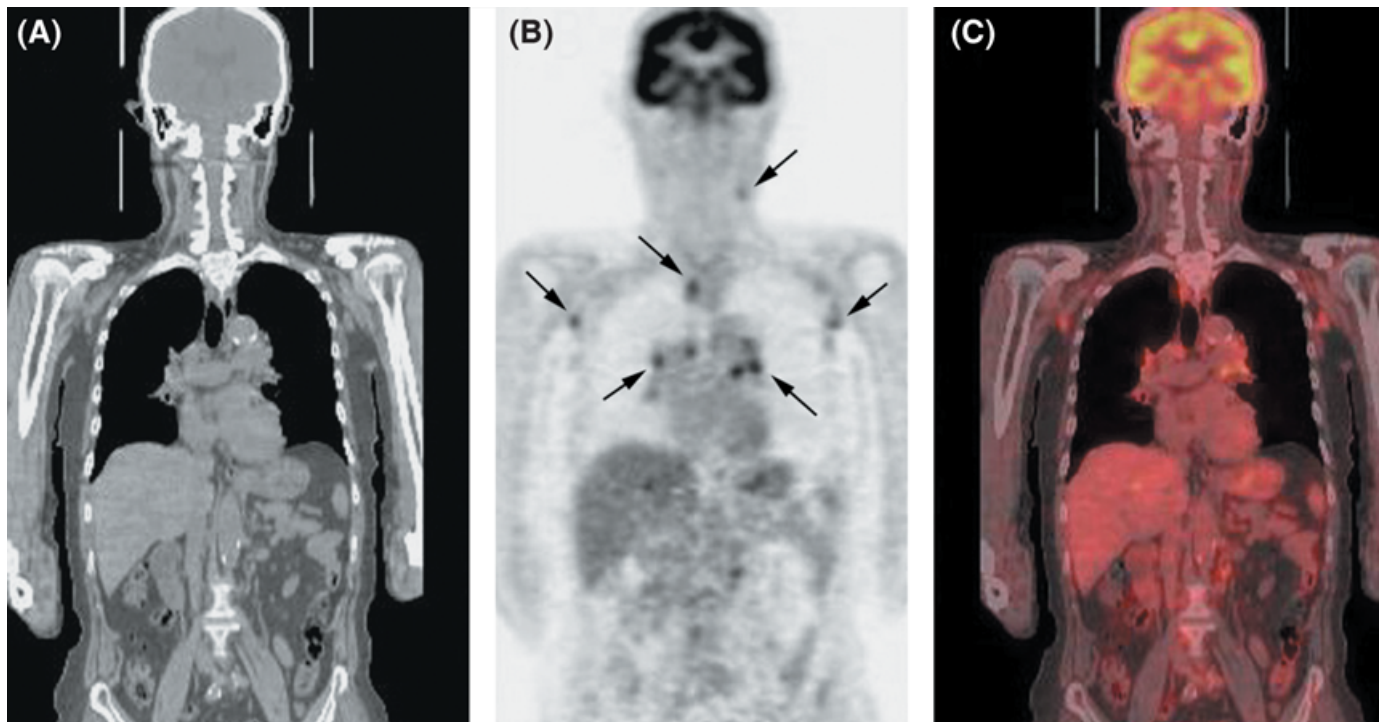
Fig. 3. Detection of recurrent lymphoma by positron emission tomography-computed tomography (PET-CT) with ^{18}F-FDG. A 73-year-old man with peripheral T-cell lymphoma in the left cervix underwent six courses of chemotherapy with THP-COP. After 2 years, cervical CT demonstrated recurrence at a left cervical lymph node. PET-CT was performed for restaging. (A) CT, (B) PET and (C) coronal view on PET-CT show increased uptake of ^{18}F-FDG in multiple lymph nodes <1 cm (arrows).

assessment of estrogen receptors specifically expressed in hormone-refractory tumors that are not accurately evaluated by *in vitro* estrogen receptor (ER) assay with biopsy specimen. Absence of FES uptake in the tumor implies that the tumor should be treated with chemotherapy other than hormonal therapy. Imaging with 16β-[^{18}F]-fluoro-5α-dihydrotestosterone (FDHT) has been investigated in patients with prostate cancer.[32] The results show the utility of FDHT in predicting response to androgen ablation therapy.

PET and conventional imaging

Diagnostic imaging, such as CT, magnetic resonance imaging and ultrasonography, has advanced remarkably and has become indispensable for the management of cancer patients. Although clinical oncologists have been using these imaging techniques for many years to evaluate primary tumor and metastases, they have become aware of PET as a new technique to provide additional information. Conventional imaging techniques assess morphological aspects of the tumor, whereas PET assesses functional or metabolic characteristics. Considering these differences, PET is more suitable for the differentiation of malignant tumors from benign processes, assessment of the grade of malignancy, and monitoring tumor response to therapy. Although health insurance coverage is on a disease basis, indication of PET is categorized into diagnosis, staging, restaging, and monitoring response to therapy.

There are many studies that have demonstrated evidence of the usefulness of PET for the diagnosis and staging of various cancers. Recent PET investigations have been more focused on restaging and monitoring tumor response.

Restaging

Positron emission tomography is used for the restaging of various cancers, when recurrence is suspected by clinical findings or by conventional imaging (Fig. 3). Restaging is also performed for accurate assessment of the tumor in order to determine further treatment even when the results of conventional imaging are negative or equivocal (Fig. 4). PET is used for accurate differentiation between viable tumor and necrosis or scar in patients with residual mass. PET is not indicated until 2–3 months after radiation or chemoradiation or until 1–2 months after surgery because post-therapeutic inflammation causes accumulation of ^{18}F-FDG and false-positive findings at the site of radiation or surgery. PET performed during this time should be interpreted with knowledge of the radiation field and type of surgery.

The diagnostic performance of PET in restaging is excellent for non-small-cell lung,[33] breast,[34] esophageal,[35–37] colorectal,[38,39] and head and neck[40,41] cancer, as well as lymphoma,[42,43] melanoma,[44] and sarcoma.[45] Sensitivity, specificity, and accuracy of PET in restaging these tumor types are 80–95%, 75–90%, and 80–90%, respectively.

The typical use of PET in tumor restaging is in the detection of recurrence in patients who have elevated levels of tumor markers without symptoms. PET is suitable due to the non-invasive nature of the examination and the high-contrast visualization of recurrent tumors in many organs, even if tumors are deep inside the abdominal cavity.

Monitoring tumor response

Owing to its characteristics of functional or metabolic imaging, PET may have an advantage for the monitoring of tumor response. Conventional imaging assesses tumor response based on the morphological changes in the tumor. These changes usually occur after a certain time interval following effective chemotherapy. Therefore, multiple doses of cytotoxic drugs are sometimes administered even if they are ineffective. It would be beneficial
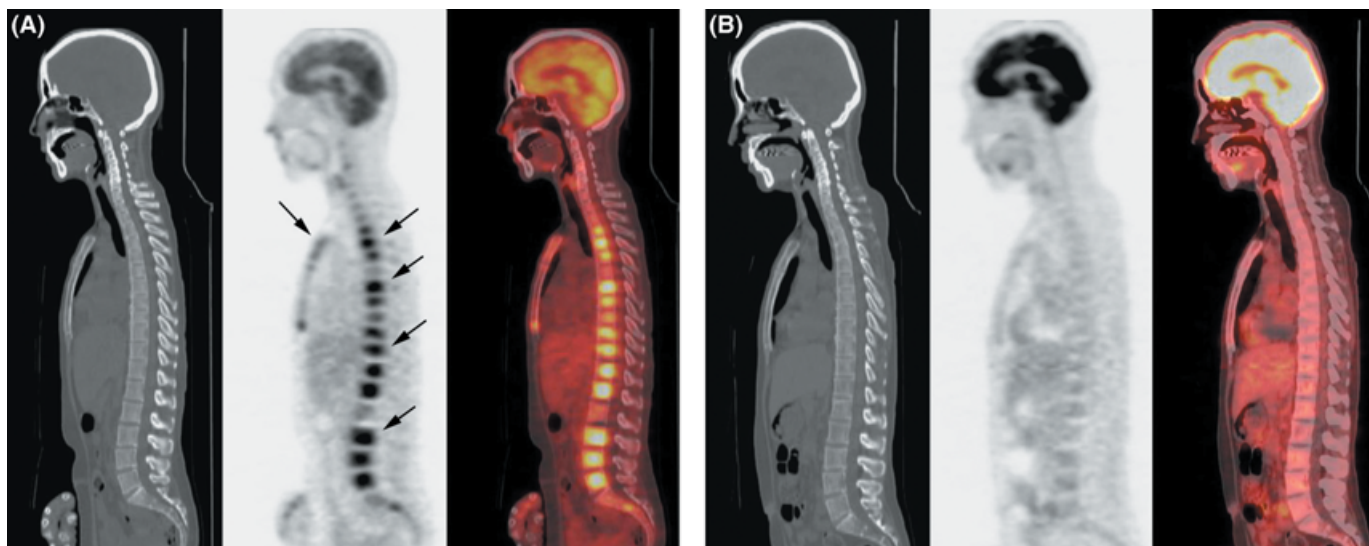
Fig. 4. Positron emission tomography-computed tomography (PET-CT) with ^{18}F-FDG before and after therapy. PET-CT in a 43-year-old woman with intravascular lymphoma. (A) PET-CT before therapy clearly shows increased uptake of ^{18}F-FDG diffusely in the bone marrow (arrows). CT on the left does not show any abnormality. (B) After six cycles of therapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, PET-CT shows no evidence of increased uptake in the bone marrow, indicating that there was no residual lymphoma.
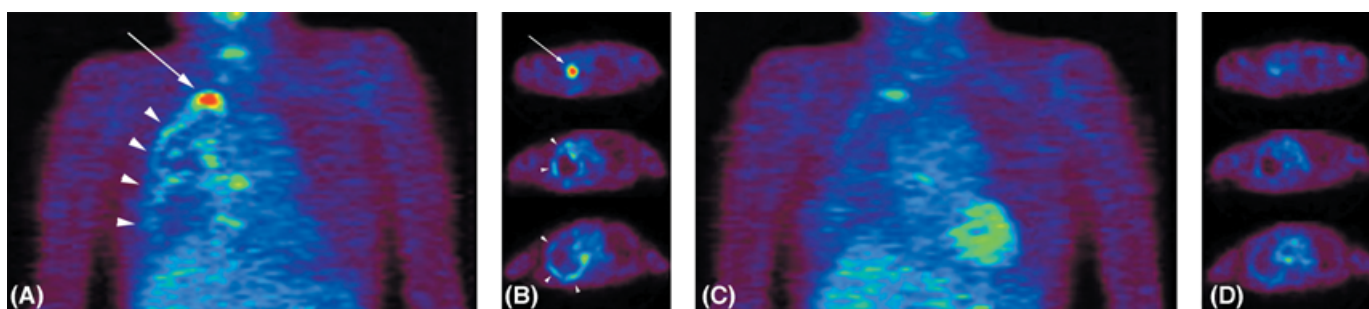

Fig. 5. Positron emission tomography (PET) with ^{18}F-FDG before and after two doses of chemotherapy. A 57-year-old woman with non-small-cell lung cancer developed pleural dissemination of the tumor 9 months after upper and middle lobectomy of the right lung. (A) Coronal view and (B) axial view on PET performed at that time showed a markedly increased uptake of ^{18}F-FDG in the right apical portion (arrow) and also along the pleura (arrowheads). (C) Coronal view and (D) axial view on PET performed after two doses of gefitinib (250 mg/day) clearly shows decreased uptake of ^{18}F-FDG, indicating that the therapy was effective.

if patients without response could be identified early enough to avoid ineffective treatment and to reduce undesirable side-effects and cost, and then to determine the alternative therapy. Patients who demonstrate a response at an early stage can continue treatment, thereby tailoring the therapy for the individual patient.

Previous studies have demonstrated the ability of PET to detect early changes in metabolism shortly after chemotherapy and radiotherapy.[46,47] Evaluation of tumor response to therapy has previously been made according to changes in tumor size measured by CT. A growing body of evidence proves that metabolic change in a tumor is more accurate for the assessment of tumor response. Guidelines for the evaluation of tumor response and response classification criteria may be revised in future to take this into account.

Decreases in cellular glucose transport and glycolysis occur before shrinkage of the tumor mass. Clinical studies clearly demonstrated that PET predicts the pathological response of breast cancer to neoadjuvant chemotherapy.[48,49] In these studies, PET could accurately predict the pathological response after just a single course of chemotherapy. Thus the value of PET in monitoring the response to treatment is clarified in breast cancer. Other neoplasms, such as lymphoma,[50] and non-small-cell lung,[51] head and neck,[52] esophageal,[53] and gastric[54] cancer as well as liver metastasis[55] show decreases in glucose metabolism after early stages of chemotherapy.

Molecular-targeted therapy also decreases ^{18}F-FDG uptake in the early stage. Preliminary observation of gefitinib therapy for patients with epidermal growth factor receptor (EGFR) mutation-positive adenocarcinoma of the lung has demonstrated a rapid and significant decrease in the uptake of ^{18}F-FDG in responding tumors after two doses of gefitinib therapy (Fig. 5).

For patients whose tumors do not show a decrease in the ^{18}F-FDG uptake, the present therapy may be ineffective. The clinical significance of PET has been strengthened by the finding that a decrease in ^{18}F-FDG uptake as early as 1–2 weeks after the first course of therapy may be correlated with the outcome of patients with a variety of neoplasms.[48,49,51,52] Lack of decrease in the uptake implies that the present therapeutic regimen may be ineffective; however, the optimal time course to evaluate the responsiveness has to be determined according to the type of cancer and therapy. Evaluation of the efficacy of the present therapy and determination of the best therapeutic options could be accelerated by use of PET.

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