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Review

Pioneering and Fundamental Achievements on the Development of Positron Emission Tomography (PET) in Oncology

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Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a glucose analog, is widely used throughout the world as an indispensable imaging modality for the management of cancer treatment. This article reviews the pioneering achievements of PET in oncology with a focus on the development of PET that occurred from 1980 through the early-1990s. ^{18}F-FDG was first applied for imaging of animal tumors in 1980 and for brain tumor imaging clinically in 1982. ^{18}F-FDG enabled to visualize liver metastasis as clear positive image that could not be obtained by conventional nuclear imaging. Subsequently, ^{18}F-FDG was used for imaging various cancers, such as lung, pancreas, colorectal and hepatoma. ^{11}C-L-methionine (^{11}C-MET) that reflects amino acid transport of cancers has an advantage that its uptake is lower in the brain and inflammatory tissue compared to ^{18}F-FDG, and was first applied for imaging lung cancer and brain tumor. ^{18}F-FDG and ^{11}C-MET were proved to be sensitive tracers that can be used to objectively evaluate the effectiveness of cancer treatment. The diagnostic accuracy of PET, which is critical in clinical practice, was evaluated for the differential diagnosis of malignant and benign lung nodules using ^{18}F-FDG or ^{11}C-MET. In addition to ^{18}F-FDG and ^{11}C-MET, many radiopharmaceuticals were developed, such as ^{18}F-labled thymidine analogs for evaluating proliferative activity, ^{18}F-fluoromisonidazole for imaging of hypoxia, and ^{18}F-fluorodeoxygalactose for evaluating liver-specific galactose metabolism and for imaging of hepatoma that retains galactose metabolic activity. These early efforts and achievements have greatly contributed to the development and clinical application of ^{18}F-FDG PET in oncology.

Keywords: cancer imaging; cancer management; ^{11}C-methionine; ^{18}F-fluorodeoxyglucose; positron emission tomography
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Introduction

Positron emission tomography (PET) using radiopharmaceuticals labeled with short-lived positron emitter can provide biochemical information of living human though quantitative tomographic images. ^{18}F-fluorodeoxyglucose (^{18}F-FDG), an analog of glucose and 2-deoxyglucose, was first developed by Ido et al. (1978). ^{18}F-FDG is transported into the cells by glucose transporter, where it is phosphorylated to ^{18}F-FDG-6-phophate by hexokinase and then remains trapped. Thus, accumulation of ^{18}F-FDG in the tissue represents glucose consumption, or energy metabolism, in the tissue. ^{18}F-FDG was developed firstly for the visualization and quantification of glucose utilization of the human brain using PET based on a rat model using ^{14}C-2-deoxyglucose (Sokoloff et al. 1977). Later, Phelps et al. (1979) developed and validated a method for the tomographic measurement of glucose utilization in the human brain with ^{18}F-FDG using PET. The method was applied for the evaluation of regional glucose consumption in diseased brain (Benson et al. 1981) and normal brain under stimulated conditions (Phelps et al. 1981). ^{18}F-FDG has been used also for the imaging and evaluation of metabolism in the heart (Phelps et al. 1978).

An increased rate of glycolysis is one of the characteristics of cancer cells (Warburg 1956), and therefore, ^{18}F-FDG accumulates and remains trapped in cancer cells. PET using ^{18}F-FDG enables to visualize and quantify amount of glucose metabolism in cancers, which is closely correlated to viability of the tumors. In addition to glucose metabolism, Itoh et al. (1982) examined oxygen consumption of human brain tumors using $^{15}O_2$ with PET and confirmed that

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brain tumor does not demand much oxygen even in relatively hypoxic condition. This is the first report that elucidated Warburg effect in human cancers. Currently, the most frequent clinical application of ^{18}F-FDG PET is in oncology. In particular, ^{18}F-FDG PET/CT, a PET system combined with X-ray computed tomography, is widely used as an indispensable diagnostic tool for the cancer management in the clinical setting (Gambhir et al. 2002). For example, ^{18}F-FDG PET has been used to assess the staging of lung cancer patients (Fischer et al. 2001; Schrevens et al. 2002). Determining the stage of cancers are essential in not only determining optimal therapeutic strategy, such as surgery, radiotherapy or chemotherapy but also for predicting patient outcome. ^{18}F-FDG PET is also used to monitor various malignancies (Poeppel et al. 2009). The uptake of ^{18}F-FDG in cancer cells is correlated to tumor viability; therefore, ^{18}F-FDG PET is useful to evaluate the effectiveness of therapies and for monitor recurrence of tumors. Recently, ^{18}F-FDG PET was adopted as a method to objectively evaluate the effectiveness of tumor therapies (Wahl et al. 2009).

In addition to glucose metabolism, increased amino acid transport and protein synthesis are also characteristics of cancer cells. ^{11}C-methionine (^{11}C-MET) is currently the most commonly used for PET tumor imaging at present time because of its high tumor uptake and ease of radiosynthesis, although many labeled amino acids were developed.

Using labeled thymidine or -uridine analogs, PET enables to visualize and quantify non-invasively proliferative activity of human tumor, which is important to manage cancer treatment. Although many radiopharmaceuticals have been developed, ^{18}F-fluorothymidine (Shields et al. 1998) is most commonly used.

Cancer cells occasionally express the phenotypes of their original tissues and the level of expression may represent the degree of differentiation. For example, iodine is a source for the synthesis of thyroid hormone, and radioiodine accumulates in well-differentiated thyroid cancers. Thus, in addition to evaluation of growth activity of tumors, another direction of PET tumor imaging is the visualization of distinct cancer cell phenotypes using phenotype specific radiopharmaceuticals. ^{18}F-fluorodeoxygalactose (^{18}F-FDGal) was developed to evaluate liver specific galactose metabolism (Fukuda et al. 1986). Another example is imaging of hypoxic cells in the tumor, which are resistant to radiotherapy or chemotherapy. Imaging of tumor receptor expression using labeled receptor ligands is the typical examples of this concept, however, no paper was published during the selected period in this article (1980-to the early 1990s).

As described above, PET tumor imaging has become an indispensable imaging modality for the evaluation and management of cancer. This article reviews the original and pioneering achievements of PET in oncology with a central focus on the development of PET that occurred from 1980 through early 1990s. Many Japanese research groups, especially from Tohoku University, significantly contributed to the development of PET in oncology. Based on these achievements, Matsuzawa et al. (1985) organized the first international symposium on "Current and Future Aspects of Cancer Diagnosis with Positron Emission Tomography: Biological and Clinical aspects." This symposium was held two years prior to the second international symposium on "Positron Emission Tomography and Magnetic Resonance in Oncology" organized by Strauss et al. The fundamental achievements discussed in this review article are valuable for the further development and innovation of PET in oncology.

Imaging of various cancers with PET using ^{18}F-FDG

Som et al. (1980) was a pioneer in using ^{18}F-FDG in oncological field. She published a paper describing the high and rapid accumulation of ^{18}F-FDG in leukemia cells transplanted into mice, although she did not present any image. ^{18}F-FDG was first utilized clinically for the visualization and evaluation of human brain tumors by Di Chiro et al. (1982). They showed that ^{18}F-FDG uptakes of high-grade gliomas were higher than low-grade gliomas, although high uptake of ^{18}F-FDG in the normal brain is disadvantage for brain tumor imaging. ^{18}F-FDG PET has also been used for the differential diagnosis between recurrence of brain tumor and necrosis of the normal brain after treatment (Patronas et al. 1982). Subsequently, ^{18}F-FDG has been used for imaging of various types of tumors.

Intrahepatic tumors (liver metastasis)

Fukuda et al. (1982a, b) showed an increased uptake of ^{18}F-FDG in a rat tumor model and visualized intrahepatic tumor clearly (Fig. 1). Yonekura et al. (1983) and Fukuda et al. (1983a, b, 1984) were the first to image clinically liver metastases from colon cancer using ^{18}F-FDG-PET. Immediately after ^{18}F-FDG injection, a dynamic scan was performed every 5 min for a total of 50 min. They observed that tumor radioactivity increased with time, whereas liver radioactivity decreased with time, which resulted in the clear visualization of the intrahepatic tumor (Fig. 2). This

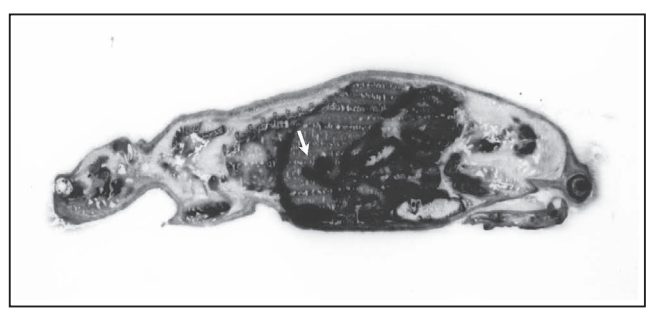

Fig. 1. An autoradiogram of a AH109A tumor-bearing rat one hour after injection of ^{18}F-FDG.
The intrahepatic tumor, which was directly inoculated into the liver, was clearly visualized as a highly radioactive area (arrow). Fukuda, H., et al. (1982) *Eur. J. Nucl. Med.*, **7**, 294-297 (reproduced with permission of Springer-Verlag GmbH).

Table 1. Chronological table for the development of PET in oncology.

Year	Author / Institution, Nation	Achievements (animal/human)
1978	Ido T et al. / BNL, USA	^{18}F-FDG radio-synthesis
1980	Som P et al. / BNL, USA	Rapid accumulation of ^{18}F-FDG in transplanted mouse leukemia cells (mouse)
1982	Fukuda H et al. / TU, Japan	^{18}F-FDG, visualization of intrahepatic rat tumor with ^{18}F-autoradiography, ^{18}F-Fluorodeoxymannose (^{18}F-FDM) for cancer imaging agent (rat)
1982	Di Chiro G et al. / NIH, USA	^{18}F-FDG, imaging and grading of glioma (human)
1982	Itoh M / Hammersmith Hosp., UK (Tohoku Univ., Japan)	^{15}O gas, oxygen extraction ratio (OER) in ischemic tumor did not increase (human)
1983	Yonekura Y et al. / BNL, USA (Kyoto Univ., Japan)	^{18}F-FDG, PET imaging of liver metastasis (human)
1983	Fukuda H et al. / TU, Japan	^{18}F-FDG, PET imaging of liver metastasis, pancreatic cancer, and hepatocellular carcinoma (human). Proposal of DAR (= SUV)
1983	Kubota K et al. / TU, Japan	^{11}C-MET, lung cancer imaging (human)
1983	Abe Y et al. / TU, Japan	^{18}F-FDG, radio-therapeutic response (mice and rats), (human)
1983	Abe Y et al. / TU, Japan	^{18}F labeled pyrimidine analogs (^{18}F-FdUrd) (rat, human)
1983	Kiyosawa M et al. / TU, Japan	^{18}F-FDG, imaging of orbital tumor (rabbit)
1984	Fujiwara T et al. / TU, Japan	^{18}F-FDG, imaging of lung cancer (human)
1985	Yamada K et al. / TU, Japan	^{18}F-FDG uptake pattern in the brain, myocardium and tumor (rat)
1985	Matsuzawa T et al. / TU, Japan	First International symposium on PET in oncology, Sendai, Japan
1985	Paul R et al. / Turk Univ., Finland	^{18}F-FDG, imaging of hepatocellular carcinoma (human)
1985	Ericson K et al. / Karolinska Hosp., Sweden	^{11}C-MET, imaging of brain tumors (human)
1986	Fukuda H et al. / TU, Japan	^{18}F-fluorodeoxygalactose (^{18}F-FDGal) for liver function imaging (rat)
1987	Strauss G et al. / Heidelberg, FRG	Second International symposium on PET in oncology, Heidelberg, Germany
1987	Paul R et al. / Turk Univ., Finland	^{18}F-FDG, imaging of malignant lymphoma (human)
1987	Fukuda H et al. / TU, Japan	^{18}F-FDGal, imaging of hepatocellular carcinoma (human, rat)
1988	Abe Y et al. / TU, Japan	^{11}C-MET, regional coupling of ^{11}C-Met uptake and blood flow intra-tumoral tissue (mouse)
1989	Strauss G et al./ Heidelberg, FRG	^{18}F-FDG, PET evaluation of recurrent colorectal cancer (human)
1989	Kubota K et al. / TU, Japan	^{11}C-Met, radio-therapeutic response (mouse)
1989	Kubota K et al. / TU, Japan	^{18}F-FDG, ^{18}F-FDG, imaging of a breast cancer (human)
1990	Kubota K et al. / TU, Japan	^{18}F-FDG, ^{11}C-Met, diagnostic accuracy of PET for differential diagnosis of lung nodules (human)
1991	Okada J et al. / Chiba Univ., Japan	^{18}F-FDG, imaging of malignant lymphoma, correlation between uptakes and outcome (human)
1991	Wahl R et al. / Mishigan U, USA	^{18}F-FDG, ^{18}F-FDG, imaging of breast cancers (human)
1991	Kubota K et al. / TU, Japan	Five tracer (^{18}F-FDG, ^{11}C-MET, ^{3}H-thymidine, ^{18}F-FdUrd, ^{67}Ga) feasibility study for monitoring tumor radiotherapy (rat).
1991	Ishiwata K / TU, Japan	Synthesis of ^{18}F-fluoroparaboronophenylalanine, PET imaging for boron neutron capture therapy (BNCT) for cancer
1992	Okada J et al. / Chiba Univ., Japan	Correlation between ^{18}F-FDG uptakes and Ki-67 index (human).
1992	Kubota R et al. / TU, Japan	^{18}F-FDG, high uptake of ^{18}F-FDG in macrophages and granulation tissues (mouse) ^{11}C-MET uptake by tumor tissue comparison with ^{18}F-FDG (mouse)
1992	Klever P et al. / TUA, Germany	^{18}F-FDG, PET imaging of pancreatic cancer (human)
1992	Koh WJ et al. / Univ. Washington, USA	^{18}F-fluoromisonidazole, imaging of hypoxic cells in tumors (human)
1992	Ito K et al. / Nagoya Univ., Japan	^{18}F-FDG, differentiation between recurrent rectal cancers and scar, comparison with MRI (human)
1992	Okazumi S et al. / Chiba Univ., Japan	^{18}F-FDG, hepatocellular carcinoma, correlation between ^{18}F-FDG uptake and grade of differentiation, 2-compartment analysis (human)

BNL, Brookhaven National Laboratory; TU, Tohoku University; Heidelberg, Heidelberg Cancer Center; TUA, Technical University of Aachen.

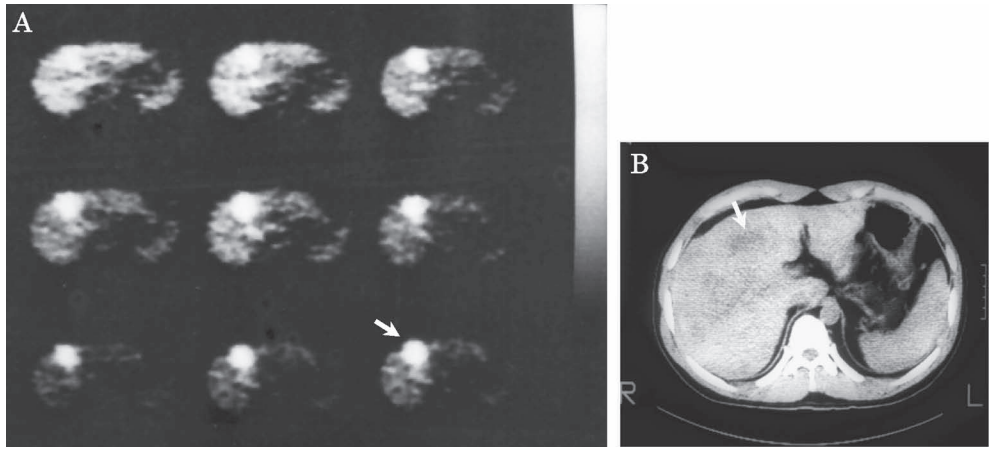

Fig. 2. PET imaging of liver metastases with ^{18}F-FDG.
A dynamic scan every 5 min after injection of ^{18}F-FDG (from top left to bottom right). Increased uptake of ^{18}F-FDG with time (A: arrow) was observed in liver metastases from colon cancer on CT (B: arrow), while the uptake in the normal liver and spleen decreased with time. The PET image was obtained by ECAT-II (EG & G ORTEC), a single-slice PET with spatial resolution of 15 mm.

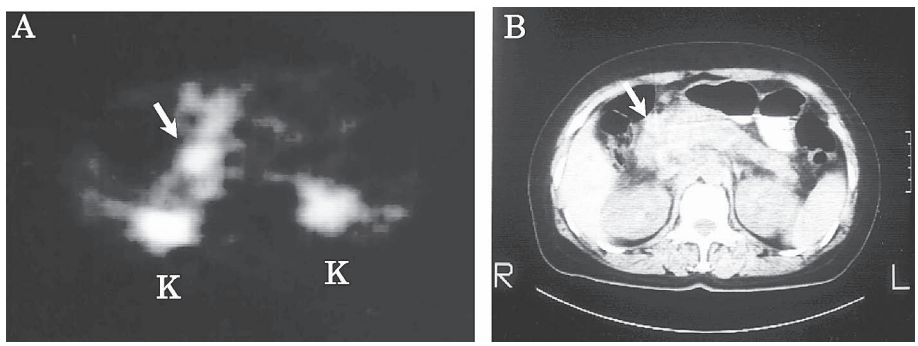

Fig. 3. PET imaging of pancreatic cancer with ^{18}F-FDG.
A: A PET image with ^{18}F-FDG in a pancreatic cancer patient. The accumulation of ^{18}F-FDG was observed in the pancreas head tumor (arrow), which was shown on the CT image (B). K: kidney
B: CT image. Pancreas head tumor (arrow).
Fukuda, H. et al. (1984) CYRIC Annual Report 1983, 244-249.

was difficult to achieve using gallium-67, which is mainly used in nuclear oncology performed in hospitals where PET is not available. The ability to obtain positive and clear images of intrahepatic tumor is attributed to the relatively low uptake of ^{18}F-FDG in the normal liver. This is because the liver has a high activity of glucose-6-phosphatase, which de-phosphorylates ^{18}F-FDG-6-phosphate to ^{18}F-FDG so that it can easily re-enter into the blood stream.

Hepatocellular carcinoma

Fukuda et al. (1983a) were the first to report successful imaging of hepatocellular carcinomas (HCC) with ^{18}F-FDG. The uptakes of ^{18}F-FDG in 3 tumors was semi-quantified by differential absorption ratio (DAR), which normalizes tissue tracer uptake to subject body weight and amount of injected radioactivity and were determined to 2.10, 3.87 and 4.10 at 50 min after the injection of ^{18}F-FDG were. Later, Paul et al. (1985) reported ^{18}F-FDG imaging of a HCC using a gamma camera and not PET. Relatively low uptake of ^{18}F-FDG in HCC might be attributed to high glucose-6-phosphatase activity in well-differentiated HCCs. Okazumi et al. (1992) confirmed this hypothesis by comparing the uptake of ^{18}F-FDG and HCC of various grade. A 2-compartment, 4-parameter (k1-k4) analysis of ^{18}F-FDG uptake in HCC revealed that a higher grade of HCC had larger k4 values, which is a back flow constant from the second to first compartment and may correspond to glucose-6- phosphatase activity.

Pancreatic cancer

Increased ^{18}F-FDG uptake in pancreatic cancers was first reported by Fukuda et al. (1983a, 1984, 1987a). Fig. 3 shows the increased uptake of ^{18}F-FDG that was observed in a pancreatic head tumor by X-CT. ^{18}F-FDG was injected in 3 separate cases of pancreatic cancer, including one with liver metastasis. After 50 min, DAR values were determined to be. 2.83, 1.94 and 3.55. Later, Klever et al. (1992) and Bares et al. (1993) reported on several cases of pancre-

atic cancer.

Lung cancer

Fujiwara et al. (1984) were the first to report increased ^{18}F-FDG uptakes in the malignant lung tumors of 9 patients. They performed a dynamic scan every 5 min and showed that ^{18}F-FDG uptake in the lung tumor increased with time in all cases. The results were confirmed by DAR values that increased from initial value of 3.0 to 9.4 after 50 min. By fitting an ^{18}F-FDG-accumulation curve, they calculated the increase rate of DAR (γDAR) and showed that squamous cell carcinomas had larger γ DAR than adenocarcinomas. Later, Nolop et al. (1987) expanded the initial experience of them (Fujiwara et al. 1984).

Orbital tumor

Kiyosawa et al. (1983) examined ^{18}F-FDG uptakes in a VX2 tumor transplanted into the orbit of rabbits. ^{18}F-FDG uptake in the VX2 tumor was high, whereas uptake in chemically induced inflammation was relatively low. Kiyosawa et al. (1985) extended this study to clinical trials and performed ^{18}F-FDG PET imaging of orbital tumors. They observed high uptake of ^{18}F-FDG uptake in malignant lymphomas were high; however, they observed high uptake in inflammatory lymphoid tumors. These were the initial applications of FDG PET in ophthalmology.

Breast cancer

Kubota et al. (1989a) reported a focally increased uptake of ^{18}F-FDG in a breast cancer patient. Subsequently, Wahl et al. (1991) showed that 12 breast cancer patients with primary tumors larger than 3 cm had increased glucose metabolism. Several authors have confirmed these findings in small study groups and Adler et al. (1993) evaluated the diagnostic accuracy of FDG-PET in 28 patients.

Malignant lymphomas and the correlation with patient outcome

Paul (1987) the first to image lymphoma with ^{18}F-FDG, but Okada et al. (1991) evaluated the correlation between the ^{18}F-FDG uptake of 21 patients with malignant lymphoma and the initial outcome. ^{18}F-FDG uptake was evaluated by the tumor-to-normal soft tissue contrast ratio (TCR) and the glucose utilization rate (GUR), which was calculated by a graphical plot method by Patlak and Blasberg (1985). Higher TCRs and GURs were observed in patients with poor prognoses. Okada et al. (1992) compared the uptake of ^{18}F-FDG in malignant lymphomas to the tumor proliferative activity of the tumor using Ki-67 labeling index. The ^{18}F-FDG uptake as quantified by TCR or DAR correlated well with Ki-67 labeling index.

Colorectal cancer recurrence

Strauss et al. (1989) first reported the significance of PET imaging in 29 patients with recurrent colorectal cancers. Ito et al. (1992) further investigated the value of ^{18}F-FDG PET and MR imaging in differentiating recurrent rectal cancer from scar tissue in 15 patients with suspected recurrence. All 11 masses with confirmed cancer recurrence showed significantly higher uptakes as expressed by DAR with values of 4.73 ± 2.28, whereas 4 scar tissues that were confirmed by biopsy had decreased ^{18}F-FDG with low DAR values of 0.97 ± 0.15. Combined with MR imaging, most recurrent tumors could be differentiated from scar tissues except one case. They concluded that PET and MR were complementary modalities for the differential diagnosis of tumor recurrence and scar tissue. Ito et al. (1996) also examined the correlation between the ^{18}F-FDG uptakes in rectal cancer and the tumor histology and observed that the amount of ^{18}F-FDG uptake correlated with the cellularity of the tumor tissue in histology.

^{18}F-Fluorodeoxymannose (^{18}F-FDM): a glucose analog and potential of substitute for ^{18}F-FDG

^{18}F-FDM is an isomer of ^{18}F-FDG and was obtained as a byproduct of an electrophilic substitution reaction of ^{18}F-FDG synthesis. Fukuda et al. (1982b) showed that the uptake of ^{18}F-FDM and ^{18}F-FDG in a poorly differentiated rat hepatoma was almost identical. In addition, ^{18}F-FDM uptake was found to be 30% less than ^{18}F-FDG uptake in the brain and ^{18}F-FDM was cleared more rapidly from the blood. PET with ^{18}F-FDM successfully visualized a VX2 tumor that was transplanted into a rabbit. These results suggested that ^{18}F-FDM could be a more suitable radiopharmaceutical for PET cancer imaging than ^{18}F-FDG. However, a clinical PET study was not performed at the time because of difficulty in synthesizing ^{18}F-FDM with a high yield and purity. Since then, substantial improvements and developments in radio-synthesis have been achieved in recent years. Recently, Furumoto et al. (2009) developed a new method of ^{18}F-FDM synthesis using a nucleophilic substitution reaction to with a high yield and purity, and bio-distribution and PET imaging studies of tumor bearing rats confirmed the potential of this tracer in clinical application (Furumoto et al. 2013, in press).

Cancer imaging using labeled amino acids

^{11}C-methinine (^{11}C-MET)

In addition to increased glucose metabolism, increased amino acid transport and metabolism is also characteristics of cancer cells. Methionine is a physiological amino acid that is transported into cells by neutral amino acid transporter and metabolized. ^{11}C-MET was developed by Comar et al. (1976) and the first clinical application of ^{11}C-MET PET for pancreatic cancer imaging was reported by Syrota et al. (1982). However, pancreatic cancer could not be distinguished from chronic pancreatitis because both lesions were visualized as a decreased uptake of ^{11}C-MET MET. However, Kubota et al. (1983) successfully imaged a lung cancer using PET with ^{11}C-MET (Fig. 4). Later, Kubota et al. (1985) analyzed 10 cases of lung tumors and reported that 8 lung cancers showed higher uptake than 2 benign

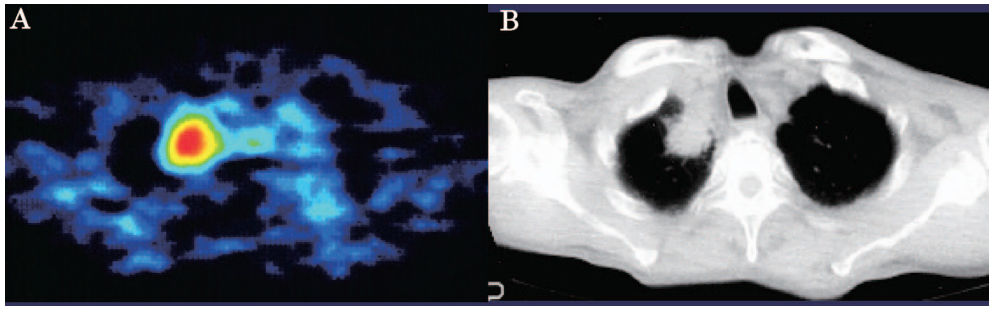

Fig. 4. Imaging of lung cancer with ^{11}C-MET
Twenty minutes after injection of ^{11}C-MET, the tumor in right upper lobe was clearly visualized. Kubota, K., et al. (1983) *The Lancet*, **2**, 1192-1193 (reproduced with permission of Elsevier Limited).

lung tumors. Fujiwara et al. (1989) evaluated the correlation between the histological type of 16 lung cancers and ^{11}C-MET uptake and reported that large cell carcinomas had higher ^{11}C-MET uptake compared to squamous cell carcinomas.

Although many labeled amino acids have been developed, such as ^{11}C-luecin (Barrio et al. 1983), ^{11}C-tyrosine (Bolster et al. 1986) and the non-natural amino acid-^{11}C-aminocyclo-pentanecarboxylic acid (ACPC) (Conti et al. 1986), ^{11}C-MET is commonly used at present time because of its higher tumor uptake and ease of radio-synthesis. Kubota et al. (1984) compared the uptakes of 10 different ^{11}C-labeled amino acids in rat tumors and found that ^{11}C-MET demonstrated the highest tumor uptake followed by ^{11}C-ACPC.

Because of their low uptake in the normal brain tissue, ^{11}C-MET and other amino acids are superior to ^{18}F-FDG in brain tumor imaging. Lilja et al. (1985) and Ericson et al. (1985) were the first to report successful brain tumor imaging with PET using ^{11}C-MET. Another advantage of ^{11}C-MET compared to^{18}F-FDG is relatively low uptake in the inflammatory tissues (Kubota et al. 1995).

^{18}F-^{10}B-paraboronophenylalanine (^{18}F-FBPA) PET in boron neutron capture therapy (BNCT) for cancer

Boron neutron capture therapy (BNCT) is a radiotherapy for cancer utilizing boron-10 (^{10}B), which efficiently absorbs thermal neutrons and releases high LET α-particles (230 keV/μm) via a ^{10}B(n, α)^{7}Li reaction. The range of high LET α particle is only approximately 10 μm, which is comparable to the diameter of a cell, therefore, thermal neutron irradiation causes substantial damage limited to cells that take up the tumor-seeking ^{10}B-compound. Mishima and Fukuda et al. initiated a clinical trial of BNCT for malignant melanoma with successful results (Mishima et al. 1989a, b; Fukuda et al. 1989, 1994, 1999, 2003). However, ^{10}B-concentrations in both the tumor and normal tissues could not be directly measured during neutron irradiation, which cause an inaccurate estimation of radiation dose. Therefore, use of PET preferred to visualize and quantify ^{10}B-content in the tumor by the fluorine-18 fluorination of BPA. Ishiwata et al. (1991) developed the ^{18}F-fluorination of ^{10}B-BPA and Imahori et al. (1996, 1998a, b) performed clinical trials and proposed the ^{18}F-FBPA PET system for BNCT. Currently, ^{18}F-FBPA PET is an indispensable method for BNCT for determining indication of BNCT, predicting absorbed dose by BNCT and evaluating effectiveness of treatment after BNCT. A tumor-to-normal tissue uptake ratio of 2.5 or more with ^{18}F-FBPA is considered to be indicative of BNCT (Fig. 5), and the ratio is subsequently used for the estimation of radiation dose to be delivered to the tumors and normal tissues by BNCT.

The evaluation of proliferative activity using labeled nucleic acids analogs

Proliferative activity can be evaluated using labeled thymidine analogs such as ^{14}C or ^{3}H-labeled thymidine and ^{125}I-lableled iodo-deoxyuridine in animals or in vitro models. Fluorinated pyrimidine analogs such as 5-furuorouracil (5-FU), 5-fluoro-uridine (5-FUR) and 5-fluorodeoxyuridine (5-FdUR) have been used as antitumor agents, and their effects have been well acknowledged. Accordingly, ^{18}F labeling of these compounds enables visualization of tumor proliferative activity with PET. Abe et al. (1983a) and Ishiwata et al. (1984) compared the uptakes of ^{18}F-fluorinated pyrimidines, ^{18}F-5-FU, ^{18}F-5-FUR, and ^{18}F-5-FdUR in an animal tumor model. They performed bio-distribution studies in tumor-bearing rats and obtained PET image of rabbit tumors before concluding that ^{18}F-5-FdUR was superior in terms of tumor uptake and tumor-to-normal tissue ratio. A preliminary PET study with ^{18}F-5-FdUR in lung cancer patients revealed a clear visualization of the tumors (Abe et al. 1985). Kiyosawa et al. (1986) performed PET imaging of rabbit orbital tumors with ^{18}F-5-FdUR and clearly visualized the tumor with a high tumor-to-normal orbit ratio. Tsurumi et al. (1990) tested the feasibility of ^{18}F-5-FdUR for PET imaging of nucleic metabolism using a rat brain tumor model. A double tracer autoradiogram with ^{18}F-5-FdUR and ^{14}C-thymidine revealed similar brain-tumor images. Furthermore, a metabolite study revealed that the radioactivity of the nucleotide and acid-insoluble fractions increased with time, whereas the radioactivity of entire tumor remained unchanged. These results indicated that ^{18}F-5-FdUR uptake in brain tumors correlates with nucleic

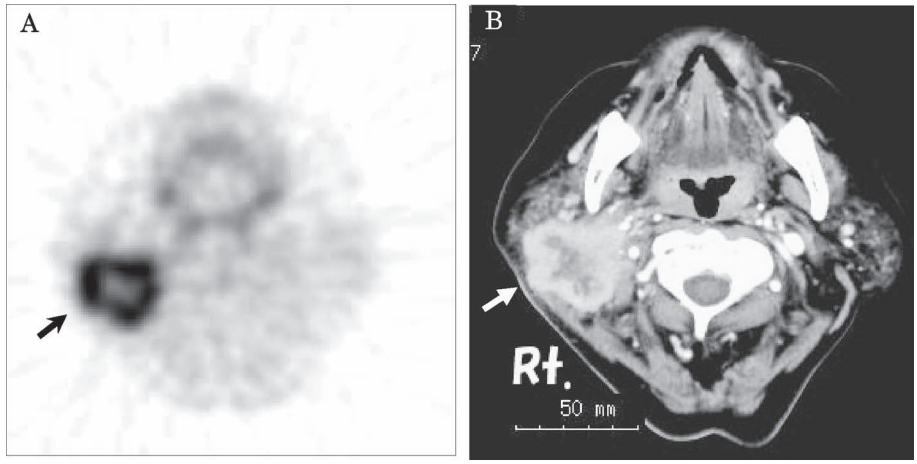

Fig. 5. PET image using ^{18}F-^{10}B-parabononophenylalanine (BPA) in a patient with a right parotid cancer. ^{18}F-^{10}B-BPA PET clearly visualized the submandibular tumor (arrow) with a tumor-to-contralateral normal tissue ratio of 5.0. A: PET image, B: contrast-enhanced CT (Courtesy of Prof. Jun-ichi Hiratsuka).

acid metabolism and that ^{18}F-5-FdUR might be a useful tracer for PET tumor imaging.

However, ^{18}F-5-FdUR had not been used in further studies, because of its low tumor-to-background ratio. ^{11}C-thymidine was developed by Sundro-Wu et al. (1984), however, the tracer yielded many labeled metabolites in the blood, which made it difficult to evaluate rate of proliferative activity. Shields et al. (1998) developed ^{18}F-fluoromethyl-thymidine, which is an effective substrate for thymidine kinase, found to be trapped in proliferating cells, and it has been now commonly used.

Imaging of specific cancer phenotypes using PET

^{18}F-fluorodeoxygalactose (^{18}F-FDGal)-imaging liver specific galactose metabolism in tumors

The ability to eliminate galactose is an important function of the liver and was used as liver function test. Tada et al. (1984, 1987) developed ^{18}F-FDGal to image galactose metabolism in the liver using PET. Fukuda et al. (1986) demonstrated high ^{18}F-FDGal uptake in the normal rat liver (4.47% injected dose/g of tissue), however, uptake decreased by 13% (3.89% ID/g) in livers damaged by CCl_4 treatment. Ishiwata et al. (1988) confirmed that ^{18}F-FDGal is phosphorylated by galactokinase in the liver and remains trapped after the second metabolic step of the galactose pathway. Ishiwata et al. (1989) confirmed that this two-step metabolic trap also occurs in hepatomas. Because pronounced activity of these enzymes is found specifically in the liver, ^{18}F-FDGal can be used to evaluate cirrhotic liver function and to image hepatocellular carcinoma. After confirming the acute toxicity of the compound and determining the radiation dose (Fukuda et al. 1987c), Fukuda et al. (1987d) initiated a clinical PET study. They observed a high accumulation in the liver, relatively high in the kidney and small intestine, and low uptake in other tissues. In a preliminary PET study, Fukuda et al. (1987b, 1988) found that ^{18}F-FDGal accumulates in hepatocellular carcinomas (HCCs) that originate from hepatocytes, but not in metastatic liver tumors of other origins. To investigate the mechanisms underlying the high uptake in HCCs, Fukuda et al. (1993) examined ^{18}F-FDGal uptake in the following animal tumor model: well-differentiated spontaneous hepatoma (Spt HCC) in C3H mice, well-differentiated Morris hepatoma (5123D) in Buffalo rats and poorly differentiated hepatoma (AH109A) in Donryu rats. The uptake of ^{18}F-FDGal by well-differentiated spHCC and 5123D tumors was 92% and 33% of the normal liver uptake, respectively. However, the uptake by the poorly differentiated AH109A tumors was only 16% of the normal liver uptake (Fig. 6). Later, Fukuda et al. (1994) reported visualization of bone metastases from HCC with very low background levels using ^{18}F-FDGal PET. Fig. 7 demonstrates an orbital metastasis from HCC. Currently, a whole body PET scan with ^{18}F-FDGal would be useful for a systemic survey of HCC metastases.

N-[^{18}F]fluoroacetyl-D-glucosamine — a potential agent for the imaging of cell surface glycoprotein metabolism in cancers

Glucosamine and its derivatives are essential structural components of many important biological macromolecules, including membrane glycoproteins and mucopolysaccharides. Hyaluronic acid is the most abundant mucopolysaccharide present in the cell membrane. It was reported that an invasive VX2 carcinoma grown in rabbit contained a greater quantity of hyaluronic acid than the same tumor grown in nude mice, where it was less aggressive. The evaluation of hyaluronic acid synthesis in vivo may be useful for the evaluation of the invasiveness of cancer cells. Therefore, Tada et al. (1989) synthesized a structural analog of N-acetyl-glucosamine, N-[^{18}F]fluoroacetly-D-glucosamine (^{18}F-FAG). Fujiwara et al. (1990) demonstrated that the uptake of ^{18}F-FAG in well-differentiated, spontaneous hepatoma of C3H mice (Spt HCC) was substantially high,

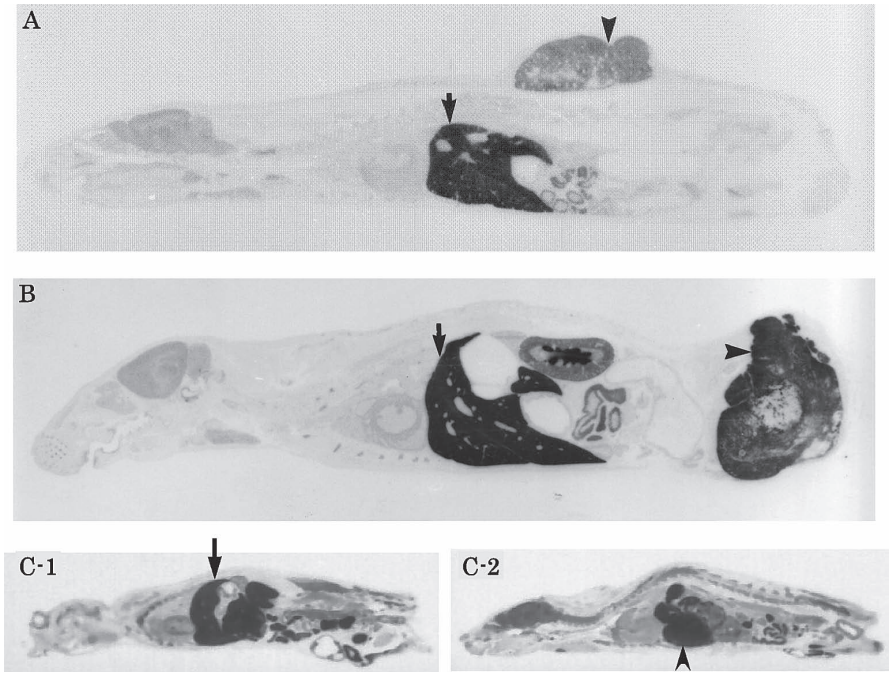

Fig. 6. Autoradiograms of tumor-bearing rats and mice with ^{18}F-FDGal.
A: A Donryu rat bearing a poorly differentiated hepatoma, AH109A.
B: A Buffalo rat bearing a well-differentiated Morris hepatoma, 5123D.
C: A highly differentiated spontaneous hepatoma of a C3H mouse. Arrow heads and arrows indicate tumor and normal liver, respectively. Fukuda, H. et al. (1993) *J. Nucl. Med.*, **34**,780-786 (reproduced with permission of Society of Nuclear Medicine).

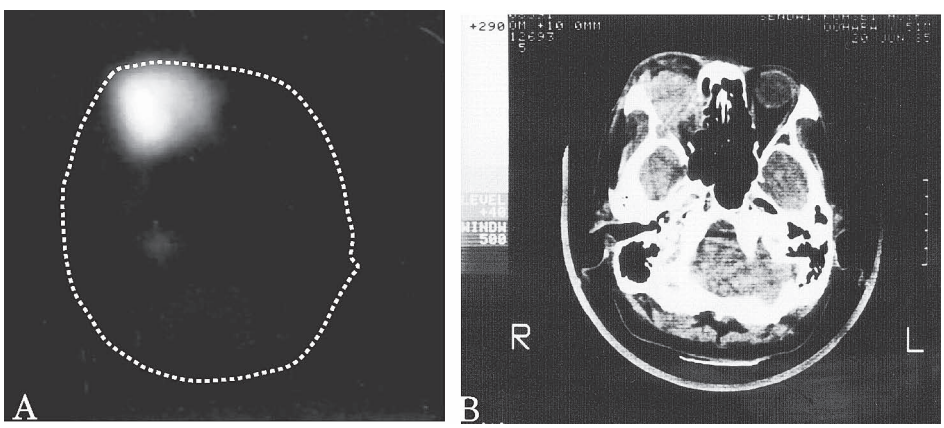

Fig. 7. PET images of an orbital metastasis from hepatocellular carcinoma with ^{18}F-FDGal and ^{18}F-FDG.
The mass in the right orbit on CT (B) was confirmed by a biopsy to be a metastasis from hepato-cellular carcinoma. The ^{18}F-FDGal uptake by the tumor was high with a low background activity (A). Dashed line; contour of the head.

suggesting that ^{18}F-FAG might be a potential tumor-imaging agent.

^{18}F-fluoromisonidazole: imaging of hypoxic cells in the tumor

Misonidazole and its derivatives are metabolically trapped in hypoxic cells, which are resistant to radiotherapy and chemotherapy. Therefore, visualization and quantification of hypoxic fraction within a tumor are useful tools in determining effective treatment strategy. ^{18}F-fluoromisonidazole (^{18}F-FMISO) was developed by Jerabeck et al. (1986) and Koh et al. (1992) reported initial success with PET imaging of 8 human malignant tumor. Currently, ^{18}F-FMISO is used to determine treatment methods and predict patient's outcome after radiotherapy, which based on the kinetic behavior of FMISO in tumor tissue (Eschmann et al. 2005).

The evaluation of response of cancers treatment with ^{18}F-FDG or ^{11}C-MET

Radiotherapy

Abe et al. (1983b, 1986) first assessed the effect of radiotherapy on experimental mouse and rat tumor models

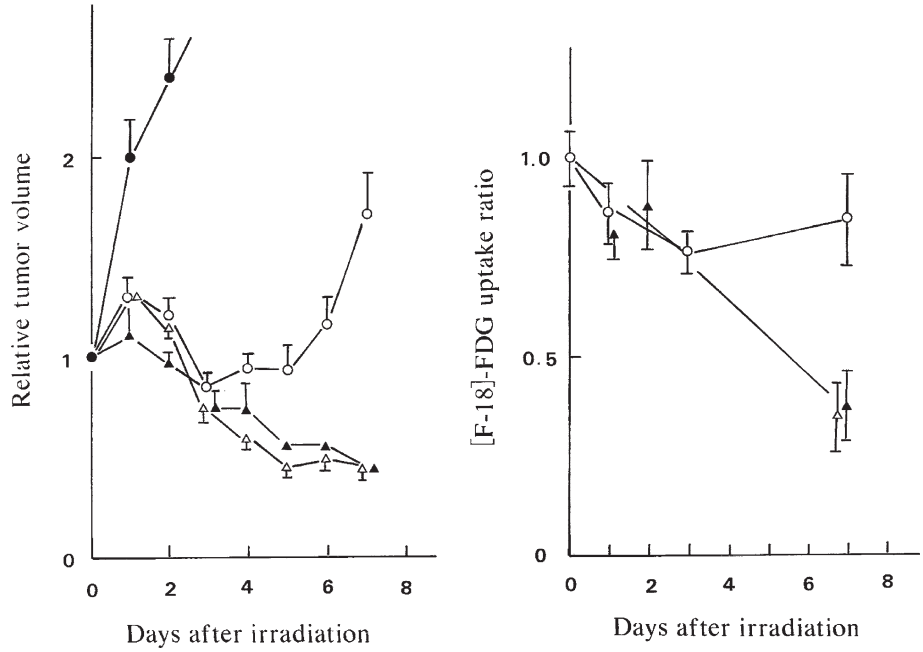

Fig. 8. ^{18}F-FDG uptakes of rat tumor after different radiation doses.
^{18}F-FDG uptake continuously decreased after irradiation except for the 10-Gy-irradiation group, where uptake again increased at 7 days. The secondary increase in uptake corresponded with tumor re-growth after 4 days (left panel). Left: tumor volume, Right: ^{18}F-FDG uptakes. Control (●), 10 Gy (○), 20 Gy (▲), 40 Gy (△). Abe, Y., et al. (1986) *Eur J Nucl Med*., **12**, 325-328 (reproduced with permission of Springer-Verlag GmbH).

using ^{18}F-FDG. They used two types of mouse mammary carcinomas models, FM3A and MM48 that were radiosensitive and radio-resistant, respectively. The tumor volume of the radiosensitive FM3A began to decrease two days after 20-Gy irradiation and the uptake of ^{18}F-FDG rapidly decreased 1 day after irradiation. However, the tumor volume of the radio-resistant MM48 tumor continued to increase even after irradiation, with no decrease in ^{18}F-FDG uptakes. Using the rat hepatoma line AH109A, they evaluated the radiation dose-response of tumor growth and the ^{18}F-FDG uptake kinetics (Fig. 8). After 10-Gy irradiation, the tumor volume decreased one day after irradiation and increased again at 6 days. The decrease and increase of tumor ^{18}F-FDG uptake after irradiation well correlated with tumor volume changes. Abe et al. (1990) first evaluated the ^{18}F-FDG uptake of the human lung cancer before and after irradiation and showed that ^{18}F-FDG can be used for the assessment of radio-therapeutic effectiveness in the clinical setting.

Kubota et al. (1989b) examined the effects of radiation on ^{11}C-MET uptake by tumors. The ^{11}C-MET uptake by tumors decreased 50% 12 hours after 20-Gy irradiation. However, the tumor volume continued to increase until one day after irradiation, and then decreased. He measured the necrotic fraction within the tumor after irradiation and found that the decreased rate of ^{11}C-MET was larger than the decreased viable fraction of the tumor as measured by histological section. He concluded that ^{11}C-MET could be a more sensitive marker for the radiation response of the tumor than ^{18}F-FDG. Next, Kubota et al. (1991) compared the different uptake patterns after irradiation of 5 tracers (^{18}F-FDG, ^{18}F-Flurodeoxyuridine, ^{11}C-MET, ^{3}H-Tdr and ^{67}Ga citrate) and showed that ^{11}C-MET and ^{3}H-Tdr were the most rapid and sensitive tracers for monitoring the effects of radiotherapy. This paper was also the first to demonstrate that the decrease in ^{18}F-FDG uptake by tumors after irradiation was almost parallel to the decrease in the viable cell fraction in the tumor. Later, Higashi et al. (1993) demonstrated that the ^{18}F-FDG uptakes by tumors correspond to the fraction of viable tumor cells but not to proliferating cells. Kubota et al. (1992a) showed that after 10 Gy irradiation, the ^{11}C-MET uptake decreased earlier than the tumor volume reduction and later, it significantly increased earlier than the recurrent tumor growth and that ^{11}C-MET is a sensitive indicator for monitoring radiotherapeutic effect and recurrence.

Kubota et al. (1993) extended the ^{11}C-MET study to the clinical setting and examined ^{11}C-MET uptake in 21 patients with lung cancer before and during the two weeks after radiotherapy. The group with local control (no recurrence) showed a larger decrease in ^{11}C-MET uptake. The early-recurrence group showed the smallest decrease in ^{11}C-MET uptake. The late-recurrence group (after 11 months or more) showed a similar decrease to the no-recurrence group in the amount of ^{11}C-MET uptake. However, no recurrence- and late-recurrence groups could be distinguished by the amount of tumor volume decrease observed by CT. The late-recurrence group showed a smaller volume decrease. This report was the first to use ^{11}C-MET for the evaluation of the radio-therapeutic effect on cancers in the clinical set-

ting except for a case report by Kubota et al. (1992b), in which they demonstrated that ^{11}C-MET could detect lung cancer recurrence, while the residual mass volume remained almost constant during the follow-up period after radiotherapy.

Chemotherapy

The evaluation of the effectiveness of anti-cancer chemotherapy is commonly performed based on changes in tumor size. As described above, ^{18}F-FDG and ^{11}C-MET are more sensitive markers for the evaluation of radio-therapeutic effects on cancers than tumor size change. Takahashi et al. (1985) examined the ^{18}F-FDG uptake changes of rat AH272 tumors after chemotherapy with mitomycin C (MMC) or Adriamycin (ADR). The former is an effective chemotherapy agent against AH272 tumors, and the latter is not. A substantial decrease (−63%) of ^{18}F-FDG uptake was observed after the administration of 1.25 mg/kg of MMC with a 29% decrease in tumor volume. In contrast, the administration of 4.0 mg/kg of ADR yielded no tumor volume reduction and only a small reduction (−8%) in ^{18}F-FDG uptake. Takahashi et al. (1986) examined the changes in ^{18}F-FDG uptake of the tumor before and after chemotherapy in 4 advanced-cancer patients. The response estimated by the DAR ratio (DAR_{before} / DAR_{after}) of ^{18}F-FDG correlated well with conventional response criteria. He concluded that ^{18}F-FDG appeared to be promising for the evaluation of the efficacy of cancer chemotherapy.

The diagnostic accuracy for the differential diagnosis of lung nodules using ^{18}F-FDG or ^{11}C-MET

Kubota et al. (1990) first reported the diagnostic accuracy of ^{18}F-FDG PET with a prospective study for the differential diagnosis of 22 lung nodules. The sensitivity, specificity and accuracy for the differential diagnosis of benign and malignant lung nodules were 83%, 90% and 86%, respectively. These values were confirmed in many later papers (Gambhir et al. 2002; Schrevens et al. 2002). This may be a key paper that promoted and realized clinical PET using ^{18}F-FDG in oncology because high diagnostic accuracy is very important in clinical setting. In this paper, he also first reported the diagnostic accuracy of ^{11}C-MET PET for the differential diagnosis of 24 lung nodules in a prospective study with a sensitivity, specificity and accuracy of 93%, 60% and 79%, respectively.

Intra-tumoral distribution of ^{11}C-MET or ^{18}F-FDG

Macroscopic auto-radiographic study

Abe et al. (1988) compared the intra-tumoral regional distribution of ^{14}C-MET and a blood flow tracer, ^{18}F-fluoroantipyrine (FAP), using a double-labeled autoradiogram. The density of the film was digitized, and their correlation was tested by a (x, y) scatter plot of the two tracers. The results revealed that the regional distribution of ^{14}C-MET was almost linearly correlated with FAP. Metabolite analysis revealed that 50% of the ^{14}C-MET was found in the acid-insoluble fraction 10 min after administration. The results indicated a coupling of ^{14}C-MET metabolism and blood flow within an experimental tumor. He also examined correlation between regional uptake of ^{18}F-FDG and FAP and found no correlation between two.

Microscopic auto-radiographic study

Kubota et al. (1992) developed micro-autoradiogram techniques using the short-lived F-18. Using this technique, they examined the intra-tumoral distribution of ^{18}F-FDG at the tissue or cellular level and reported a substantially high uptake of ^{18}F-FDG in macrophages and the granulation tissue around the tumor and in tumor cells. This paper had a striking impact on ^{18}F-FDG PET in oncology. We should consider that the ^{18}F-FDG uptake of tumors includes the substantially high fraction of uptake by infiltrating immune cells and granulation tissues. In particular, we should consider that the ^{18}F-FDG uptake of tumors after anti-cancer treatment includes not only the residual uptake by tumors but also uptake by inflammatory tissues induced by the therapy. Kubota et al. (1994) examined the ^{18}F-FDG uptake dynamics in cancer cells, macrophages, granulation tissue and pre-necrotic tissues and showed that the uptake per unit volume in macrophages was the highest and most rapid among the tissues and continued to increase during the 60-min study period. However, uptakes in the FM3A and MH134 mouse mammary carcinomas and in the granulation tissue were relatively lower than in macrophages and reached a plateau approximately 30 min after injection of ^{18}F-FDG. From these results, she concluded that viable neoplastic tissue could be differentiated from non-neoplastic tissue by means of a dynamic analysis of the tracer uptake.

Kubota et al. (1995) compared the intra-tumoral distribution of ^{11}C-MET and ^{18}F-FDG at the cellular level using micro-autoradiography. A substantial uptake of ^{11}C-MET was found mainly in viable tumor cells with a relatively low uptake in granulation cells and macrophages. This is in contrast to the ^{18}F-FDG uptake, which was found in granulation cells and macrophages as high as in the tumor cell. From these results, she concluded that ^{11}C-MET might be suitable for treatment evaluation.

Parameters of tumor ^{18}F-FDG uptake and characteristics of cancer glucose metabolism

Fukuda et al. (1983a) first proposed the differential absorption ratio (DAR) as a semi-quantitative parameter of the ^{18}F-FDG uptakes in tumors. DAR represents tissue uptake (%dose /g tissue) normalized by injected radioactivity and body weight of the animal, and has been used as a measure of the relative tissue uptake of radiotracers in animal studies. Kubota et al. (1985) used the differential uptake ratio (DUR) instead of the DAR in his paper. Strauss et al. (1989) referred to DAR and used it as a parameter for ^{18}F-FDG uptakes in his paper describing PET imaging of recurrent colorectal cancers. After Fukuda

introduced DAR, the standardized uptake value (SUV) (Hübner et al. 1996; Freedman et al. 1996) was proposed and has been commonly used instead of DAR, although the definition of SUV was completely identical to that of DAR or DUR.

When Fukuda et al. (1983a) first introduced DAR as a semi-quantitative parameter for ^{18}F-FDG uptake of tumors, most of the scientists in PET research claimed that the absolute glucose utilization CMR_{glc} (mg/ml-tissue/min) should be used, even for tumors. However, there are at least two reasons for not calculating the tumor CMR_{glc}, which is based on the normal brain model. First, lumped constant (LC), which is a total efficiency of glucose consumption in a given glucose analog compared to that by glucose, may be higher in cancers than that in normal brains, and LC may vary depending on tumor type or aggressiveness. There are classical papers in biochemistry describing the low substrate specificity of tumor hexokinase for glucose and the higher uptake of deoxyhexoses (Bessel et al. 1972). This is comparable to higher LC values for cancers. Therefore, the LC values for the normal brain, 0.42 (Phelps et al. 1979), or 0.52 (Reivich et al. 1985), should not be applied to cancers. Later, a paper was published describing higher (LC = 1.4) and variable LC values in human brain tumors (Spence et al. 1998) compared to the normal brain. Another reason for not using the CMR_{glc} is that the brain and the tumor show different competition patterns of ^{18}F-FDG uptakes with blood glucose levels (transport and phosphorylation levels). The ^{18}F-FDG uptakes by the brain negatively correlated with blood glucose levels for a certain range of blood glucose; however, the tumor ^{18}F-FDG uptakes are relatively insensitive to blood glucose levels (Yamada et al. 1985; Ishizu et al. 1994). Currently, the SUV (DAR) is widely accepted as a parameter for relative tumor ^{18}F-FDG uptakes.

Conclusion

As introduced here, Japanese scientists, mainly members at Tohoku University, published many original papers and substantially contributed to the development of PET in oncology, in particular at the initial developmental stage from 1980 to early 1990s. These distinguished achievements were summarized in Table 1. Kubota et al. (2001) has already summarized the clinical significance of PET and their biological bases obtained from our studies in a previous review article. A review article on "oncological application of FDG-PET" by Czernin (2004) was helpful for preparing this manuscript and determining who performed it first in PET oncology.

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Conflict of Interest

We declare no conflict of interest.

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