REVIEW

Clinical utility of FDG PET

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Abstract : The aim of this article is to introduce the clinical utility of FDG PET as oncologic imaging. PET (positron emission tomography) is a newly developed imaging tool, and it has increased the accuracy of metabolic mapping of numerous malignancies, with significant impact on the management of cancer patients for initial staging, restaging and therapy monitoring. PET can provide functional information in addition to morphology from conventional imaging modalities. ^{18}F-labeled 2-fluoro-2-deoxyglucose (FDG) is the most commonly used PET tracer and FDG PET can demonstrate the activity of glucose metabolism throughout the entire body in a single session. We describe the clinical utility of FDG in PET and display images of normal distribution and of patients with head and neck and lung cancer.

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INTRODUCTION

PET (positron emission tomography) is a newly developed clinical imaging modality with remarkable accuracy for metabolic mapping of numerous malignancies. It is beginning to have significant impact on the management of cancer patients at different stages of their disease (1-8). PET provides functional information in addition to the morphology obtained with conventional imaging modalities. PET depends on positrons colliding with negative electrons to create two 511 keV photons emitted at 180 degrees to each other. These simultaneous photons are detected by paired detectors encircling the body. In oncologic imaging using PET, ^{18}F-labeled 2-fluoro-2-deoxyglucose (FDG) has been a favored metabolic tracer because of several advantages. FDG is an analogue of glucose labeled with the short-lived positron emitting isotope ^{18}F with a half life of 110 min. It acts very similarly to glucose and is transported into cells and converted to ^{18}F-FDG-6-phosphate by hexokinase. After conversion to FDG-6-phosphate, it is not metabolized further and accumulates within the cells. Low membrane permeability to charged ions causes its entrapment within the cell and glucose utilization rates can be determined from FDG tissue concentration. This metabolic trapping of FDG in the cell constitutes the rationale for imaging the *in vivo* distribution of the tracer. FDG uptake in tumors is proportional to the metabolic rate of viable tumor cells, which have increased demand for glucose compared to normal tissue. It is possible to image the whole body in a single session, which increases the opportunity for finding unsuspected disease sites which are not evident on routine CT or MRI. The oncologic indications of FDG PET include the following ; diagnosis, initial staging, and restaging of non-small cell lung cancer, colorectal cancer, Hodgkin and non-Hodgkin lymphoma, esophageal cancer, melanoma, head and neck cancer (excluding neoplasms of central nervous system and thyroid gland), breast cancer and characterization of solitary pulmonary nodules, which are covered by Medicare in the USA. The following diseases are recognized as appropriate indications in Japan since April 2002 ; lung cancer, breast cancer, colorectal cancer, pancreatic cancer, metastatic liver

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tumor, malignant lymphoma, head and neck cancer, brain tumor, unknown primary cancer and melanoma. Hepatocellular carcinoma, gastric cancer, and genitourinary neoplasms like prostate cancer are not imaged as effectively with FDG but some studies have been published (2, 6).

We are currently imaging over 900 PET studies a year, and more than half of them consist of head and neck cancer and lung cancer patients. Here we describe the clinical utility of FDG PET, illustrated with PET images of head and neck cancer and lung cancer.

FDG PET studies

Patients preparation

Patients were instructed to fast for at least 4 hours before injection of ^{18}F-FDG (except for glucose-free oral hydration). Blood glucose level was measured before injection of the tracer. Patients were not studied if the blood glucose was greater than 150 mg/dl. After injection of FDG, patients were kept lying comfortably. No urinary bladder catheterization was performed. Some of the head and neck cancer patients were sedated with 1 mg alprazolam, given orally 30 minutes before FDG injection. These patients rested quietly un the supine position during uptake and were asked to minimize muscular activity, including vocalization to minimize muscle uptake which can occasionally result in false positive interpretaion.

PET scan

FDG was produced with a 17 meV Scandatronix cyclotron in our PET Center. The injection dose was between 10 and 20 mCi (370-740 MBq). The dose was adjusted for patient body weight using the following protocol is following ; 10 mCi for less than 80 kg, 12.5 mCi for 80-100 kg, 15.0 mCi for 100-120 kg and 17.0 mCi for 120-140 kg. PET scans were obtained using a PET scanner (Siemens HR+, biograph) 90 min after injection of the tracer. We have recently begun to use a Biograph (Siemens, CTI) system, which is a hybrid PET/CT system, for oncologic imaging. An essential part of the study with conventional PET system is the transmission scan with 68 Ge rotating rods for attenuation correction. In the PET/CT system, transmission scanning with 68 Ge is not necessary, since we use the CT data, which is obtained along with the PET scan, for attenuation correction and anatomic characterization. The range of the scan depended on the patient's disease, and most of the studies were acquired from the level of the OM line through the level of the umbilicus. The patient is positioned on the table in the supine position and is scanned at 5-7 bed positions, 180 sec per position. The total scanning time is approximately 15-20 min. It takes somewhat more time when imaging the entire body, from the top of the head to the toes, such as for patients with melanoma or soft tissue tumors in the lower extremities.

Data analysis

The data are reconstructed with the system computer and displayed on a separate workstation monitor for imaging evaluation. Orthogonal images are reviewed with and without attenuation correction by physicians. PET provides not only static views but also quantitative data in the form of standardized uptake value (SUV). This is an uptake measurement that provides a means of comparison of FDG uptake between different lesions. For this measurement, a region of interest (ROI) was placed manually. SUV [=tissue concentration (kBq/ml)/injected FDG dose (kBq)/body weight (g)] was calculated for each ROI. The SUV that is reported is usually the maximum SUV since that value best reflects the most metabolically active part of the tumor. Measurement of SUV requires attenuation correction to avoid the apparent variability in FDG uptake due to the differences in tumor depth within the body. The administered dose, corrected for residual activity in the syringe and tubing, was also accurately determined and the dose was decay corrected to the time of imaging.

Normal distribution of FDG (Fig.1)

FDG uptake depicts tissue glucose metabolism and there are several sites of normal physiologic accumulation of FDG (9, 10). The brain, heart and urinary tract are the most prominent sites of tracer accumulation. The brain uses glucose as its primary substrate. Consequently, accumulation is physiologically high in the cortex, basal ganglia, thalamus, and cerebellum. Brain tumors sometimes overlap these regions of high physiological uptake, which can make image interpretations difficult and may lead to false negatives. The myocardium uses free fatty acids as its primary substrate, but also uses glucose as an alternate substrate. Up to 4% of the injected dose can accumulate within the myocardium depending on the relative availability of free fatty acids versus glucose. With a sufficiently long fast, the myocardial metabolism shifts to fatty acids as a source of energy. The tracer is filtered by the renal glomerulus and not reabsorbed,

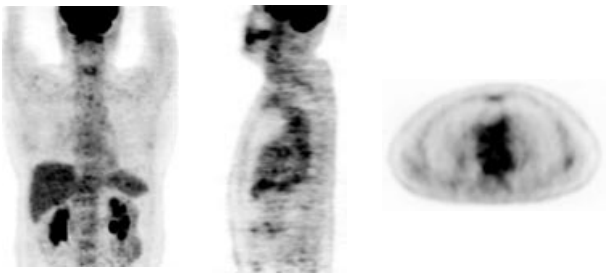

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Fig. 1. Normal distribution of FDG of 62 year old male. a) Attenuation-corrected anterior projection image. FDG accumulates in the brain, adenoid tonsil, larynx, liver, spleen, kidneys and vertebral bodies. Some bowel uptake is also seen inferior to left kidney. b) Sagittal image. Soft palate uptake is seen. c) Axial image at mid lung level.

thus renal uptake is not related to glucose metabolism. Hydration should be encouraged to promote diuresis and decrease activity in the renal collecting system and bladder. In the absence of hydration, diuretics, and urinary catheterization, FDG is present in the bladder and, to varying degrees, in the renal pelvis and urinary tract. Significant FDG in the urinary excretory route may interfere with identification of renal or pelvic tumors. In the resting state, skeletal muscle relies on fatty acid oxidative metabolism for energy, and muscular uptake of FDG is negligible. After exercise, however, significant uptake is observed in skeletal muscles because glycolysis becomes the major source of energy. Hyperventilation may induce uptake in the diaphragm, and stress-related muscle uptake is often observed in the cervical, trapezius, and paraspinal muscles. Uptake in the tonsils and associated, lymphoid tissue, salivary glands, and thyroid may also be seen as a normal variant. Intense thyroid uptake is indicative of thyroiditis. FDG accumulates in laryngeal muscles in proportion to contractile activity during vocalization, however, this uptake is nearly always symmetric. Uptake in the alimentary tract, from esophagus to rectum, is variable in distribution and intensity. A small area of focal FDG uptake is frequently seen at the gastroesophageal junction, probably related to reflux. The wall of the stomach is sometimes seen. The normal colon and small intestine may demonstrate increased uptake, probably due to smooth muscle activity, bacterial uptake, and metabolically active mucosa. Uptake in the cecum may be related to lymphoid tissue in this region. The liver and spleen are almost always identified in the abdomen. Uptake in the bone marrow is normally mild to moderate in the vertebral bodies, pelvis, hips, long bones and sternum. Patients undergoing treatment with granulocyte-stimulating factor have diffuse, intense uptake in the bone marrow. The accumulation of FDG can be affected by the blood glucose level via competitive displacement of FDG by the circulating glucose. In type I diabetic patients, insulin is not recommended and FDG PET should be performed in the morning after an overnight fast. In type II patients, insulin may be used to control glucose levels, although it may cause muscle uptake of glucose, and may result in diffusely increased muscle uptake. At least one hour should elapse after administration of regular insulin to minimize muscle uptake.

Head and Neck cancer (Fig.2)

FDG PET has been used for staging, restaging and evaluation of response to treatment (chemotherapy, radiation therapy, surgery or the combination) (3-5). In patients with a neck mass and unknown primary, PET frequently is able to detect the primary site. Most head and neck cancers consist of squamous cell carcinomas of nasopharynx, oral cavity, and larynx. Accurate pretherapy evaluation of the primary site, nodal disease and distant metastases is critical to determine the appropriate therapeutic approach and prognosis. CT and MR imaging lack sensitivity and specificity in evaluating regional lymph nodes, due to their dependence on size criteria.

Lymph node staging with FDG PET is more accurate than with conventional imaging modalities, with a sensitivity and a specificity of up to 90% and 94%, respectively, compared with CT values of up to 82% and 85%, and MR imaging values of up to 88% and 79% (11-14). Radiation therapy and surgery can significantly distort the anatomic structures. This limits the ability of CT and MR imaging to differentiate post-therapeutic changes from residual or recurrent disease. Accurate detection of residual disease or early recurrence with FDG PET allows earlier change of patient treatment. The sen-

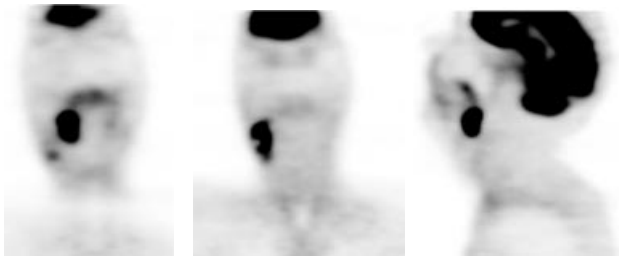

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Fig. 2. Head and neck cancer patient of 42 year old male with a squamous cell carcinoma of the right tonsil. a) Intense uptake is present in the primary tumor of the right tonsil with metastatic node. b) A nodal disease is obvious in the right neck with necrotic part. c) Sagittal image of the primary tumor. Maximum SUVs of primary tumor : 10.7, right neck node : 8.5

sitivity of FDG PET in detecting residual or recurrent disease at the primary site is comparable with those of CT and MR imaging (88%-100% vs 70%-92%), but its specificity is superior (75%-100% vs 50%-57%)(15-17).

Early identification of response to chemotherapy may help to improve survival in treatment of locally advanced head and neck cancer. A greater reduction between pre and post therapy FDG uptake may predict a better remission (18). Chemotherapeutic regimens may be changed earlier or additional surgery could be performed earlier if nonresponders could be accurately identified after their first chemotherapy.

The waiting period before doing FDG PET after some treatment or procedure is now not well defined. Our current recommendations are to wait 7 days after needle biopsy, 2 weeks after chemotherapy, 4 weeks after surgical resection, and 3 months after the completion of radiotherapy to avoid the false positive findings that can occur due to post inflammatory changes after the procedure. False negative results can occur due to necrotic tumors and small tumors.

Lung cancer (Fig.3)

With the improvements in high resolution CT (HRCT) and multi-detector CT (MDCT), it is becoming more common to detect pulmonary nodules. However, it is frequently difficult to determine the benign vs. malignant status in the case of multiple nodules or tiny nodules. There are no specific CT criteria that allow reliable distinction of benign from malignant pulmonary nodules. In a recent meta-analysis, FDG PET was reported to have a sensitivity of 97% and a specificity of 78% in characterizing solitary pulmonary nodules (19). SUVs of more than 2.5 are considered very worrisome for cancer. In addition to initial staging, restaging, and evaluation of response to therapy, evaluation of solitary pulmonary nodules showing low uptake with FDG PET allows patients to be followed up with sequential imaging rather than invasive procedures. In initial staging of lung cancer, FDG PET has been successfully used in mediastinal nodal staging with a sensitivity of 93% and a specificity of 99% (20). At least 10% of patients are found to have unsuspected metastatic disease at FDG PET when results of routine CT are not definitive for metastasis. In addition, some false-positive findings at CT, including adrenal nodules which are often benign adenomas, are correctly interpreted as negative with FDG PET (21). FDG PET can avoid some invasive procedures by identifying distant or more accessible sites in patients who are surgical can-

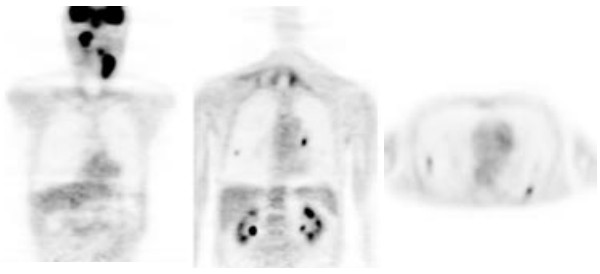

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Fig. 3. Recurrent head and neck cancer patient, a 71 year old male with squamous cell carcinoma of right piriform sinus after surgery and radiation therapy. a) The local recurrence and left neck disease are apparent. SUVs of local recurrence:14.5, neck disease : 13.9. b) Right lung and left hilar metastases are also displayed. SUVs of right lung metastasis : 2.2, left hilar node : 6.3. c) Axial view at the level of right lung metastasis. Another lesion of left lung is seen. SUV of this lesion is 3.3.

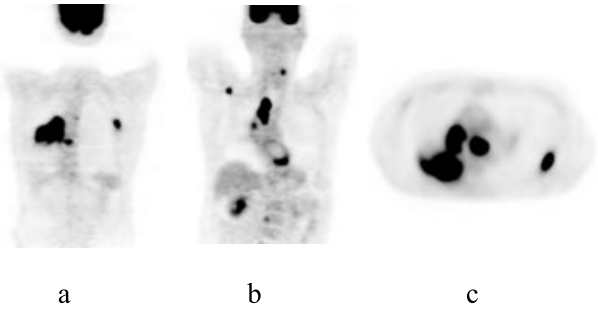

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Fig. 4. Lung cancer patient of 68 year old male with a non small cell carcinoma of the right lung. Primary tumor, multiple nodal and bone metastases are present. a) Primary tumor and bone mets. b) Mediastinal, right supraclavicular and left neck nodal diseases. c) Axial image. Maximum SUVs of primary tumor:11.5, mediastinal lymph node : 13.9, left rib : 11.7, thoracic spine : 7.1, left neck node : 7.4, right supraclavicular node : 13.6

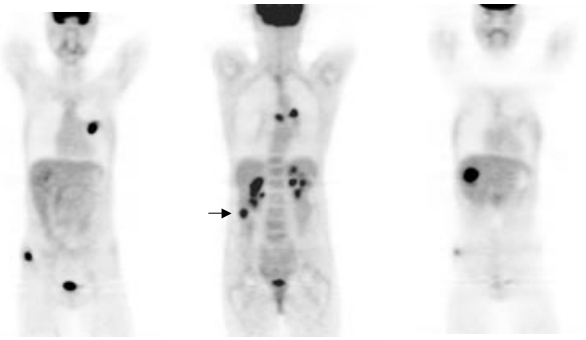

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Fig. 5. Lung cancer patient, a 44 year old female with poorly differentiated adenocarcinoma of the left upper lobe with bone and liver metastases. a) Primary tumor (SUV=9.3), and right iliac bone metastasis (SUV=7.9). The intense uptake in the center of the pelvis corresponds to bladder. b) Posterior view of image a). Left hilar (SUV=9.6) and subcarinal (SUV=5.6) lymph nodes are demonstrated. The metastatic liver tumor in the lower posterior segment (SUV= 7.7) is also seen (arrow). c) Another liver lesion in middle lobe (SUV=12.3). This patient had two liver metastasis.

didates but are found to have unresectable tumors. Accordingly, treatment is altered in up to 41% of cases on the basis of the FDG PET findings (22, 23).

Postsurgical anatomical distortion makes it difficult to distinguish residual or recurrent disease from postoperative fibrosis with routine follow up CT. Equivocal findings suggestive of tumor recurrence or residual disease can be accurately characterized with FDG PET. FDG PET can identify changes in glucose metabolism after treatment and may be a better indicator of a favorable response to therapy than the decrease in tumor size determined with CT (24). It has been suggested that a relative decrease in FDG uptake may only indicate a partial response due to destruction of cells sensitive to the therapy and while other resistant cells continue to be viable. It may be important to evaluate the magnitude of the decline in uptake of SUV. The larger decline of SUV is considered as a better response to therapy.

There are some pitfalls that may result in false-positive or negative findings. Granulomatous disease such as sarcoidosis, tuberculosis, histoplasmosis, aspergillosis, mycobacterium avium-intracellulare, coccidiomycosis, and other infectious processes, such as pneumonia, may result in false-positive findings. Malignant tumors with low glucose metabolism such as bronchioloalveolar carcinoma can give rise to false-negative results. Well-differentiated adenocarcinomas have relatively less intense FDG accumulation, particularly lesions smaller than 1.0 cm in diameter.

CONCLUSION

We have described the clinical utility of FDG PET. PET is a noninvasive diagnostic technique that allows identification of biochemical and physiologic alterations in tumors. FDG PET is becoming widely accepted in the initial staging of cancer, management of recurrent disease, and therapy monitoring. FDG PET and anatomic imaging modalities, such as CT or MRI, play complementary roles in allowing a more accurate overall evaluation of cancer management. Moreover, newly developed hybrid PET/CT systems should be a more powerful tool. In conclusion, the role of PET in tumor imaging will continue to increase as more indications are approved and newer tumor-specific tracers are developed.

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