Guidelines for the Clinical Use of ^{18}F-FDG-PET/MRI 2012 (Ver 1.0): Part 1

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Introduction

In FDG, the hydroxyl group at the C2 position of glucose is substituted with ^{18}F. It is taken up into cells through glucose transporter proteins and phosphorylated by hexokinase. Phosphorylated glucose undergoes glycolysis, and is eventually degraded into water and carbon dioxide, whereas FDG undergoes no further metabolism after the phosphorylation and accumulates in cells. The accumulation reflects glucose metabolism in tissues. This property of FDG is recognized as useful for diagnosis of diseases such as brain disease (epilepsy and dementia), ischemic heart disease, malignancy, and inflammatory disease. In this article, we describe guidelines for FDG PET/MRI indications, procedures, and cautions for the interpretation of images, choosing as our focus malignant diseases for which this modality is considered a useful diagnostic tool. The guidelines were developed from the perspective of specialists of the Japanese Radiologic Society, Japanese Society of Nuclear Medicine, and Japasene Society of Magnetic Resonance Imaging.

1. Epilepsy

(1) Clinical significance

Since glucose metabolism decreases in epileptic foci during the interictal phase, FDG-PET can be used for diagnosis of the foci. The hypometabolism is observed in extensive areas including epileptic foci. FDG-PET is especially useful for determining the site of subdural electrodes placement when surgery is considered for temporal lobe epilepsy. During the ictal phase, glucose metabolism increases, but persistent input to the brain reduces time resolution, making FDG-PET unsuitable for the measurement during this phase. The rate of focus localization determined by FDG-PET in temporal lobe epilepsy during the interictal phase, although varying among reports, is around 90%, which is higher than the rate of focus localization determined by cerebral perfusion SPECT.[1)] Like other nuclear medicine examinations, the diagnostic performance of FDG-PET is lower for extratemporal lobe epilepsy than for temporal lobe epilepsy. Statistical image analysis is useful as an adjunct to diagnosis.[2)] In focal cortical dysplasia (a cause of extratemporal lobe epilepsy), the lesion is visualized as a region of reduced uptake during the interictal phase.[3,4)] When using a PET/MRI system, addition of simultaneously-obtained MRI data increases the detectability of abnormal uptake that is difficult to detect and evaluate by PET alone.

(2) Principles underlying the diagnostic method

Glucose metabolism decreases in the epileptic focus and its surrounding areas, producing a region with reduced uptake of FDG during the interictal phase, and increases in the focus and its surrounding areas, resulting in a region with increased uptake of FDG during the ictal phase.

(3) Examination procedures

(a) Dose and administration route of FDG

FDG is administered intravenously at a dose of 185–444 MBq (3–7 MBq/kg) and 111–259 MBq (2–

5 MBq/kg) for two-dimensional (2D) and three-dimensional (3D) data acquisition, respectively. The dose of FDG is increased or decreased according to the model used for imaging and the age and weight of patients. For quantification of glucose metabolism using arterial blood sampling, injection rate around 1 minute may ensure the detection of peak of radioactivity in the arteries.

(b) Imaging procedures

FDG is administered to patients in the supine position with eyes closed. PET imaging is performed after 40–60 minutes of rest. To obtain images with less noise, the preferable dose and acquisition time are 185 MBq and 10 minutes for 3D mode, and 370 MBq and 10 minutes, respectively, for 2D mode.

(c) Quantification of glucose metabolism

Quantification of glucose metabolism is rarely used to localize epileptic foci. The autoradiography (ARG) method based on a 3-compartment model is the most widely used FDG approach for quantification of cerebral glucose metabolism. This method is designed to collect arterial blood and determine the rate of glucose metabolism from a single measurement using rate constants (K1-K4) in healthy persons.

(d) Cautions for the examination

1) Preparation

Fasting is required for at least 4–5 hours before the scan. Only water can be taken. Blood glucose levels are measured just before the scan. High level of blood glucose reduces uptake in the brain. Specifically, for the quantification of cerebral glucose metabolism by the ARG method, a blood glucose level of 120 mg/dL or lower is preferable. A route for arterial blood sampling needs to be secured for the measurement of cerebral glucose metabolism.

2) Cautions for the measurement

Since not only absolute value but also relative distribution of radioactivity in the brain vary with time after FDG administration, imaging time must be kept as constant as possible. Cerebral blood flow affects the uptake until about 40 minutes after the administration, and therefore about 60 minutes of imaging time is recommended and takes into consideration attenuation and scan waiting time when only one session is planned. Measures to minimize head motion during the scan are needed. It is also important to avoid misalignment of data from the transmission scan or CT used for attenuation correction and data from the emission scan. Since cerebral glucose metabolism tends to vary according to neural activity, patients are required to rest starting 30 minutes before FDG administration, close their eyes during the administration, and keep as quiet as possible on the bed after the administration until the start of the scan.

(4) Cautions for the interpretation

Even in the normal state, FDG uptake is lower in the cerebellum and the inferior temporal lobe relative to other regions of the cerebral cortex; the reduced uptake in those regions should not be

considered pathologic. This tendency becomes more prominent at later time points during imaging. Reduced uptake of FDG is observed in areas of neuronal degeneration, loss, or diaschisis; these disorders cannot be distinguished by FDG accumulation alone. Increased uptake of FDG is observed in involuntary movement or epilepsy. Glucose metabolism is increased in the primary motor cortex in cases of involuntary movement disorder and in extensive areas including epileptic foci in cases of epilepsy, but hypermetabolism may also be induced by subclinical seizure without symptoms. Caution is needed to discriminate between them.

2. Ischemic heart disease (viability assessment)

For cardiac MRI examinations, please refer to the chapter 3-5 (page **). The general recommendation for FDG-PET of ischemic heart disease is as follows:

(1) Clinical significance

Assessment of myocardial viability is often used to predict improvement in cardiac function after revascularization, and radiological evaluations therefore become clinically important to select patients with ischemic heart disease for such invasive treatment. Especially, since the risk of revascularization seems high in patients with reduced cardiac function caused by severe ischemic heart diseases, accurate assessment of myocardial viability is required to determine treatment strategy. Although myocardial perfusion SPECT offers acceptable diagnostic performance in clinical practice, FDG-PET is regarded as the most appropriate method to assess myocardial viability; FDG-PET often detects myocardial viability in some cases which might otherwise be overlooked with general viability testing including SPECT.

(2) Principles underlying the examination method

Myocardial cell activity is basically dependent on the metabolisms of fatty acid and glucose, and the former substrate is mainly utilized in aerobic conditions. In ischemic myocardium, however, glucose metabolism is increased in exchange for fatty acid in order to effectively generate energy (i.e. adenosine triphosphate). FDG, a glucose analogue, is therefore considered a suitable tracer for imaging of ischemic but viable myocardium.

(3) Examination procedures

(a) Dose and administration route of FDG

FDG is administered intravenously at a dose of 185–444 MBq (3–7 MBq/kg) for 2D and 111–259 MBq (2–5 MBq/kg) for 3D data acquisition. The dose of FDG may be arranged on the basis of imaging protocol, age, patient weight, or other factors.

(b) Imaging procedures

Emission and transmission scans are performed 45-60 minutes after FDG administration. Since CT-based transmission scan is unable to be obtained by PET/MRI system, an external transmission source should be used. MRI-based transmission might be available in the future.

(c) Control of blood glucose

There are two representative protocols for non-invasive assessment of myocardial viability: fasting and glucose loading. Fasting triggers a metabolic shift to increased glucose consumption in ischemic myocardium, making it possible to visualize ischemic but viable regions. However, FDG uptake in ischemic myocardium in some diabetic patients or non-pathological myocardium may be insufficient for viability testing. Glucose loading method is to promote accumulation of FDG mediated by insulin-dependent GLUT 4 expression. Oral glucose (50–75 g) loading followed by fasting is performed 60 minutes before the FDG administration so that blood glucose is increased (120–150

mg/dL) at the time of the administration. According to the ACC/AHA/ASNC guidelines, glucose loading method can be applied to patients with glucose intolerance such as diabetes mellitus as long as additional insulin injection is considered [5,6]; FDG is administered without pretreatment when blood glucose level is under 130 mg/dL. By contrast, it is recommended that 1, 2, 3, and 5 units of regular insulin are administered when blood glucose level is 130–140, 140–160, 160–180, and 180–200 mg/dL, respectively.

The other viability testing with FDG-PET, which tends to be applied in Europe, is to administer FDG while maintaining a constant blood glucose level by intravenous infusion of insulin and glucose (so-called “insulin clamp”). [7]

(4) Cautions for diagnostic image interpretation

Myocardial FDG uptake revealed in recommended protocols described above accounts for the area of viable myocardium. %uptake, which is the ratio of uptake in the lesion to maximum uptake in the myocardium, is commonly used for semi-quantitative analysis.

Comparing myocardial viability and myocardial blood flow facilitates to classify myocardium as: 1) normal myocardium (normal blood flow and viability); 2) ischemic myocardium (reduced blood flow with mismatch between blood flow and viability); and 3) infarcted myocardium on PET (matched reduction of blood flow and viability), which is clinically important. [8] Blood flow is measured with ^{13}N-ammonia PET, ^{82}Rb-PET, ^{201}Tl SPECT, or SPECT with ^{99m}Tc-labeled agent.

3. Malignancy (Overview)

(1) Clinical significance [9,10)]

Glucose metabolism is generally increased in malignant tumors, most of which show intense uptake of FDG, whereas most benign tumors show low uptake. Unlike CT or MRI diagnosis, FDG-PET diagnosis is based on metabolic activity, instead of morphology or size of the lesion. In principle, FDG-PET is considered to be effective for diagnosis of almost all cancers with increased glucose metabolism.

(a) For initial or pretreatment staging.

(b) For patients receiving two-phase treatment in whom staging cannot be established after the completion of the first-phase and hence strategy for the second-phase cannot be decided; for example, patients in whom pre-surgical staging after neoadjuvant chemotherapy or chemoradiation cannot be established by other examinations or imaging studies.

(c) For cases in which metastasis or recurrence is suspected on the basis of clinical signs and examination, but cannot be confirmed by other imaging studies.

(d) For cases in which the presence or absence of recurrence cannot be confirmed by other methods because of deformation and scar induced by surgery or radiotherapy.

(e) For cases in which, despite apparent efficacy of the treatment during follow-up, the mass is still present on other imaging studies and differentiation between a residual tumor and a remnant of non-tumor tissue, such as granulation or fibrosis tissue, is needed.

(f) For patients receiving chemotherapy in whom continuation of the current treatment or switching to another protocol needs to be decided, but early response evaluation is difficult with other examinations or imaging studies (FDG-PET examination for diseases other than malignant lymphoma is not covered by insurance as of April 2012 in Japan, although its usefulness has been reported in the literature).

(g) For cases in which, after the completion of chemotherapy or chemoradiation, response evaluation is difficult with other imaging studies because of limited change in size of the tumor or residual scar-like tissues.

(h) For early response evaluation of treatment with molecular-targeted drugs for malignant tumors, like rituximab treatment for malignant lymphoma.

(2) Principles underlying the examination method [9,10)]

FDG uptake is high in most malignant tumors because of the increased activities of glucose transporter and hexokinase as well as extremely low activity of phosphatase.

(3) Examination procedures [9-11)]

(a) Dose and administration route of FDG

FDG is administered intravenously at a dose of 185–444 MBq (3–7 MBq/kg) for 2D and 111–259 MBq (2–5 MBq/kg) for 3D data acquisition. The dose of FDG is increased or decreased according to

the model used for imaging and the age and weight of patients.

(b) Imaging procedures

Following 60 minutes of rest after the FDG administration, imaging is performed using a PET/MRI system. Subsequent delayed imaging is added as needed.

(c) Cautions for the examination

1) In preparation, at least 4 hours of fasting is required. High level of blood glucose reduces FDG uptake in tumors. Even after normalization of blood glucose, the persistent effect of insulin may increase background uptake in muscle and other organs and decrease detection performance.

2) Resting is required because exercise (muscle tension and contraction) before or especially after the FDG injection increases uptake in the skeletal muscle.

3) Since FDG is excreted mainly in urine, water intake and diuresis decrease background uptake and reduce exposure.

4) Since FDG is excreted from kidney to urinary bladder, voiding before imaging reduces exposure in the urinary region and removes obstacles to interpretation of results in the pelvic region.

5) Degree of uptake is assessed visually as well as semi-quantitatively by calculating SUV (standardized uptake value), the ratio of tumor uptake to injected dose per unit body weight. SUV is 1.00 when injected FDG distributes uniformly throughout the body with no excretion.

SUV = (tumor radioactivity concentration)/{(injected radioactivity)/(body weight)} × cross-calibration factor}

6) Reconstructed images obtained from emission data alone can be visually assessed to some degree, but, for more accurate diagnosis, reconstructed images with attenuation correction using MRI data are essential. [11-16)]

7) FDG uptake continues to increase beyond 1 hour after the injection in malignant tumors, whereas it decreases in most benign diseases. The addition of delayed imaging may help differentiate benign from malignant lesions. When imaging is performed only once, imaging at 2 hours after the injection may be superior to that at 1 hour.

8) For diagnosis using FDG-PET, anatomical information obtained by MRI is important. It is recommended that FDG-PET image be interpreted in reference to anatomical images obtained by MRI wherever possible. By using a PET/MRI system, a homotopic MR image is easily obtained and the images can be easily fused. [11-16)]

(d) Usefulness of PET/MRI systems

The diagnostic performance of PET/MRI (compared with that of PET or MRI alone) is reported to be improved; for example, the addition of simultaneously-obtained MRI data may confirm a diagnosis for abnormal uptake that is difficult to detect and evaluate by PET alone. [17-22)]

(4) Cautions for diagnostic image interpretation [9,10)]

In the normal state, FDG uptake is high in the brain and in the urinary system, an excretory route,

where glucose metabolism is active, including kidney, ureter, and bladder. Relatively high uptake is observed in the palatine tonsil, gastrointestinal tract including stomach and large intestine, and liver. Physiological uptake may be observed in the myocardium, hilar area of the lung, and bone marrow. High uptake is sometimes observed in brown adipose tissues in the neck and supraclavicular fossa region and the paravertebral region upon cold stimulation.

Notably, uptake is not necessarily high in some malignant tumors, such as well-differentiated tumors and slow-dividing and growing tumors. The uptake may be underestimated in small-sized lesions because of low spatial resolution. Active inflammation and granulomatous disease often show intense FDG uptake, which is difficult to differentiate from uptake due to tumor metabolism.

Malignancy (Specifics)

3.1 Brain

(1) Clinical significance

Small brain tumors are difficult to assess with FDG-PET alone because physiological uptake is high in the brain. But when combined with MRI, FDG-PET is expected to be a more sensitive detector of tumors than CT or PET/CT. For example, MRI is thought to be able to detect significantly smaller brain metastases from lung cancer (about 5 mm in diameter) than can CT. [23)] Using MRI as a reference standard, PET/CT performs poorly, i.e., has a sensitivity of 50%, a specificity of 97%, and an accuracy of 76% for detection of metastatic brain tumors. [24)] Using PET/MRI, more accurate staging and diagnosis of recurrence may be possible. The addition of delayed image to the assessment of FDG uptake is considered to be effective for differentiating brain metastasis from post-treatment necrosis[25)] and useful for treatment selection. Novel tracers, such as ^{11}C-methionine and ^{18}F-fluorocholine, will become available in the future and may be useful for differentiating metastatic brain tumors from high-grade gliomas or benign brain tumors. [26)]

(2) Examination procedures

1) PET: Following at least 4 hours of fasting before the scan, FDG is administered intravenously at a dose of 185–444 MBq (3–7 MBq/kg) for 2D and 111–259 MBq (2–5 MBq/kg) for 3D data acquisition. The dose of FDG is increased or decreased according to the model used for imaging and the age and weight of patients. Following 40–60 minutes of resting after the FDG injection, PET imaging is performed over a 10-minute period. During the waiting time after the injection, it is recommended that patients close their eyes and keep quiet wherever possible. For quantification of glucose metabolism, constant-rate injection of FDG and the ARG method based on the 3-compartment model are widely used. When appropriate, delayed imaging is performed a few hours after the FDG injection.

2) MRI: For the purpose of coregistration with PET, whole-brain 3D imaging is desirable. Gadolinium-enhanced T1-weighted imaging is the sequence of choice, but for cases in which contrast enhancement cannot be used or lesions are poorly delineated on the contrast-enhanced image, T2-weighted imaging or fluid-attenuated inversion recovery (FLAIR) is recommended. The 3D acquisition of T1- and T2-weighted images or 2D acquisition of cross-sections suited for observation of the lesion is performed, as needed.

(3) Other imaging procedures

For the assessment of brain tumors, addition of MRI sequence as needed may provide valuable information. For example, MR spectroscopy (MRS) enables quantitative assessment of amino acid components and is considered useful for differential diagnosis of brain tumors. [27,28)] The assessment of cellular density with diffusion-weighted imaging (DWI) [29,30)] or the assessment of blood flow status with perfusion-weighted imaging (PWI) [31)] may help diagnosis. For diagnosis of pituitary

adenoma, dynamic gadolinium-enhanced T1-weighted imaging is considered useful. [32)]

3-2. Head and neck

(1) Clinical significance

Glucose metabolism is generally increased in malignant tumors, most of which show intense uptake of FDG. In FDG-PET, diagnosis is based on metabolic activity instead of morphology or size of the lesion as in CT or MRI. Therefore, FDG-PET commonly shows a higher diagnostic accuracy than CT or MRI and a superior diagnostic performance to that of conventional tumor scintigraphy. Intense uptake of FDG is often observed in salivary or thyroid gland tumors, even when they are benign, and PET is known to have limitations in the differentiation of benign from malignant tumors. [33,34)] In cases diagnosed with a malignant tumor, however, PET contributes to the staging and diagnosis of recurrence in the head and neck region, as in other regions. Consequently, in principle, FDG-PET should be effective for the assessment of almost all head and neck malignancies with increased glucose metabolism. [35)] Head and neck malignancy presents relatively frequently as synchronous multiple cancers, for which FDG-PET is useful as a screening method. [36)] In malignant tumors that respond to chemotherapy, reduction in glucose metabolism precedes morphological change or size reduction of the lesion. Early evaluation of response to chemotherapy with FDG-PET may be useful for deciding a more appropriate treatment strategy. [37)] In examinations using a PET/MRI system, addition of simultaneously-obtained MRI data might provide more accurate diagnosis of abnormal uptake, which is difficult to evaluate with PET alone. Also, assessment using fused PET/MRI images is reported to be diagnostically more reliable compared with that using MRI images alone, especially in diagnosis of recurrence. [38)] MRI suffers slightly from the small effects of metal artifacts, such as dentures, compared with CT, and is suitable for evaluation of the oral cavity, oropharynx, and upper cervical lymph nodes. MRI has excellent tissue contrast and so is effective for assessment of the extent of a primary tumor (specifically for basilar or intracranial invasion), discrimination between the tumor itself and areas of secondary inflammation, and evaluation of the intrinsic properties of the tumor. [39)]

(2) Examination procedures

1) Dose and administration route of FDG

FDG is administered intravenously at a dose of 185–444 MBq (3–7 MBq/kg) for 2D and 111–259 MBq (2–5 MBq/kg) for 3D data acquisition. The dose of FDG is increased or decreased according to the model used for imaging and the age and weight of patients.

2) Imaging procedures

At 60 minutes after the FDG injection, whole-body emission scan and MRI are performed using a PET/MRI system.

In the MRI, a (1) scout image, (2) transverse T1-weighted image for attenuation correction (gradient

echo sequence, 3D acquisition, and thin slice), (3) transverse T2-weighted image, and (4) coronal T2-weighted image must be acquired; (3) and/or (4) should be combined with fat suppression. For some organs including nasopharynx and nasal sinus, a (5) sagittal (fat-suppressed) T2-weighted image is additionally acquired depending on the site or morphology of the primary tumor. Diffusion-weighted imaging with apparent diffusion coefficient (ADC) measurement is useful for detection of the primary lesion and for differentiating benign from malignant lymph nodes in head and neck malignancy, [40)] and may play a complementary role when concurrently used with FDG-PET. MR spectroscopy (MRS) can provide additional information on metabolism of various compounds other than glucose and therefore may be useful when combined with FDG-PET. MR angiography (MRA) is additionally performed for the assessment of blood vessels in the neck. Detailed PET and MRI acquisition parameters are set according to the specifications of each model used.

(3) Cautions for diagnostic image interpretation

1) In the head and neck region, many organs take up FDG physiologically, including the tonsils, soft palate, and salivary glands. [41)] Since most of these uptakes are symmetric, an asymmetric pattern of uptake generally indicates the presence of a lesion on the side with higher uptake. [42)] It should be noted, however, that uptake in one vocal cord may reflect contralateral recurrent laryngeal nerve paralysis.

2) Although rare, uptake of FDG can be high in brown adipose tissues in the neck and supraclavicular fossa region. This uptake pattern could be misdiagnosed as cervical lymph node metastasis. [43)] The pattern is especially common in women during the cold months, and can be recognized by referring to typical distribution and coregistered PET/MRI images.

3) A basilar or intracranial lesion that is close to the site of physiological FDG uptake is sometimes difficult to evaluate. MRI is useful for assessment of progression of these lesions.

4) It should be noted that uptake is not necessarily high in some malignant tumors, such as well-differentiated tumors, slow-dividing and growing tumors, small-sized lesions, and highly necrotic lesions. Active inflammation and granulomatous disease often show intense FDG uptake, which is difficult to differentiate from uptake due to a tumor.

3-3. Chest

3-3-1. Lung cancer

(1) Clinical significance

For lung cancers, the usefulness of PET or PET/CT using FDG is already established. Meanwhile, in early studies, the diagnostic performance of PET/MRI is reported to be comparable to that of PET/CT. [44)] The features of MRI may add to PET's usefulness as follows:

1) Diagnosis of lung cancer with chest wall or mediastinal involvement, including Pancoast tumors, by utilizing the good contrast resolution of MRI [45,46)]

2) Differentiation of benign from malignant primary lesions or lymph nodes, viability assessment, treatment response evaluation, and prognosis prediction, using diffusion-weighted imaging (DWI) or a short inversion time inversion recovery (STIR) sequence [47-51)]

3) Diagnosis of metastases in the brain, liver, or adrenal gland, which are common sites of metastasis [52,53)]

MRI data combined with glucose metabolism data obtained with FDG-PET may enable kinds of assessments that were impossible with conventional PET or PET/CT. On the other hand, because of low proton density in the lungs and significant susceptibility due to air, especially in high-magnetic-field MRI, assessment of lung field lesions is more difficult with MRI than with CT. Therefore, in PET/MRI examination of lung cancers, chest CT might need to be performed separately for the assessment of lung fields. However, assessment of lung fields with MRI has become possible through advances in imaging techniques. Future investigation is needed to determine the position of chest CT.

(2) Examination procedures

1) Dose and administration route of FDG

Imaging procedures for PET examinations are in accordance with those for PET or PET/CT examinations. Generally, FDG is administered intravenously at a dose of 111–259 MBq (2–5 MBq) for 3D acquisition, depending on the body weight of patients.

2) Dose and administration route of gadolinium contrast agent

Especially for diagnosis of brain metastasis, gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), a contrast agent for MRI, is effective. After confirming that patients have no renal dysfunction, Gd-DTPA is commonly administered intravenously at a dose of 0.2 mL/kg of body weight. For assessment of blood flow in tumors using dynamic contrast enhancement (DCE), bolus injection is performed using an automatic device.

3) Imaging method

a) PET

In accordance with procedures for PET or PET/CT examinations, the whole-body emission scan is generally performed at about 60 minutes after the FDG injection. A delayed image is obtained after at least 2 hours postinjection, as needed.

b) MRI

Whole-body MRI for attenuation correction of PET (acquisition of MRI images for attenuation correction of PET images, including the Dixon technique; MR-transmission, thereafter) is performed. Also, STIR sequence or fat-suppressed T2-weighted imaging (for evaluation of distant metastasis), or contrast-enhanced T1-weighted imaging is performed as needed. For detailed assessment of lung field lesions and hilar or mediastinal lymph nodes, ECG-gated imaging, DWI, or STIR with Dark-blood (DB) technique under respiratory gating or breath holding conditions is performed.

(3) Cautions for diagnostic image interpretation

Particularly during diagnosis of lung cancer, inflammatory uptake in the hilar or mediastinal lymph nodes due to chronic inflammation in the lung fields may be observed; the inflammation needs to be carefully differentiated from lymph node metastasis. Because the spatial resolution of PET imaging is limited, low uptake in small lesions or tumors with low cell density may generate false-negative results.

In MRI, because of the susceptibility artifacts caused by air and low proton density in the lung fields, assessment of small or air-containing lesions could be difficult. In DWI or the STIR sequence, signal intensity may be high in normal lymph nodes, which consequently need to be carefully differentiated from metastasis.

3-3-2. Mediastinal tumor

(1) Clinical significance

MRI is useful for qualitative diagnosis of mediastinal tumors (especially for detection of fat components using chemical shift imaging, [54)] and hemorrhagic components, necrosis, cystic degeneration, and blood flow [55,56)]). Glucose metabolism in lesions is assessed by FDG-PET, which is considered useful for grading of the lesions, treatment response evaluation, and prognosis prediction. [57,58)] Combining these two imaging modalities may provide more detailed diagnosis. MRI also has good contrast resolution and is useful for assessing the extent of lesions in the mediastinum. The addition of DWI or gadolinium enhancement to MRI enables differentiation of benign from malignant lesions, assessment of viability, and evaluation of an early treatment response. [59,60)]

(2) Examination procedures

1) PET

Procedures are in accordance with those used for lung cancer.

2). MRI

Whole-body MRI data are used for the attenuation correction of PET images (including the Dixon technique). Also, STIR sequence or fat-suppressed T2-weighted imaging (for evaluation of distant metastasis) or contrast-enhanced T1-weighted imaging is performed as needed.

For detailed diagnosis of mediastinal tumors, imaging under respiratory gating or breath holding conditions is combined with the dark blood (DB) technique. For detection of fat components, T1-weighted in/out-of- phase imaging is effective.

(3) Cautions for diagnostic image interpretation

MRI alone is not suitable for detection of calcified components that are important in the diagnosis of mediastinal tumors, and MRI data need to be combined with CT data. In MRI, especially when not combined with the DB technique, flow artifacts from vessels in the mediastinum sometimes impede diagnosis. In those cases, a change of phase direction is needed to prevent artifacts from obscuring

the lesion.

3-3-3. Pleural mesothelioma

(1) Clinical significance

MRI is superior to CT in assessment of the extent of pleural lesions, particularly those on the surface of the diaphragm. [61,62)] In combination with dynamic imaging or DWI, MRI is also useful for differentiating benign from malignant pleural lesions. [63)] Treatment response can be evaluated by quantitatively assessing the dynamic MR image or measuring tumor volume, although the evaluation requires time-consuming image processing. [64,65)] On the other hand, data on glucose metabolism obtained with FDG-PET is useful for treatment response evaluation and prognosis prediction and can be assessed more easily than MRI data. [66-72)] The diagnostic performance of the combination of these two methods may be better than that of PET/CT.

(2) Examination procedures

1) PET

Procedures are in accordance with those for examination of lung cancer.

2) MRI

Whole-body MRI data are used for attenuation correction of PET images (including the Dixon technique). Also, STIR sequence or fat-suppressed T2-weighted imaging (for evaluation of distant metastasis), or contrast-enhanced T1-weighted imaging is performed as needed. Pleural lesions are assessed mainly on coronal or sagittal images. 3D imaging of the whole pleura might be done, but it requires high spatial resolution and prolonged imaging time. For assessment of blood flow in pleural lesions, dynamic imaging is used. When temporal resolution is improved, perfusion data can be evaluated quantitatively, to help differentiate benign from malignant tumors and evaluate the treatment response.

(3) Cautions for diagnostic image interpretation

Since pleura are widely distributed in the chest cavity and tumors invade diffusely, images with high spatial resolution should be used to determine tumor extent; however, its imaging time tends to be prolonged.

3-4. Breast

(1) Clinical significance

Glucose metabolism is generally increased in breast cancers, most of which show intense uptake of FDG. Small-sized lesions, however, frequently show low uptake. Detection or accurate evaluation of the extent of those small lesions may be difficult with FDG-PET alone. Breast MRI is considered to have the highest sensitivity for detection of lesions (i.e., 90% [52–100%]) and a specificity of 72%

(21–100%). [9,23,73-76] Therefore in Japan, breast MRI is widely used for qualitative diagnosis or evaluation of tumor extent. On the other hand, pseudolesions are sometimes detected because uptake by benign lesions and normal mammary gland is enhanced, thus slightly reducing the specificity of breast MRI. In addition to the classification of mass or non-mass lesions and the morphological data, blood flow data obtained by using contrast enhancement (analysis of dynamic blood flow) improve diagnostic performance. FDG-PET combined with MRI makes possible the detection of small lesions that are difficult to detect with PET alone. [77] Detection of confusing pseudolesions by MRI alone needs to be decreased. Construction of a fused PET/MRI image may improve the accuracy of evaluations of tumor extent and qualitative diagnosis. For differentiation of mass lesions found by palpation or other examinations, pathological diagnosis using ultrasound- or mammography-guided needle biopsy is preferred. Therefore, use of PET/MRI is not recommended for the sole purpose of differentiating benign from malignant mass lesions.

Diagnosis of axillary lymph node metastasis is important for staging and risk stratification. The sensitivity and specificity of MRI is reported to be 90% (65–100%) and 90% (54–100%), respectively, and that of PET is reported to be 63% (20–100%) and 94% (75–100%), respectively. [78-82] Because MRI or PET alone does not have an adequate sensitivity, confirmation of the presence or absence of metastasis diagnosed by sentinel lymph node biopsy cannot be omitted at present. Given the high specificity of PET, however, positive nodes on PET can be regarded as clinically positive. The combination of PET and MRI may further improve diagnostic performance.

Because changes in metabolism precede those in size, evidence of progression or improvement can be detected earlier by examining uptake intensity than by examining changes in diameter or blood flow. From this perspective, evaluation of the early response to chemotherapy (after 1–2 courses of treatment) has been attempted. When response to the drug used is known early, disease progression can be prevented by switching from the ineffective drug to an appropriate one, thereby reducing the usage of ineffective medications, which may be economically beneficial. For determining complete remission during the final evaluation of the treatment response, MRI is considered to be specific, while FDG-PET/CT is considered to be sensitive. It is desirable to combine these modalities to improve diagnostic performance.

(2) Examination procedures

In the PET examination, breast or whole-body imaging is performed. In MRI, simultaneous bilateral breast imaging in a prone position using a breast-dedicated coil at high resolution is desirable. But in practice, availability of coils for PET/MRI systems is limited and balance with PET imaging should be considered. For delineating lesions, gadolinium-enhanced imaging is essential. Bolus injection of the agent at a standard dose of 0.1 mmol/kg with a saline flush is recommended. In breast cancers, enhancement peaks in the early phase (generally within 2 minutes), whereas enhancement increases gradually in most benign lesions or normal mammary gland tissues; therefore dynamic imaging

should be performed. During an imaging time of 2 minutes or less, images should be obtained before contrast enhancement, in the early phase (within 2 minutes), and in the delayed phase (5–7 minutes later). During imaging, concurrent use of fat suppression is recommended. Imaging at high resolution within a slice (1 × 1 mm or smaller; slice thickness, 3 mm or smaller) is also recommended.

When contrast enhancement cannot be used due to asthma or decreased renal function, patients should be considered ineligible for MRI evaluation of the mammary gland. Although useful as a reference, diffusion-weighted imaging alone cannot provide a diagnosis. It is also desirable to regard the results of T2-weighted imaging with fat suppression as reference findings.

In premenopausal women, uptake of contrast agent in the normal mammary gland depends on the menstrual cycle phase, and increased uptake in mammary gland tissue during the second 2 weeks of the menstrual cycle (luteal or secretory phase) is likely to generate false-positive results. Therefore, it is highly recommended that imaging be performed 5–12 days after the start of the menstrual cycle.

For constructing a fused image, use of PET and MRI images that best delineate the lesion is recommended. Thus, the early image obtained with dynamic MRI will be mainly used.

(3) Other considerations and cautions for the interpretation

BI-RADS (Breast Imaging Reporting and Data System), developed by the American College of Radiology (ACR), is used globally for the interpretation of breast MRI findings. Also, the use of common terms in reporting should be preferred in accordance with the BI-RADS. [85)] In PET/MRI examinations, however, most primary tumors may already be diagnosed and therefore categorical assessment of the degree of malignancy can be omitted. Treatment response evaluation with MRI is mainly based on changes in size. Although the Response Evaluation Criteria In Solid Tumors (RECIST) guideline (RECIST1.1) was developed for the purpose of response evaluation in clinical trials, it is commonly used in clinical practice. [86)] For evaluation of treatment response the changes in degree of uptake are recommended by the European Organisation for Research and Treatment of Cancer (EORTC) PET study group. [87)] PET Response Criteria in Solid Tumors (PERCIST) based on the measurement of SUV lean (SUL; SUV adjusted for lean body mass) proposed by Wahl et al.[88)] are useful as a reference.

3-5. Heart (non-malignant disease)

(1) Clinical significance

Although there has been little evidence of PET/MRI application to the field of cardiology, MRI examinations including cine MRI, delayed enhancement MRI, coronary MRA, and stress myocardial perfusion MRI are used for evaluating various kinds of heart diseases. [89-92)] Clinical advantage of simultaneous PET and MRI examinations over the combination of each individual test is largely unclear. Especially, it must be kept in mind that performing a stress test in a magnetic field requires

training and preparations in terms of safe testing. Considering the situation above, cardiac sarcoidosis might be a proper indication for PET/MRI examination.

(2) Cautions for performing cardiac PET/MRI examination safely

1) Equipment

Since it is assumed that patients with serious heart disease are examined, PET/MRI examination areas should be secured with following equipment before initiating clinical practice.

a) 12-lead electrocardiography (ECG) devices

b) Equipment required for exercise or pharmacological stress tests (such as the ergometer)

c) ECG monitoring devices usable in the MRI room (also capable of measuring blood pressure, pulse, and oxygen saturation)

d) Emergency call alarm systems

e) Defibrillators

f) Emergency carts (carrying a set of tools for emergency aid)

2) Preparation for emergency evacuation of patients from PET/MRI room

The procedure of emergency aid needs to be practiced routinely and manualized. If it is considered difficult to handle problems related to patient conditions in a PET/MRI room, the patient should be evacuated promptly and safely.

3) Preparation for possible adverse reactions to drugs or contrast media

Since imaging protocols of cardiac PET or MRI may differ among institutions, possible adverse reactions to drugs or contrast media should fully be understood at each institution. Also, the treatment procedure needs to be practiced routinely and manualized. Supplies and drugs for the treatment (probably in the emergency cart) should be checked periodically.

4) Informed consent

Types of tracers or preparation methods for PET are probably different depending on the purpose of the examinations. Also, imaging procedures including use of contrast media for MRI may be changed by the corresponding simultaneous PET examinations; details of the series of PET/MRI examinations should be explained before informed consent is obtained from patients.

(3) Cardiac indications for PET/MRI examination

As of August 2012, a large amount of evidence has indicated the usefulness of either cardiac PET or MRI examination. However, there has been little information about integrated PET/MRI scanner in the field of cardiology. There may be some cardiac diseases in which simultaneous or sequential PET/MRI acquisition is more useful than the combination of separate PET and MRI acquisitions:

1) Cardiac sarcoidosis

In patients with cardiac sarcoidosis, regions of abnormal FDG uptake on FDG-PET after appropriate preparation is considered to represent active inflammation.[93,94)] In addition, it is reported that regions showing contrast enhancement areas on MR images obtained 10-15 min after the injection of

contrast media (so-called “delayed enhancement”) were not consistent with abnormal FDG uptake areas; the discrepancy may be explained by the fact that delayed enhancement represents myocardial fibrosis. [95] Simultaneous PET/MRI data acquisition allows to clearly demonstrate not only the intramyocardial distributions of inflammation and fibrosis but disease activity in cardiac sarcoidosis.
2) Ischemic heart disease (excluding acute phase): please refer to section 2, “Ischemic heart disease”.
Either MRI or PET is proven to be useful for evaluation of ischemic heart disease. However, given that the imaging findings offered by the two examinations possibly include similar information from the clinical point of view, imaging protocol should carefully be determined on the basis of safety concerns and time constraints (especially when the stress test is performed).
3) Acute ischemic heart disease, cardiomyopathy, and others
Although neither examination is covered by insurance at present, comparison of MRI (which provides anatomical information and blood flow) with PET (which provides metabolic condition) in acute ischemic heart disease and cardiomyopathy is worth investigating.
(4) Disease-specific PET/MRI examination protocol
For cardiac MRI examinations, please refer to the protocol suggested by the Society of Cardiovascular Magnetic Resonance (SCMR), which aims to expand clinical use, standardization, and improve the quality of the examination. [96] A feasible and safe protocol for simultaneous MRI and PET examinations, should be developed. Guidelines for PET examination of ischemic heart disease are suggested by the Japan Circulation Society. [97] The basic protocol for FDG-PET examination of cardiac sarcoidosis is as follows: restriction of sugar intake for 24 hours; administration of heparin at 50 IU/kg, followed by FDG injection 15 minutes later; and the start of imaging 60 minutes later. However, this procedure will possibly be modified after the evidence concerning cardiac sarcoidosis is further accumulated.

3-6. Upper abdomen
3-6-1. Upper abdomen (Overview)
(1) Clinical significance [9,98]
Glucose metabolism is generally increased in malignant tumors, most of which show intense uptake of FDG. Most benign tumors show low uptake. In FDG-PET, diagnosis is based on metabolic activity instead of morphology or size of the lesion as in CT or MRI, and diagnostic accuracy is commonly higher than that in CT or MRI. In principle, FDG-PET is considered to be effective for detection of almost all cancers in which glucose metabolism is increased.
(2) Examination procedures (common procedures for upper abdominal MRI)
Following the sequence for attenuation correction, coronal fast spin echo (SE) T1-weighted or short-tau inversion recovery (STIR) MR images, or single-shot fast SE T2-weighted MR images are obtained for the primary purpose of mapping. Additional sequences that are considered necessary for

each organ are described in each subsection. Unless otherwise indicated, a transverse image is obtained.

3-6-2. Upper abdomen (Specifics)

3-6-2-1. Liver tumors (including hepatocellular carcinoma, cholangiocellular carcinoma, and metastatic liver cancer)

(1) Clinical significance

MRI has excellent tissue contrast and delineates liver tumors well. [22,99-103)] In addition to providing mapping images for PET, MRI is useful for qualitative diagnosis. [22,99-103)] Simultaneous imaging of PET and MRI has a great advantage. For the diagnosis of metastasis to lymph nodes or other organs and the assessment of primary lesions, which is required in cases with metastatic liver cancer, the PET/MRI combination is believed to perform at least as well as PET/CT. [22,99-103)] PET/MRI, which provides both PET and MRI data, is also expected to be useful for diagnosis of recurrence, treatment selection, and treatment response evaluation. [22,99-103)]

(2) Examination procedures (for MRI)

In patients with hepatocellular carcinoma, T1-weighted in-phase and opposed-phase images with 2D dual gradient echo (GRE) sequences, as well as fat-suppressed fast SE T2-weighted images, are added. [103)] For the assessment of liver tumors, diffusion-weighted or intravenous contrast-enhanced MR images may be added.

3-6-2-2. Biliary tract tumors (including gallbladder cancer and bile duct cancer)

(1) Clinical significance

The gallbladder and bile duct are easily recognizable on T2-weighted MR images because of the presence of bile. When magnetic resonance cholangiopancreatography (MRCP) is combined with T2-weighted MRI, conditions can be grasped more accurately. [104-106)] The performance of simultaneous PET and MRI imaging is expected to be at least equivalent to that of existing PET/CT imaging for the assessment of primary lesions, diagnosis of metastasis or recurrence, treatment selection, and treatment response evaluation. [104-106)]

(2) Examination procedures (for MRI)

For delineating gallbladder and bile duct, coronal and oblique images are added. MRCP images are obtained by using an oral contrast agent.

3-6-2-3. Pancreas (including pancreatic cancer and pancreatic neuroendocrine tumor)

(1) Clinical significance

Normal pancreatic parenchyma shows higher signal intensity than liver on T1-weighted MR images due to high protein content of the pancreatic juice. Specifically, the pancreatic parenchyma is clearly

delineated on fat-suppressed T1-weighted images, which serve as good mapping images for PET. T2-weighted images are useful for determining the degree of dilatation of main pancreatic duct or detecting cystic lesions. [103,107-109)] The performance of simultaneous PET and MRI imaging is expected to be at least equivalent to that of existing PET/CT imaging for the assessment of primary lesions of pancreatic cancer, diagnosis of metastasis or recurrence, treatment selection, and treatment response evaluation. [103,107-109)]

(2) Examination procedures (for MRI)

Fat-suppressed T1-weighted images are added.[112)] MRCP images are obtained by using an oral contrast agent.

3-6-2-4. Stomach, small intestine, and others (including gastric cancer and gastrointestinal stromal tumor)

(1) Clinical significance

As of 2012, PET examination for early gastric cancer is not covered by insurance, and the combination of PET and MRI seems to make little contribution in clinical practice. For non-early-stage gastric cancers, the role of PET/MRI is limited to the detection of distant (liver) metastasis and the diagnosis of recurrence. [109,110)]

Gastrointestinal stromal tumor: Given that MRI has excellent tissue contrast and provides mapping images for PET, PET/MRI is expected to be useful for diagnosis of metastasis or recurrence. [111,112)] Given the excellence of MR images, PET/MRI is also believed to be useful for evaluation of the response to molecular-targeted therapy, which is not covered by insurance at present. [111,112)]

(2) Examination procedures (for MRI)

Fat-suppressed fast SE T2-weighted images or diffusion-weighted images are added.

3-7. Rectum

(1) Clinical significance

Glucose metabolism is generally increased in rectal cancers, most of which show intense uptake of FDG. Small-sized lesions, however, often show low uptake, which may not be detected or distinguished from physiological uptake in the large intestine[9,113)]. Accurate evaluation of the extent of the lesion may be difficult with FDG-PET alone. Rectal MRI has a high degree of accuracy in delineating rectal cancer, with a reported sensitivity and specificity of 87% and of 75%, respectively for assessing local depth of invasion and 77% and 71%, respectively, for diagnosing lymph node metastasis[114)]. Rectal MRI is used for qualitative diagnosis and evaluation of the extent. MRI alone does not have sufficient accuracy for diagnosing metastasis to lymph nodes, including lateral nodes, which are important for staging and therapeutic decision-making (operative procedures, indications for chemoradiation). Combined FDG-PET and MRI is reported to have increased sensitivity,

specificity, positive predictive value, and negative predictive value, and may improve diagnostic performance[115].

In the assessment of local recurrence of rectal cancer, MRI examination is reported to have a sensitivity of 84–100% and a specificity of 74–83%. The accuracy may be further improved by the addition of functional MRI, including diffusion-weighted imaging (DWI)[116,117]. However, imaging findings obtained in locally recurrent lesions of rectal cancer vary due to fibrosis, edema, or scars associated with treatment, and therefore differentiation is often difficult with MRI alone. FDG-PET combined with MRI may improve diagnostic performance[118,119]. Although local recurrence is frequently associated with metastasis to other organs, patients with local recurrence without involvement of other organs are eligible for surgical resection, and therefore an efficient and accurate search for metastasis is desired. PET is a very sensitive detector of metastasis to other organs. By combining MRI with PET, efficient and accurate detection of local recurrences and distant metastases may become possible.

Diagnosis with MRI after chemoradiation is currently based mainly on morphological analysis. It is used to assess changes in tumor size and tumor-free margin as prognostic factors[120]. It has also been reported that addition of functional MRI, including DWI, may enable more accurate assessment. FDG-PET combined with MRI (functional MRI) may be used for evaluation of the early response to chemotherapy[121]. When it is known whether the tumor is unresponsive to a drug, disease progression can be prevented by switching the ineffective drug to an appropriate one, thereby reducing the usage of ineffective medications, which may be economically beneficial.

For differentiation of mass lesions in the rectum, pathological diagnosis is based on colonoscopy preferably with biopsy. Therefore, use of PET/MRI is not recommended for the sole purpose of differentiating benign from malignant lesions.

(2) Examination procedures

For evaluation of the rectum, patients are examined in the supine position with the pelvic region placed between phased-array coils. Endorectal coils are not commonly used because the imaging techniques are complicated and the imaging range is limited. For patients who have no contraindication, administration of anticonvulsant is recommended in order to reduce artifacts.

For delineating primary lesions, T2-weighted thin-section MRI (in-plane resolution, about 0.6 × 0.6 mm; slice thickness, 3 mm) is considered useful. Good contrast between the three-layered structure of the bowel wall and the tumor is obtained. Degree of intramural and extramural invasion of the primary lesion, involvement of the surrounding organs, and metastasis to other organs, including lymph nodes, may be evaluated. T1-weighted images are regarded as less useful for assessing depth of invasion. Although useful as a reference, DWI alone cannot provide diagnosis. Analysis of blood flow data (dynamic curve analysis) using gadolinium as a contrast agent has been attempted, but this method is not common. The significance of contrast-enhanced images in preoperative diagnosis of

rectal cancer has not been established.
After neoadjuvant chemoradiation or in cases with local recurrence of rectal cancer, lesions may not be clearly delineated from anatomical data alone on T2-weighted images, because of fibrosis, edema, or scars associated with treatment. Gadolinium-enhanced examination will help diagnosis.
For constructing fused PET/MRI images, use of PET and MRI images that best delineate the lesion is recommended. Thus, T2-weighted MR images will be mainly used.
(3) Cautions for diagnostic image interpretation
For high-resolution MRI of the rectum, bowel preparation with enemas or rectal infusions of water or jelly has been attempted in order to improve delineation of lesions, but the effectiveness and impact of these measures during PET/MRI examination are unknown.

3-8. Urinary organs[9,122-134)]
(1) Clinical significance
Localization and qualitative diagnosis of urological cancers, including those of kidney[122-124)], renal pelvis, ureter, urinary bladder[125,126)], and prostate[125)], are often difficult with PET alone due to intense tracer uptake in the urinary tract[127-129)]. In the anatomically complex pelvis, distinguishing physiological uptake in the ureter or other organs from pathological uptake in tumors or lymph nodes is frequently complicated. With non-enhanced CT, tissue contrast between these urological cancers and each primary organ is poor and localization can be difficult. For these reasons, diagnostic performance for urological cancers has not dramatically improved even with combined PET/CT, which has not been widely applied[9)].
MRI provides better tissue contrast resolution compared with CT or PET, and its usefulness for urological cancers has been established. In Japan, MRI is already widely used in clinical practice, for detection, qualitative diagnosis, evaluation of response to chemotherapy or radiotherapy, and diagnosis of recurrence. By using MRI, the relationship with surrounding organs can be easily assessed in the anatomically highly complex pelvic region (including ureter, bladder, and prostate), and lymph nodes and vessels can be delineated accurately. With MRI using contrast agents, anatomical analysis, functional imaging (such as DWI and MR spectroscopy), or analysis of blood flow data (dynamic curve analysis) may be possible, resulting in improved qualitative diagnostic performance[130,131)]. Combining PET with MRI, which has a good performance in detection and qualitative diagnosis, may improve diagnostic performance of PET in urological tumors.
Because changes in metabolism precede those in size, progression or improvement can be detected earlier by examining uptake intensity than by examining changes in diameter or blood flow. PET evaluation of the response to chemotherapy containing molecular-targeted drugs for urological cancers has recently been attempted[132)]. When it is known that the tumor is unresponsive to a drug, disease progression can be prevented by switching from the ineffective drug to an appropriate one,

thereby reducing the usage of ineffective medications, which may be economically beneficial.

(2) Examination procedures

Patients are examined in the supine position with the region that completely includes organs of interest placed between phased-array coils. T2-weighted imaging, which has excellent tissue contrast resolution and clearly delineates anatomical structures, is fundamental. It is combined with T1-weighted imaging, gadolinium-enhanced dynamic imaging, diffusion-weighted imaging (DWI), or MR spectroscopy (for prostate cancer). For imaging of the pelvic region, administration of an anticonvulsant is recommended to reduce artifacts in patients without contraindications.

T1-weighted imaging, T2-weighted imaging, DWI, and gadolinium-enhanced dynamic imaging are used for cancers of the kidney, renal pelvis, ureter, urinary bladder, and prostate. Clear cell renal cell carcinoma, which accounts for about 70% of renal cell carcinomas, is known to contain lipids in the cytoplasm. For this carcinoma, lipids can be detected on T1-weighted in-phase and out-of-phase images, which will help diagnosis[133)]. For renal pelvis and ureter cancers, whole images, extending from the renal pelvis to the ureter, can be obtained with MR urography. For bladder cancer, urine volume in the bladder may affect morphology of lesion or change delineation. Balance with PET imaging might be an issue. For dynamic imaging of bladder cancer, contrast obtained at about 90 seconds after contrast agent infusion is suitable for diagnosis[134)]. For prostate cancer, because T2-weighted imaging alone has a low accuracy for localization, DWI, dynamic imaging, or MR spectroscopy is added to improve diagnostic performance. Although accuracy for localization of prostate cancer is increased by using an endorectal coil, imaging procedures involving the coil are complicated, imaging range is limited, and these procedures are far from common in Japan.

Even when contrast-enhanced examination cannot be performed because of asthma or reduced renal function, primary lesions of urological cancers can be identified with T2-weighted imaging, DWI, or a combined sequence in most cases. For constructing fused images, use of PET and MRI images that best delineate the lesion is recommended. Thus, dynamic MR or T2-weighted MR images will be mainly used.

(3) Cautions for diagnostic image interpretation

For prostate MRI, the rectal lumen may be emptied by enema or laxative administration as a preparation in order to reduce artifacts, but the effectiveness and impact of these measures during PET/MRI examination are unknown.

3-9. Female Pelvis

(1) Clinical significance

Positron emission tomography (PET) using [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) is frequently used for the diagnosis, staging, and follow-up surveillance for recurrence of gynecologic cancers.

1. Ovarian Cancer

Because glucose uptake during the menstrual cycle from ovulation to luteinization increases temporarily even in normal ovaries, the detection sensitivity for small primary lesions is not particularly high. In ovarian cancer cases, the formation of cystic masses is common and uptake is abnormal in septa and solid components. PET/CT is most commonly used for staging, although it also has an important role as an alternative to re-staging and second look surgery prior to second reductive surgery. The usefulness of PET/CT for diagnosis of dissemination is high[135-137)].

2. Endometrial Cancer

MRI data are crucial in determining the extent of primary lesion progression, and PET/MRI is useful in diagnosing early stage cancer with superficial endometrial spread or progressive cancer with deep myometrial invasion. While the diagnostic accuracy of lymph node metastasis varies greatly depending on the size of the nodes, its usefulness in assessing swollen lymph nodes of 10–12 mm or larger is high[138,139)]. As with PET/CT, PET/MRI is thought to make a concrete contribution to the diagnosis of distant metastasis and recurrent neoplasms. Further, future investigation may be warranted into its use in assessing treatment response, activity of residual tumors, and the need for additional treatment.

3. Cervical Cancer

PET/MRI (as with MRI alone or PET/CT) can provide visualization of most cancers stage 1b and above, and detection sensitivity is thought to be high. PET/MRI is very useful for assessing the extent of local progression, for which PET/CT has limited value. In particular, PET/MRI can provide a more detailed assessment of cervical cancer with invasion into the corpus, vagina, and parametria. In cervical cancer as with endometrial cancer, the accuracy of lymph node diagnosis varies significantly depending on the size of the lymph node. Assessment is thought to be accurate if the nodes are at least 10–12 mm or more in diameter [140,141)]. As with PET/CT, PET/MRI is thought to be useful for diagnosis of distant metastasis and recurrent neoplasms. Further, future investigation may be warranted into its use in assessing treatment response, activity of residual tumors, and the need for additional treatment.

(2) Examination procedures

1. Dose and administration route of FDG

FDG is administered intravenously at a dose of 185–444 MBq (3–7 MBq/kg) for 2D and 111–259 MBq (2–5 MBq/kg) for 3D data acquisition. The dose of FDG is increased or decreased according to the model used for imaging and the age and weight of patients.

2. Imaging procedures

At 60 minutes after the FDG injection, a whole-body emission scan and MRI are performed using a PET/MRI system.

In the MRI, a (1) scout image, (2) transverse T1-weighted image for attenuation correction (gradient echo sequence, 3D acquisition, and thin slice), (3) sagittal T2-weighted image, and (4) transverse

T2-weighted image must be acquired; fat suppression should be combined as necessary. For some organs, a (6) coronal (fat-suppressed) T2-weighted image is additionally acquired depending on the site or morphology of primary tumor. Diffusion-weighted imaging with apparent diffusion coefficient (ADC) measurement is useful for detection of primary and lymph node lesions, and may play a complementary role when concurrently used with FDG-PET. MR spectroscopy (MRS) can provide additional information on metabolism of various compounds other than glucose and therefore may be useful when combined with FDG-PET. The PET and MRI acquisition parameters are set according to the specifications of each model used.

(3) Cautions for the interpretation

1. Ovarian cancer

During the menstrual cycle, as uptake by corpus luteum cysts is seen following ovulation, the appropriate time for imaging is within one week following the end of the menstrual cycle. For largely cystic tumors or stromal tumors with low cellularity, particularly borderline malignant tumors, mucinous cystadenocarcinoma, well-differentiated serous cystadenocarcinoma and others, uptake is low.

Ovarian cancer causes peritoneal metastasis in a large number of cases, although detection with PET/MRI is anticipated to enable PET/CT to discover diffuse lesions difficult to detect with CT alone. Matching with the site is very important for diagnosis, with particular attention required to sites of predilection including the pouch of Douglas, small bowel mesentery, ileocecal region, left and right paracolic gutters, Morison’s pouch, right sub-phrenic space, umbilical subcutaneous nodules, and greater omentum.

2. Endometrial cancer

Many early-stage cancers without myometrial invasion do not exhibit any significant uptake. When the orifice of the fallopian tubes is enlarged, observation of abnormal uptake extending to the adnexa makes it easy to establish the extent of disease progression. Meanwhile, when progression is extensive, the possibility of peritoneal dissemination should be kept in mind, and attention should be paid to the presence or absence of abnormal extraluminal uptake in the pelvis.

3. Cervical cancer

As with diagnosis through MRI, carcinoma in situ or stage Ia cancer may not be visualized by FDG-PET/MRI. Uptake of FDG by adenomyosis, uterine leiomyoma, menorrhagia, and inflammation is known to produce false positive results, and uptake of FDG by well-differentiated cervical adenocarcinoma and borderline lesions is known to produce false negative results[142)]. For bladder and rectal invasion, the presence or absence of continuous uptake must be ascertained at this point, although differentiation from excretory uptake and physiological uptake is problematic.

3-10. Musculoskeletal System

(1) Clinical significance

The accelerated glycometabolism seen in malignant tumor cells is observable because of abnormal uptake of the glucose analog [^{18}F]-Fluoro-2-Deoxy-D-Glucose (FDG) on FDG-PET. The current mainstream PET/CT examination procedures enable simultaneous metabolic and morphological image diagnosis in one sitting and have been used for staging, metastasis/recurrence diagnosis, and treatment response evaluation of malignant tumors[9,143-147], although the low tissue contrast resolution has been problematic. As PET/MRI of musculoskeletal tissue provides high contrast resolution images, it possesses diagnostic performance for malignant musculoskeletal tumors that is unachievable with PET/CT.

The diagnostic performance of PET/MRI is reported to be almost equal to that of conventional PET/CT for both visual and semiquantitative evaluation. The usefulness of PET/MRI for staging malignant musculoskeletal tumors (determining the extent of progression for primary tumors (T), the presence or absence of regional lymph node metastasis (N) and distant metastasis (M)) is reported as described below. Regarding T-factor, the implementation of the high contrast resolution of MRI has been useful in quantifying the extent of tumor invasion[148], enabling diagnostic performance to surpass that of PET/CT. For N-factor, the diagnostic performance of PET/MRI is reported to be equal to that of PET/CT[149]. For M-factor, the diagnostic performances of PET/MRI and PET/CT are equivalent, although the diagnostic performance of PET/MRI is said to be better for liver metastasis and bone (bone marrow) metastasis[150]. Using PET/CT to assess the early effect of chemotherapy against high-grade malignant soft tissue sarcoma, a reduction in the semiquantitative standard uptake value (SUV) is reported to reflect tumor necrosis. Further, it is reported as a potential important biomarker for estimating prognosis[23,151-157]. In this way, PET/MRI is thought to be useful for assessing the effect of early treatment. In addition, MR spectroscopy using 3 Tesla MRI has been reported to be useful in distinguishing benign from malignant musculoskeletal tumors[156]. A choline peak is said to be a malignancy marker.

(2) Examination procedures

The decision whether to use whole body PET/MRI or localized PET/MRI depends on the patient and the purpose of testing. The field of view (FOV) can differ between whole body and localized PET/MRI and influence detectability of the lesion site. Careful consideration is required when choosing between these two modalities.

The basic scans conducted to accurately evaluate the signal strength of tumor tissue are T1-weighted and T2-weighted spin echo images. Additional fat-suppressed T2-weighted images and diffusion-weighted images are also acquired. Image evaluation is conducted using transverse, sagittal, or coronal sections. T2-weighted or fat-suppressed T2-weighted images are recommended for fused PET/MRI images, although this can be modified as appropriate to the case in question. A high

signal-to-noise ratio can also assist in shortening the exposure time. Parallel imaging using multi-channel coils is useful in reducing time. When conducting imaging of the musculoskeletal system, the placement of braces can cause problems including the expansion of metal artifacts. In these cases, interactive decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL), which is an alternative to the 3-point Dixon method, can reduce susceptibility artifacts, enabling the acquisition of satisfactory fat-suppressed images. While there is little need to use contrast enhancement with MRI, contrast-enhanced MRI is useful in differentiating solid from cystic tumors, and comparing contrast-enhanced MRI with PET images can also be useful in determining the appropriate site for biopsy.

(3) Cautions for the interpretation

1) Uptake by some low-grade malignant musculoskeletal tumors is not high, and low uptake does not necessarily eliminate the possibility of a high-grade malignant musculoskeletal tumor.

2) Due to problems with spatial resolution on PET, uptake can be overestimated in lesions with a small tumor diameter.

3) Abnormal uptake by active inflammation or granulomatous disease occurs frequently, and is hard to distinguish from abnormal uptake by a malignant tumor.

3-11. Malignant Melanoma

(1) Clinical significance

Glycometabolism in malignant melanoma lesions as with lesions of other malignant tumors is generally accelerated, and while detection in some cases can be difficult because of the size and site of the lesion, uptake of FDG is high in many lesions. For diagnosis of lymph node metastasis, a sentinel lymph node biopsy is performed clinically for tumors that exceed invasion depth of 1 mm[158)]. This is because the sensitivity of ultrasound, CT, PET, and PET/CT is insufficient, although both PET and PET/CT have high specificity[158-161)]. In contrast to CT or MRI diagnosis, which is based on morphology and size of the lesion, FDG-PET diagnosis is based on metabolic activity, meaning that it often has a higher diagnostic accuracy than CT or MRI, and, except for small-diameter micrometastasis, its diagnostic performance is excellent. Further, only in patients positive for sentinel lymph node metastasis, FDG-PET can be used to screen for and detect unforeseen distant metastasis[160)]. Successful chemotherapy for malignant melanoma is known to result in a drop in glycometabolism prior to changes in lesion morphology or reduction in size. Measuring the effect of chemotherapy using FDG-PET at an early stage enables more precise measurement of the tumor marker S-100, and may be useful in deciding on a suitable treatment plan[161)]. For tests using PET/MRI equipment, the MRI information obtained at the same time may be added to PET information, increasing the accuracy of abnormal uptake detection that would otherwise be difficult to evaluate using PET alone. PET/MRI is useful for detecting melanoma

metastasis to subcutaneous tissue, bone, liver, and brain[162-166]. Also, while there is no evidence, it can be inferred from the results of PET/CT research that PET/MRI whole body scans can assist the diagnosis of lymph node metastasis and distant metastasis in high-risk malignant melanoma cases.

(2) Examination procedures

1. Dose and administration route of FDG

FDG is administered intravenously at a dose of 185–444 MBq (3–7 MBq/kg) for 2D and 111–259 MBq (2–5 MBq/kg) for 3D data acquisition. The dose of FDG is increased or decreased according to the model used for imaging and the age and weight of patients.

2. Imaging procedures

At 60 minutes after the FDG injection, a whole-body emission scan and MRI are performed using a PET/MRI system.

In the MRI, a (1) scout image, (2) transverse T1-weighted image for attenuation correction (gradient echo sequence, 3D acquisition, and thin slice), (3) transverse (fat-suppressed) T1-weighted image, (4) coronal (fat-suppressed) T1-weighted image, and (5) transverse (fat-suppressed) T2-weighted image must be acquired. For some organs, a (6) coronal or sagittal (fat-suppressed) T2-weighted image is additionally acquired depending on the site or morphology of the primary tumor. Diffusion-weighted imaging (particularly whole body scans) with ADC measurement is useful for detection of primary and lymph node lesions, and may play a complementary role when concurrently used with FDG-PET. MR spectroscopy (MRS) can provide additional information on metabolism of various compounds other than glucose and therefore may be useful when combined with FDG-PET. The PET and MRI acquisition parameters are set according to the specifications of each model used.

(3) Cautions for the interpretation

When the primary lesion is either on the sole of the foot or unclear, the scan extending from the head to the soles is examined. For small primary or metastatic lesions on the soles of the feet, the possibility of false negatives should be considered. As FDG uptake by intracranial lesions is contiguous with physiological uptake in the brain, evaluation can be difficult. MRI is useful for evaluation of the progression of these lesions.

3-12. Malignant lymphoma and other hematopoietic malignancies

(1) Types of malignancies

Malignant lymphomas, leukemia, multiple myeloma, and other neoplasms

(2) Application

1) Staging

a) For patients with histopathologically confirmed malignant tumors that cannot be staged by other examinations or imaging studies

b) For patients without histopathologically confirmed malignant tumors that findings (i.e., medical

history, physical examination, other imaging findings, tumor markers, clinical follow-up) suggest are malignant with a high probability and that cannot be staged by other examinations or imaging studies.

2) Test for recurrence

a) For patients with clinical signs and test findings suggesting metastasis or recurrence that cannot be established by other examinations or imaging studies

b) For patients with deformity or scarring due to surgery or radiotherapy who manifest recurrence of the disease, which cannot be confirmed by other examinations or imaging studies

3) Treatment decision

a) For patients receiving adjuvant chemotherapy or chemoradiotherapy in whom staging cannot be established by other examinations or imaging studies

b) For patients with residual tumors confirmed by other imaging modalities after effective treatment with favorable course who require further imaging to differentiate malignant from benign non-tumorous tissues such as granuloma and fibroma

4) Response evaluation

a) For patients undergoing chemotherapy whose continuation of the current treatment or switch to another protocol needs to be decided, but whose early response is difficult to evaluate with other examinations or imaging studies

b) For patients, after the completion of chemotherapy or chemoradiation, whose response is difficult to evaluate with other imaging studies because of limited change in size or residual scar-like tissue

c) For patients receiving treatment with molecular-targeted drugs for malignant tumors, such as rituximab for malignant lymphoma, whose response needs to be evaluated early

(3) Clinical significance

FDG-PET is commonly used for staging, test for recurrence, evaluation of response to treatment, and prediction of response in patients with malignant lymphomas.

High FDG uptake was observed in most types of malignant lymphomas, excluding extranodal marginal zone lymphomas such as small lymphocytic lymphoma and mucosa-associated lymphoid tissue-derived (MALT) lymphoma[166,167].

Wirth et al. evaluated the usefulness of FDG-PET for treatment decisions, localization of tumors, and staging in 42 patients with untreated follicular lymphoma[168]. FDG-PET had a sensitivity of 97% (37/38, 95% confidence interval, 86% to 100%) and suggested a change of stage or change in management in 19 patients (45%; 95% CI, 30% to 61%). Seventeen patients (40%) were upstaged; the upstaging of 13 (31%) to stage III (12) or IV (1) altered their management. These results suggested the usefulness of FDG-PET in tumors with high FDG avidity.

Juweid et al. reported that the treatment response of aggressive (intermediate-grade) non-Hodgkin's lymphoma according to integrated International Workshop Criteria and evaluated by FDG-PET was

a statistically significant independent predictor of progression-free survival[169].

In 2007, Cheson et al. proposed a revision of the response criteria for non-Hodgkin's and Hodgkin's lymphoma. These incorporated FDG-PET, immunohistochemistry, and flow cytometry to standardize the response evaluation and definitions of end points in clinical study[170,171]. These criteria recommend the use of FDG-PET reflecting the FDG avidity of the lymphoma subtype and the relevant end points of the clinical trial. Diffuse large B-cell lymphoma (DLBCL) and Hodgkin's lymphoma are FDG-avid and potentially curable lymphomas; thus the use of revised response criteria is highly recommended for these lymphomas.

PET/MRI systems additionally provide simultaneously-obtained MRI data, and will enable more accurate detection of abnormal uptake, undetectable by PET alone. Malignant lymphoma lesions commonly develop in organs such as bone marrow, spleen, liver, and skin. PET/MRI systems are useful for detecting these lesions[23,172]. Although there is no evidence, it can be inferred from the results of PET/CT research that PET/CT whole-body emission scan may be useful for diagnosis of high FDG-avidity tumors such has DLBCL and Hodgkin's lymphoma.

(4) Examination procedures

1. Dose and administration route of FDG

FDG is administered intravenously at a dose of 185–444 MBq (3–7 MBq/kg) for 2D and 111–259 MBq (2–5 MBq/kg) for 3D data acquisition. The dose of FDG is increased or decreased according to the model used for imaging and the age and weight of patients.

2. Imaging procedures

At 60 minutes after the FDG injection, whole-body emission scan and MRI are performed using a PET/MRI system.

In the MRI, a (1) scout image, (2) transverse T1-weighted image for attenuation correction (gradient echo sequence, 3D acquisition, and thin slice), (3) transverse T1-weighted image, (4) coronal T1-weighted image, and (5) transverse T2-weighted image must be acquired; fat suppression should be combined as necessary. For some organs, a (6) coronal or sagittal (fat-suppressed) T2-weighted image is additionally acquired depending on the site or morphology of primary tumor.

Diffusion-weighted imaging (particularly whole body scans) with apparent diffusion coefficient (ADC) measurement is useful for detection of primary and lymph node lesions, and may play a complementary role when concurrently used with FDG-PET. MR spectroscopy (MRS) can provide additional information on the metabolism of various compounds other than glucose and therefore may be useful when combined with FDG-PET. PET and MRI acquisition parameters are set according to the specifications of each model used.

(5) Cautions for diagnostic image interpretation

1) Liver and spleen tumors: FDG-PET detects nodal tumors and most extranodal tumors in pre-treatment staging; however, assessment of tumors in some organs and tissues could be difficult.

The difficulty is due to limited visualization of tumors in tissues with high intensity background, or other characteristics of the tumor. Since the tumors in liver or spleen are detected by comparing them with normal tissues, visualization becomes difficult when normal tissues show high uptake. Hepatitis, hypersplenism, and infection should be considered as differential diagnosis.

2) Bone marrow tumors: treatment may increase the intensity of background of bone marrow and this may hamper diagnosis. In cases of B-cell lymphoma, diagnostic accuracy of bone-marrow invasion is generally estimated as 60% and the clinical usefulness is limited. Multifocal uptake in bone marrow is generally considered to be true positive, and diffuse uptake may represent false positive. Many cases of diffuse uptake, especially in Hodgkin's lymphoma, are related to myeloid hyperplasia and should be carefully evaluated[170]. When using PET/CT system, a morphological abnormality in the CT image is uncommon and helpful to diagnosis. Bone concentration increases in response to tumor treatment, while SUV decreases.

3) Brain tumors: The high intensity of the background of brain parenchyma often makes the detection of tumors difficult. These tumors show high avidity and nearly homogeneous uptake in many cases. Uptake is not homogeneous in cases other than primary malignant lymphoma. MRI should be used in combination when brain tumors are strongly suspected.

4) In the revised response criteria of Cheson, mediastinum is referred to evaluate uptake[170]. In the Deauville criteria (or London criteria) reported by Barrington et al., uptake is evaluated in the liver as well as the mediastinum[171]. When the uptake of the target lesion is higher than the mediastinum but lower than the liver, the treatment response is PR or SD. When the uptake in the target lesion is higher than in the liver, the treatment response is SD or PD[172]. Caution should be exercised to avoid the potential pitfall of misinterpretation stemming from differences in uptake between the liver and mediastinum[173].

3-13. Cancer of unknown primary origin

(1) Clinical significance

In FDG-PET, diagnosis is based on glucose metabolic activity, instead of morphology or size of the lesion as in CT or MRI. In principle, FDG-PET can detect primary tumors that are difficult to find by CT or MRI[174]. PET/MRI systems additionally provide simultaneously-obtained MRI data, and will enable more accurate detection of abnormal uptake undetectable by PET alone. Diffusion-weighted whole-body MRI is considered useful for whole-body screening as well as FDG-PET[175]. The combined use of these two technologies may detect tumors because the two mechanisms of detection (i.e., glucose metabolic activity and reduced diffusion) operate in a complementary manner.

(2) Imaging procedures

At 60 minutes after the FDG injection, a whole-body emission scan and MRI are performed using the PET/MRI system.

In the MRI, a (1) whole-body diffusion-weighted image, and, if there is a clinically suspected primary region (e.g., head and neck for cervical lymph node metastasis, pelvis for peritoneal dissemination), a (2) scout image, (3) transverse T1-weighted image for attenuation correction (gradient echo sequence, 3D acquisition, and thin slice), and (4) transverse T2-weighted image must be acquired for each region; sagittal and coronal images and fat suppression should be combined as necessary. Detailed PET and MRI acquisition parameters are set properly according to the specifications of each model used.

(3) Cautions for diagnostic image interpretation

In the normal state, FDG uptake is high in the brain (where glucose metabolism is active) and in the urinary system, an excretory route, including kidney, ureter, and bladder. Relatively high uptake is observed in the palatine tonsil, gastrointestinal tract including stomach and large intestine, and liver. Physiological uptake may be observed in the myocardium, hilar area of the lung, and bone marrow. High uptake is uncommonly observed in brown adipose tissues in the neck and supraclavicular fossa region and the paravertebral region.

It should be noted that uptake is not necessarily high in some malignant tumors, such as well-differentiated tumors, slow-dividing and growing tumors, small-sized lesions and lesions with strong necrosis. Active inflammation and granulomatous disease often show intense FDG uptake, which is difficult to differentiate from uptake by tumors[176)].

4. Other disorders

4-1. Dementia

The typical FDG-PET finding in Alzheimer's disease (AD) FDG-PETis decreased glucose metabolism in the cerebral cortex extending from the temporo-parietal association area and precuneus to the posterior cingulate gyrus. Advanced AD is associated with decreased metabolism in the frontal lobe. The glucose metabolism in the primary sensorimotor cortex, primary visual cortex, basal ganglia, and thalamus is likely to be preserved. Decreased glucose metabolism in the precuneus to posterior cingulate gyrus is considered to be an indicator of early dementia. Mild cognitive impairment (MCI) is often associated with a decrease of glucose metabolism in the temporo-parietal association area and this finding may also be an indicator of progression to AD. In the US, Medicare began covering FDG-PET scans in 2004 in cases where the differential diagnosis of fronto-temporal dementia (FTD) and AD is difficult; however, where evidence of MCI and early AD is insufficient, the conduct of further clinical studies has always been warranted.

In Japan, FDG-PET scans for the differential diagnosis of AD have not been covered by insurance.

4-2. Inflammatory diseases

Diagnosis of inflammatory diseases is based on findings of clinical signs, blood tests, plain radiography, CT, and MRI. In many cases where the identification of site and cause of inflammation is difficult, nuclear medicine can yield important diagnostic information. ^{67}Ga scintigraphy, radiolabeled leukocyte scintigraphy, and FDG-PET are commonly used for diagnosis of inflammatory diseases and infections.

In lesions of inflammation or infection, glucose consumption of activated inflammatory cells is increased dozens of times compared with that of inactive cells, which is considered to be the reason FDG uptake is high in regions of inflammation.

In Japan, FDG-PET scans for the diagnosis of inflammatory diseases and infections have not been covered by insurance. An evaluation of their clinical usefulness will be needed in future studies involving large numbers of patients.

FDG-PET scans and their interpretation should be conducted using standard procedures.

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