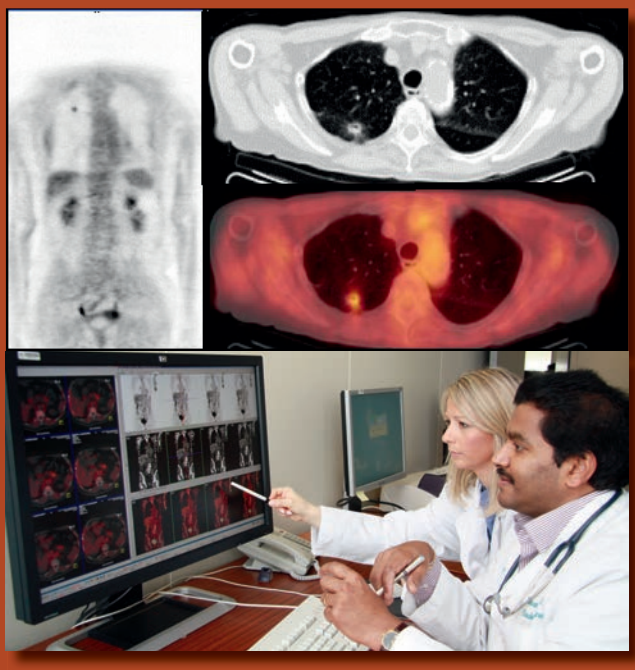

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No. 26

Standard Operating Procedures for PET/CT: A Practical Approach for Use in Adult Oncology

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STANDARD OPERATING PROCEDURES FOR PET/CT: A PRACTICAL APPROACH FOR USE IN ADULT ONCOLOGY

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FOREWORD

Over the past 20 years, positron emission tomography (PET) and PET/CT (computed tomography) have revolutionized the care of cancer patients in developed countries and are increasingly being adopted in emerging economies. PET has been, and still is, one of the fastest growing fields in medical imaging. There are several reasons for the rapid development of this imaging technology. As the populations of many countries continue to age, cancer constitutes a major health problem, with increasing incidence worldwide. In developed countries where heart disease is the primary cause of mortality, cancer is a close second and may eventually overtake it. Proper cancer management requires highly accurate imaging to characterize, stage, restage, assess response to therapy, prognosticate and detect recurrence. Such information is critical in a disease that often requires the correct initial treatment in order to improve the chance of successfully curing the patient.

The ability to provide, in a single imaging session, detailed anatomical and metabolic/functional information, which has a powerful synergistic effect that is greater than the sum of the two individual techniques, has established PET/CT as an indispensable imaging procedure in the management of many different types of cancer. The quality and reliability of the images acquired on a PET/CT scanner depend on the quality of the imaging technique. This publication addresses this important aspect of PET/CT imaging, namely, how to perform an ^{18}F-fluorodeoxyglucose (FDG) PET/CT scan in an adult patient with cancer. Although there are several publications and guidelines on different protocols for PET/CT imaging using FDG, the aim here is to provide a comprehensive overview that can be used both by new PET/CT centres in the process of starting up and by established imaging centres for updating older protocols.

Written by experts from several continents, the book provides an up to date, evidence based and comprehensive overview of operating procedures for FDG-PET/CT imaging in adult oncology patients. The text is based on consensus and agreement among the authors, following a systematic approach of relying on personal experience and the available scientific evidence on all the subjects included. Due to the evolving nature of PET/CT imaging, which is a rapidly growing technology, this publication will undoubtedly need to be updated on a regular basis. It may well be that each PET/CT centre will have to modify the recommendations provided here to suit its own particular circumstances, according to, inter alia, the type of scanner, patient population, use of intravenous contrast, availability of FDG, professional staff experience, local regulations and preferences of referring physicians.

The information provided here is felt to be important in the light of the growing need to standardize and optimize the way PET/CT scans are performed, not only to enable trials using FDG-PET/CT in different institutions to be compared and correlated, but also to allow for more accurate comparisons

of scans performed on the same patient at different points in time at a single institution. This is important when assessing the response to cancer therapy, and especially so when this evaluation is performed early and after using novel targeted treatments that very often only produce changes in metabolic activity and not in lesion/tumour size. This is the reason why strictly following a correct imaging protocol is crucial. The reliability of the PET/CT imaging information in cancer patients depends on trustworthy and consistently applied protocols. This issue has current relevance in drug discovery and development, where PET/CT imaging with FDG and other radiotracers is viewed by the pharmaceutical industry as potentially useful for shortening the process of clinical validation of new drugs.

The IAEA wishes to thank the contributors to the drafting and review of this book for contributing their knowledge, time and effort. The technical officers responsible for this publication were D. Paez and M. Dondi of the Division of Human Health.

CONTENTS

1. THE ROLE OF FDG-PET/CT IN ONCOLOGY

1.1. INTRODUCTION

1.1.1. The molecular basis behind the FDG image

In 1931, Dr Otto Warburg described the effect that now carries his name and for which he was awarded a Nobel Prize. Warburg observed that tumour tissue metabolizes glucose anaerobically under aerobic conditions. This finding brought to light the fundamental metabolic property of cancer cells by correlating the rate of cellular glycolysis to tumour growth. He showed that cancer cells use glucose anaerobically to produce lactic acid in non-hypoxic tissues, rather than relying on the supposedly more efficient tricarboxylic acid (TCA) cycle of oxidative phosphorylation to drive ATP synthesis in the mitochondria.

Various well known molecular mechanisms facilitate the molecular functionality of the Warburg effect. These include tumour suppressor genes (succinate dehydrogenase (SDH)), oncogenes (*AKT, MYC* and *RAS*) and the hypoxia inducible factor (HIF) pathway. Briefly, tumours undergo aerobic glycolysis following the activation of oncogenes, and/or the loss of tumour suppressor genes, with further stabilization of HIF in response to a hypoxic microenvironment, and also under aerobic conditions. For example, once the *AKT* oncogene is activated, glucose uptake is enhanced, followed by the activation of aerobic glycolysis independent of HIF-1 stabilization. The activated *AKT* oncogene stimulates the translocation of glucose transporters from the cytosol to the cell membrane, thereby facilitating glucose uptake by the tumour cell and subsequently activating hexokinase isoform II, which phosphorylates intracellular glucose.

The *MYC* oncogene, in contrast, activates numerous glycolytic enzyme genes and binds hexokinase type II, enolase and lactic dehydrogenase (LDHA). The loss of expression of the guardian of the genome, the tumour suppressor gene P53, also contributes to the Warburg effect by activating tumoural aerobic glycolysis. Once oxygen demand exceeds supply, the hypoxic phenotype is selected within the tumour microenvironment, with the subsequent transactivation of HIF-1α, which stimulates the expression of hundreds of genes including *GLUT1*, *GLUT3* transporters, hexokinase isoform II and vascular endothelial growth factor (VEGF). In this manner, the increase in expression and activity of the two rate-limiting steps of glucose uptake (*GLUT* and hexokinase) contribute to the Warburg effect, allowing for the conversion of glucose to lactate. On the other hand, high levels of angiogenesis (stimulated by VEGF activity) combined

with elevated glucose metabolism result in increased metastatic potential and poor survival of patients with different cancer types.

The *RAS* oncogene increases the level of HIF-1 expression and, therefore, the downstream pathway previously described.

To summarize, the activation of oncogenes such as *AKT*, *MYC* and *RAS*, as well as HIF-1, contributes to the Warburg effect by stimulating glycolytic metabolism, while in parallel attenuating mitochondrial function, thereby reducing the rate of oxidative phosphorylation taking place within the tumour cell (Fig. 1.1).

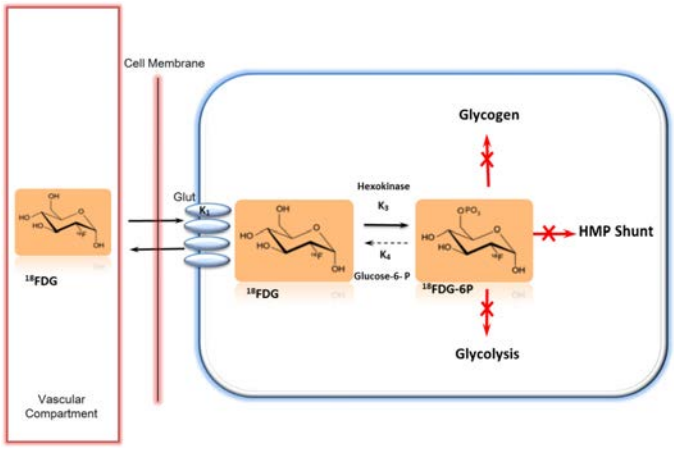

FIG. 1.1. FDG metabolism.

Aerobic glycolysis in cancer cells provides for a growth advantage in the tumour microenvironment and for the production of lactic acid, which in turn may facilitate cancer progression by degrading the extracellular matrix of the affected host organ. Finally, this increase in glucose metabolism can lead to the immortalization of cancer cells by diminishing the generation of reactive oxygen species in the mitochondria by decreasing the rate of cellular senescence.

This principle by which tumour cells take up glucose under aerobic conditions constitutes the basis for the detection and staging of human cancers with ^{18}F-fluorodeoxyglucose (FDG) and positron emission tomography (PET).

Over the past 20 years, FDG-PET imaging has evolved into a technique of proven clinical value and substantial clinical potential for addressing important aspects of the daily management of cancer patients. Its inherent ability to interrogate the biological behaviour of neoplastic molecular pathways in one whole body scan has made it a very important and in some cases an indispensable diagnostic and staging tool for cancer patients. The end result has been its

significant impact in the medical management of these patients. The accepted indications for FDG imaging include: differentiation of benign from malignant lesions, cancer staging, assessment of tumour recurrence, radiation therapy (RT) planning, monitoring the results of cancer therapy and determination of prognosis in some cancer types. Newly introduced hybrid imaging systems, such as PET/CT (computed tomography) and PET/MRI (magnetic resonance imaging), provide better assessments of disease processes by coupling the pathophysiological findings with their anatomical landscapes, therefore allowing for better characterization of the physiological or pathological nature of a particular imaging finding.

This is the reason that anatomo-metabolic imaging with FDG-PET/CT has become one of the imaging modalities of choice for the daily clinical assessment of cancer patients. As already known, certain cancer cells do not metabolize glucose and rely on alternative fuel sources, the detailed characterization of which may be interrogated with other radiotracers beyond FDG, which allow higher specificity in the functional status of other molecular targets of tumour cell metabolism and the tumour microenvironment, such as amino acid transport, programmed cell death (apoptosis), cellular proliferation, cell surface receptor recognition, angiogenesis and tumour hypoxia, among others.

1.2. FDG PHARMACOKINETICS AND PHARMACODYNAMICS

^{18}F-FDG is a structural analogue of 2-deoxyglucose and is used as a tracer of glucose metabolism (and of the Warburg effect). Its distribution is not limited to malignant tissue. Once intravenously administered, FDG is delivered to cells via blood flow and is then internalized through the same transport mechanism as plasma glucose (*GLUT* transporters). The cell membrane is not permeable to sugar molecules. Glucose and the other six-carbon glucides can only enter the cell through highly restricted portals. The principal transporter is the *GLUT* family of transporters, with its 13 isoforms. Each *GLUT* isoform facilitates the transport by binding the sugar molecule on the outer side of the membrane, inducing a conformational change in the transporter molecule, which translocates the sugar and releases it in the cytosol. Since this is not an energy dependent but a facilitated process, another sugar molecule can be transported back out again. The net result is the diffusion of sugar molecules in both directions, based on a concentration gradient. Tumours express *GLUT* at higher levels than does normal tissue, and therefore may take up FDG at higher rates than background.

Moreover, glucose can be brought into the cell by energy dependent active transport. This process takes place in the small intestine and proximal renal tubules. Transport is mediated by Na^+/glucose symporters SGLT-1 and SGLT-2. Although FDG is also a substrate, its affinity for these transporters is less than

that of natural glucose. This in fact translates into less efficient reabsorption of FDG and thereby high accumulation of the radiotracer in the renal collecting systems and the bladder on PET/CT images. Once in the cytoplasm, ^{18}F-FDG is phosphorylated to ^{18}F-FDG-6-phosphate, a reaction that is catalysed by hexokinase (mainly isoforms II and I).

Hexokinase is the first enzyme in both the glycolytic and the oxidative phosphorylation pathways of glucose metabolism. It is responsible for cytoplasmic localization of FDG, which when phosphorylated is no longer a substrate for the *GLUT* transporter. Hexokinase activity is stimulated by insulin and hypoxia, and inhibited by glucose-6-phosphate. Several isoforms of hexokinase have been identified in humans. Types I and II are activated by binding to the mitochondrial membrane. In addition, type II has anti-apoptotic action through its effect on protein kinase B (*PKB*/*AKT*) and is unregulated in cancer cells (Fig. 1.1).

^{18}F-FDG-6-phosphate is then trapped intracellularly, because further catabolysis is not possible due to the absence of an oxygen atom on the molecule's C-2 position (which holds the ^{18}F atom). FDG-6-phosphate can be dephosphorylated to FDG by glucose-6-phosphatase; however, this reaction occurs relatively slowly, especially in cancer cells, which tend to lack this enzyme. When phosphatase activity is high, ^{18}F-FDG-6-phosphate will not concentrate, resulting in poor visualization of tissues/tumours on PET imaging (i.e. hepatocellular carcinoma).

^{18}F-FDG-PET yields functional information based on altered tissue metabolism and is useful for both diagnosing and staging cancer. It should also be borne in mind that FDG metabolism in both normal and malignant tissues is affected by antineoplastic treatments, with the metabolic changes often preceding their structural counterparts. Treated malignant tissue may have reduced FDG activity because of both cell death and lower metabolism.

The proper interpretation of FDG tumour images requires familiarity with the normal distribution of the probe, as well as with all the variables influencing its uptake, including benign conditions that may be FDG avid. An educated understanding of all these variables is essential for accurate interpretation of PET images. Simplification is not uncommon and could perhaps become the most dangerous mistake when reading PET scans.

1.3. NORMAL BIODISTRIBUTION OF FDG

1.3.1. The brain and spinal cord

Based on the fact that the brain's main energy source is glucose, FDG uptake is high. Structures such as the cerebral cortex, the thalamus and the caudate nuclei

display high uptake of FDG. FDG metabolism should be symmetrical from side to side, and when comparing anterior and posterior regions of the brain. However, depending on the extrinsic stimuli that the patient was subjected to during the uptake phase post-administration of the radiotracer, some normal variations in cortical uptake may be noticed. Intense FDG uptake is common in the basal ganglia and the thalamus, reflecting high neuronal metabolic rates. White matter uptake is significantly lower than cortical grey matter uptake. Cerebellar uptake is slightly lower than in the cerebral cortex, with focally increased uptake considered normal in the vermis. Mild to moderate uptake can be seen in the cervical and lumbar spine, and should not be confused with pathology.

1.3.2. Salivary glands

When evaluating the head and neck area, it is common to observe activity at the level of the salivary glands. FDG is excreted by the salivary glands, with activities ranging from moderate to high, and so this should not be considered a positive focus of head and neck malignancy. The parotid and submandibular glands usually have symmetrical patterns of mild to moderate FDG avidity. On the other hand, when in the presence of asymmetric patterns of salivary gland uptake, the hot side could represent sialadenitis, and the cold side could be due to atrophy, ductal obstruction or radiation induced changes. Focally increased activity in a parotid gland may be due to an intraparotid lymph node (normal or diseased) or a true parotid neoplasm.

1.3.3. Tongue and vocal cords

FDG uptake is commonly seen at the insertion of the genioglossus and geniohyoid muscles to the mandible, and at times in the tongue. Although sometimes difficult to achieve, it is possible to minimize uptake by requesting the patient to refrain from speaking, drinking or chewing before and after FDG administration (the uptake period).

1.3.4. Thyroid gland

Uptake of FDG by the thyroid gland is variable, ranging from absent to low−moderate in intensity. Diffuse uptake can be normal or can represent thyroiditis (subacute thyroiditis, Graves' disease or Hashimoto's thyroiditis). Focal uptake can be consistent with thyroid cancer and should be followed up with thyroid ultrasound in all cases.

1.3.5. Thymus

Mildly increased uptake of FDG by the thymus, with its typical V shape, is not uncommon in young patients and in adults, due to rebound after chemotherapy. Thymic rebound may be bilateral as well as unilateral. Uptake may be significantly higher in patients with thymoma, thymic carcinoma or lymphoma in the list of differentials.

1.3.6. Myocardium, chest and mediastinum

Myocardial uptake of FDG is dependent on the dietary status of the patient. In the fasting state, the myocardium uses free fatty acids as an energy source, but postprandially, or after glucose loading, it preferentially uses glucose. Therefore, in the fasting state, when insulin and blood sugar levels are low, FDG uptake by the myocardium is usually also low or absent. However, this does not hold true for ischemic segments, which in the fasting state will take up FDG with greater avidity than normal segments. Because of this, it is recommended that patients receive a glucose load before myocardial FDG scanning, where normal myocardial segmental uptake will be enhanced compared with ischemic segments. In contrast, when FDG imaging is performed for tumour targeting, a long fasting state is recommended. This will minimize blood glucose levels that compete with FDG uptake as well as diminish, in the majority of the cases, cardiac activity by stimulating the shift of glycolytic metabolism to fatty acid metabolism in the myocyte, thereby minimizing the possibility of obscuring positive findings in the mediastinum. Tumour targeting could also be affected if patients are treated with aggressive insulin treatment, which will divert FDG to skeletal muscle and fat from the blood, lowering tumour uptake. Cancer imaging with PET should be performed after a long fasting period of 6−12 h (Fig. 1.2).

If scans are corrected for attenuation, mediastinal activity tends to be higher than lung activity. In uncorrected images, on the other hand, it is common to observe little to moderate lung uptake, which is always higher than mediastinal activity. If a longer time is allowed between injection and imaging, FDG activity in the lung's blood pool and in macrophages will decrease over time, allowing for a better target to background ratio when staging mediastinal structures. Activity in the blood pool decreases slightly over time, as the radiotracer is taken up by target tissues or excreted by the kidneys. However, in patients with renal failure, clearance may be delayed. Atelectasis is often characterized by low to mild uptake. In the acute or subacute phases of pulmonary embolism and infarction, mild to moderate uptake may be seen, which should be distinguished from malignancy.

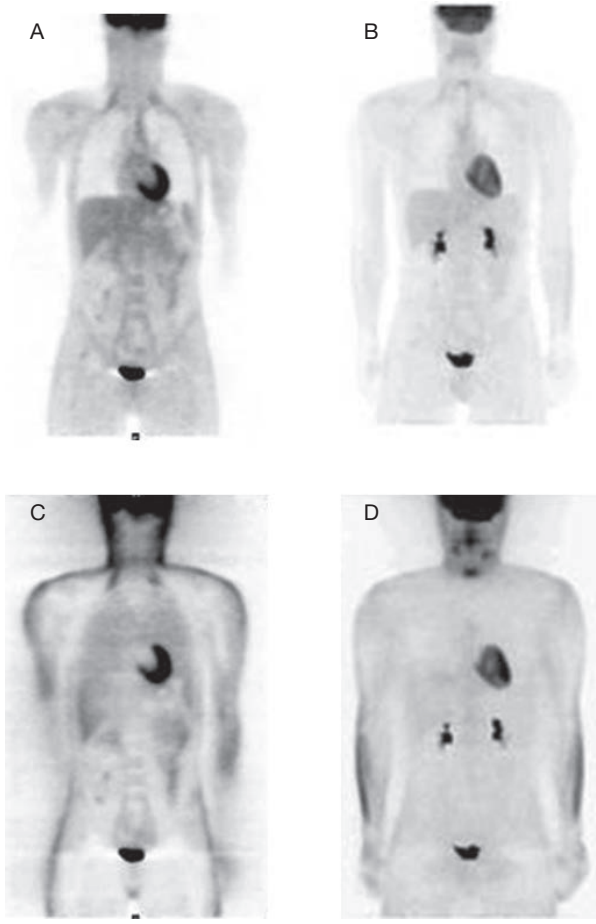

FIG. 1.2. Top row: images with attenuation correction (A: coronal, B: MIP projection). Bottom row: images without attenuation correction (C: coronal, D: MIP projection). Note that the activity in the mediastinum is higher than that in the lung in the attenuated corrected images (top row) and the moderate lung uptake in the non-corrected images (bottom row).

1.3.7. Breast

FDG uptake by the breast can be low and diffuse, and moderate to intense during lactation. In the lactating breast, the pattern of uptake tends to be diffused and symmetric. The intense uptake of FDG in the lactating breast is related to the increased expression of the insulin-independent glucose transporter *GLUT1* as well as the fact that phosphorylated FDG becomes trapped intracellularly in active glandular tissue with low excretion into milk. The measured activity

of FDG in breast milk is usually low, with an estimated cumulative dose to the infant of 0.085 mSv, which is below the 1 mSv recommended for breastfeeding cessation (see Section 3.1.3 for further information on breastfeeding).

Taking into consideration the above mentioned facts, the infant receives a higher radiation dose from close contact with the breast than from ingestion of radioactive milk. Breast uptake has mild variations with menstrual cycle, with possible moderate uptake in the post-ovulatory phase. In addition, breast uptake decreases with increasing age and lower density, and menopausal state usually has no effect on the average or maximum standardized uptake values, SUV_{avg} or SUV_{max}. Note, however, that following lumpectomy, fat necrosis may have persistent uptake in the mild–moderate range, secondary to macrophage-derived giant cells known to express the rate-limiting steps of FDG uptake (*GLUT* transporters and hexokinase).

1.3.8. Liver and spleen

The liver shows a characteristic heterogeneous pattern of FDG uptake that is mild to moderate in intensity, and small lesions may be difficult to detect against this background. In fact, small foci of FDG avidity, without CT correlates, could be either metastases or simple background noise. As a rule of thumb, if the finding is present on two or more adjacent slices on each orthogonal plane, it could signify a malignant focus, and a follow-up MRI or PET/CT scan is indicated to rule out metastasis. Liver uptake is most often slightly higher than uptake by the spleen, although it may be reduced with fatty infiltration and in hepatic cirrhosis. Cysts are typically photopenic on the PET images, whereas cavernous haemangioma tend to have uptake similar to the liver itself, and blend in with the surrounding liver background.

Splenic uptake is mostly homogeneous, mild to moderate in intensity and lower than liver activity. It can be increased in portal hypertension, as well as in anaemic patients or after chemotherapy and/or stimulation with colony-stimulating factors. This should be distinguished from the diffuse, heterogeneous pattern of intense uptake, secondary to infection or infiltration by lymphoma or leukaemia.

1.3.9. Gastrointestinal tract

The stomach wall is usually well seen in coronal slices as a focus of faint activity. In some patients, it can reach higher levels of uptake and still be considered within normal limits. The distal oesophagus can also be observed as a focus of faint uptake at the level of the gastric-oesophageal junction. This may be either physiological, or secondary to esophagitis due to gastro-oesophageal

reflux. Activity in the small and large intestines varies from patient to patient. Bowel activity may be related to smooth muscle peristaltic function and/or bacterial uptake. Frequently, low to moderate uptake can be observed in the lymphoid tissue of Waldeyer's ring as well as in the caecum (due to the concentration of lymphoid tissue in Peyer's patches). As mentioned above, gastrointestinal uptake is somehow variable; however, any focal spot of intense uptake should trigger suspicion that a pathological process may be present in the bowel. The differentials include inflammatory and tumour activity, and follow-up colonoscopy is indicated. On the other hand, intense segmental intestinal uptake is often seen in diabetics medicated with metformin, or may reflect colitis, and in the distal ileum, active Crohn's disease.

1.3.10. Musculoskeletal system

It is not uncommon to see FDG uptake in selective muscular groups. The degree of uptake could range from moderate to high, especially in those patients that are not kept in the resting state after FDG injection. Rigorous physical activity should be avoided 24 h before a scan. The muscle groups that are most frequently seen are those of the neck and of the lower extremities. Trapezius and paraspinal muscle uptake is usually a consequence of stress induced muscle tension, which could be coupled with generalized increased muscular uptake if the patient feels cold and is shivering. Low to moderate uptake of FDG is relatively common in joints, such as shoulders, knees and hips. Diffuse muscular uptake reflects increased serum insulin levels, either in diabetics or in normal patients who have eaten sugar- or starch-containing foods within 4 h prior to the examination. Low to moderate uptake of FDG is seen in the vertebral bone marrow and even weaker uptake can be appreciated in the bone marrow of the femur, pelvis and ribs. More diffused bone marrow uptake is a frequent finding in patients who have undergone chemotherapy with or without colony-stimulating factors or in anaemic patients. Another cause of increased bone marrow uptake is acute infection.

1.3.11. Kidneys and urinary collecting system

It is common to see activity in the kidneys, ureters and bladder, because unlike natural glucose, FDG is excreted through the kidneys. This can be avoided by keeping the patient well hydrated to promote diuresis. Patients should be encouraged to void prior to imaging, and if that is not possible, placement of a Foley catheter in the bladder will prove very useful for adequate visualization of pelvic structures. PET imaging is usually performed not earlier than 1 h post-injection, by which time the renal parenchyma will no longer contain much

of the injected activity. However, if the patient was not well hydrated prior to imaging, FDG in the renal collecting system could pose a problem during image interpretation. Ureters may be present as tubular or focal activity, which may be bilateral or unilateral, and it can be difficult to distinguish them from metastatic lymph nodes. In that case, the ureters must be traced on the CT slices from their origin in the renal pelvis to the site of uptake. Bladder uptake is very intense. Proper hydration, voiding prior to imaging and starting the acquisition of a whole body scan in the pelvic area will minimize false positive or negative findings in the pelvic region.

1.3.12. Ovary and uterus

Moderate uptake in the uterine cavity can be seen during the ovulatory and menstrual phases of the cycle, and post-partum. Endometritis can have a similar appearance, and needs to be excluded by history. Endometrial uptake in a postmenopausal female is always abnormal (endometrial hyperplasia or neoplasia). In the premenopausal female, endometrial and ovarian uptake may be functional or malignant. Focal ovarian uptake is common in ruptured follicles or corpora lutea. However, an ovarian malignancy can have a similar appearance, and follow-up imaging is indicated.

1.3.13. Testis and prostate

Uptake in the testis and prostate is moderate and symmetric. Asymmetric uptake may be due to a tumour (hot), or to torsion or infarct (cold). Epididymitis can be seen as a small focus of increased uptake over the testis. Prostatic uptake is low. Focal and lateral uptake may represent prostatitis or prostatic malignancy. Note, however, that many prostate cancers do not take up FDG. Figure 1.3 shows the normal biodistribution of FDG in the body.

1.3.14. FDG uptake in vascular structures

The degree of FDG uptake in the vascular compartment is time and age dependent. One hour after radionuclide administration, the original amount of intravascular FDG activity decreases. The degree of vascular activity could also be in the low–moderate range in the neck and upper extremities. It has been reported that there is increased prevalence of FDG uptake in the vascular system in older patients. Vascular uptake may be related to smooth muscle metabolism in the media, sub-endothelial smooth muscle proliferation due to ageing, and/or the FDG activity in the macrophages present in the atherosclerotic plaque. In general, the abdominal aorta is usually seen less frequently compared with the pelvic and

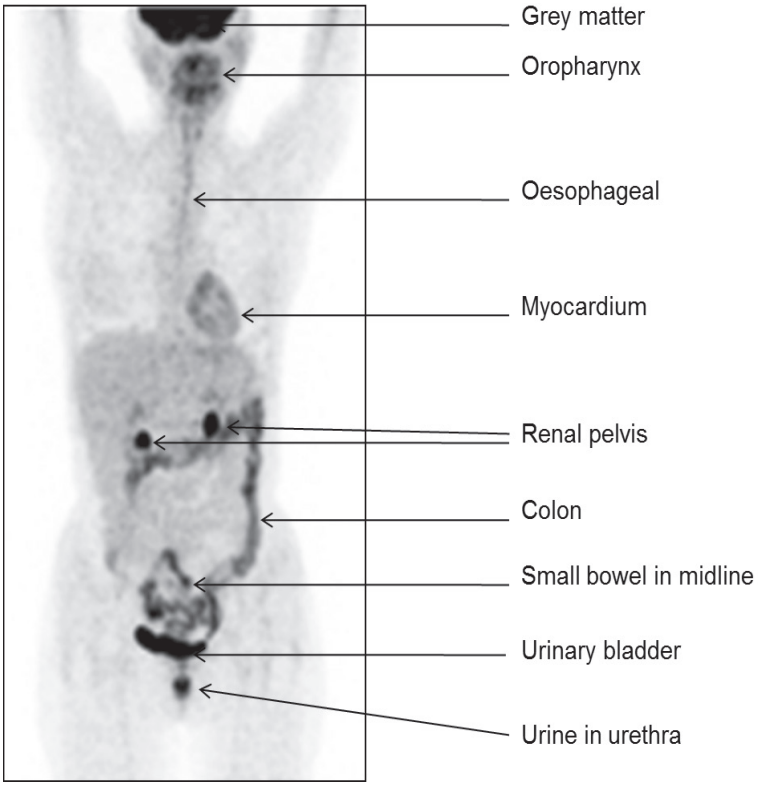

FIG. 1.3. Normal distribution of FDG.

thigh vessels. The pattern of uptake varies from patient to patient, and it can be linear as well as non-uniform in extent and intensity. Taking into consideration that scans are usually obtained later than 1 h post-injection, uptake of FDG in the vascular compartment is not strictly related to blood pool activity. This concept supports the assumption that vascular activity might be related to the smooth muscle cells in the arterial wall metabolizing glucose, coupled with FDG in the macrophages that populate atherosclerotic lesions.

1.3.15. Brown fat

Brown adipose tissue (BAT) can show moderate to intense FDG uptake, typically distributed in the lower neck and supraclavicular regions and along the thoracic costovertebral junctions. It is more frequent in children, but it may also be observed in adults, particularly women, in cold weather. On PET/CT, the foci of uptake co-localize with areas of fat density, although when uptake is

very extensive, or in those cases with significant misregistration between the CT and PET images, lymphadenopathy may be difficult to exclude. In such cases, the scan may have to be repeated. Keeping the patient in an adequately heated environment before and during the FDG uptake period can help to minimize BAT uptake. Other reported methods include pretreatment with propranolol or other beta-blockers, or with a fatty meal protocol.

Armed with knowledge of proper acquisition and processing techniques, and familiarity with the normal distribution and physiological variations of FDG uptake, observers will be able to detect the presence of pathological findings with a high degree of confidence. However, their ability to recognize the extent and location of disease will depend on the type of information in the image, in terms of interpreting what it means, and how sensitive and specific the technique used is to identify the presence of disease. This is what this publication intends to do for its readers.

For a complete gallery of PET/CT cases, please visit the Human Health Campus, an educational resource for health professionals in radiation medicine (http://humanhealth.iaea.org).

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2. INFORMATION FOR REFERRING PHYSICIANS

2.1. THE PET/CT REQUEST

It is generally recognized that FDG-PET/CT studies result in significant changes in management in 10–30% of patients studied, with significant variations between different malignancies. This impact is based on the interpretation of the degree of FDG uptake in masses, lymph nodes and other organs that determine the presence of metabolically active lesions and the extent of disease. Interpretation of these findings is challenging and depends on several technical and clinical factors. Before the PET/CT scan is approved and performed, there is clinical information that the interpreting nuclear medicine physician needs to know. The written or electronic request for an FDG-PET/CT examination should provide sufficient information to demonstrate the medical necessity for the examination and allow for its proper performance and interpretation.

In the IAEA's International Basic Safety Standards (BSS) [2.1], there are clear requirements for referring medical practitioners to ensure that no patient, whether symptomatic or asymptomatic, undergoes medical exposure unless:

— The radiological procedure has been requested by a referring medical practitioner and information on the clinical context has been provided, or it is part of an approved health screening programme;
— The medical exposure has been justified through consultation between the radiological medical practitioner and the referring medical practitioner, as appropriate, or it is part of an approved health screening programme.

Furthermore, the justification process, particularly for pregnant or breastfeeding women or paediatric patients, is to take into account the following parameters:

— The appropriateness of the request;
— The urgency of the procedure;
— The characteristics of the medical exposure;
— The characteristics of the individual patient;
— Relevant information from the patient's previous radiological procedures.

The PET/CT request form should provide pertinent patient information, both personal and clinical. All PET/CT facilities should have a request form to simplify the provision of this information. The Society of Nuclear Medicine and Medical Imaging (SNMMI) has published a generic form, 'Physician Request

Form for Oncologic PET/CT Imaging' that each PET/CT facility can easily adapt to its individual needs [2.2].

Part I of a PET/CT form should include the patient's personal information, identification and medical record number. This information will enable the facility to contact the patient with regard to appointment dates and provide instructions on the procedure (Table 2.1).

TABLE 2.1. SAMPLE PHYSICIAN REQUEST FORM FOR ONCOLOGICAL PET/CT IMAGING

PART I

Patient's name _____ Date of study_____

Medical record No. _____ Gender _____ Weight ____ kg

Patient's address _____

Patient's phone No. _____

Insurance information (if applicable) _____

PART II

Requesting physician _____

Phone No. _____ Email _____

Previous CT or MRI _____ Where _____ Date _____

Previous PET study _____ Where _____ Date _____

PART III

Diabetic No □ Yes □ Diabetic medication: _____

Latest fasting blood sugar _____

Allergy to contrast agents _____

Renal function _____ Creatinine level _____

Height (cm) _____ Body weight (kg) _____

PART IV: STUDY REQUESTED (check one)

□ Standard body study (skull base to proximal thighs)

□ Special (non-standard) body study

□ Whole body study (skull vertex to toes) for known or suspected lower extremity tumours (including melanoma)

□ Head and neck cancer study (skull vertex to thighs) or dedicated head and neck protocol

TABLE 2.1. SAMPLE PHYSICIAN REQUEST FORM FOR ONCOLOGICAL PET/CT IMAGING (cont.)

PART V: SPECIFIC REASON FOR PET STUDY

Type of cancer _____

□ **Histologically proven** □ **Suspected**

□ **Diagnosis**: To determine if suspicious lesion is cancer _____

Pulmonary nodule _____

Other (specify) _____

□ **Diagnosis**: To detect an occult primary tumour:

— In patient with known/suspected metastatic disease

— In patient with suspected paraneoplastic syndrome

□ **Initial staging** of confirmed, newly diagnosed cancer

□ **Monitoring response**

During treatment _____

Chemotherapy _____

Radiation therapy _____

Other (type)_____

□ **Restaging** after completion

Date of therapy _____

Chemotherapy _____

Radiation therapy _____

Other (type) _____

□ **Suspected recurrence** of a previously treated cancer:

Site of suspected recurrence is

_____

based on

_____

□ **Surveillance** of a previously treated cancer in a patient with no known residual disease

Date of last treatment _____

Pertinent clinical information _____

_____

_____

Instructions _____

_____

_____

Part II of the form should include the referring physician's contact details and information about prior PET/CT or other imaging studies and the facility where they were performed. The actual images and reports should be made available for comparison at the time of interpretation. This information is necessary in order to understand the morphological characteristics of a lesion and their correlation with metabolic changes, and to know if the patient has had prior PET/CT scans that can be compared to determine whether changes occurred between studies.

Part III should record information about patients with diabetes, prior intravenous contrast use and some biometric data:

— History of diabetes, as hyperglycaemia or hyperinsulinemia can alter FDG biodistribution. Diabetic patients need to be monitored before the day of the PET study to ensure that glucose levels are <180−200 mg/dL. This may require daily monitoring for a few days, and the patient should be provided with instructions regarding diet and exercise. Insulin administered within 2 h prior to the FDG injection, or endogenous insulin secondary to hyperglycaemia, may cause increased glucose uptake in muscle or other soft tissue and may compromise tumour uptake. If blood glucose levels are high and cannot be lowered on the day of the study, the patient may have to be rescheduled. In some cases, a diabetic control specialist may need to be consulted.
— If the request includes the use of intravenous (IV) contrast for the CT portion, the patient should be screened for a history of contrast allergies. If positive, premedication should be prescribed. If the renal function is abnormal, the use of intravenous contrast should be avoided or the dose reduced, as appropriate.
— In the case of standardized uptake value (SUV) measurements, the patient's height and body weight must be accurately recorded. With serial studies in the same patient, his or her weight must be measured directly prior to each PET study because body weight often changes during the course of disease. The patient's height, weight and gender should be reported to allow for other SUV normalizations such as lean body weight and body surface area (BSA). The latter is important to meet the recommendations of the European Organisation for Research and Treatment of Cancer (EORTC) and for response assessment studies, when large changes in body weight may occur during the course of treatment. For further information on response evaluation in FDG, see Section 5.

Part IV of the form should indicate the type of study requested, which should include the field of view to be covered:

— Standard body study (skull base to proximal thighs). This is done in most cases for initial staging, treatment planning or restaging.
— Head and neck cancer study (skull vertex to thighs) or dedicated head and neck protocol: from the sternal notch to proximal thighs to assess metastasis to the mediastinum, hilar regions and lung parenchyma; followed by dedicated images of the head and neck, from the top of the skull to the

aortic arch to evaluate cervical lymph node metastasis and to assess the primary tumour.
— Whole body study (skull vertex to toes), also known as the melanoma protocol. This is used for known or suspected lower extremity tumours, including melanoma or cutaneous lymphoma.
— Standard PET/CT. PET combined with diagnostic CT with intravenous contrast. This is done when a diagnostic CT scan is required.

Part V should indicate the specific reasons for the PET/CT study, including information that could have an impact on the interpretation. The type of cancer, the histological type and location of the lesion (even if it has been resected) should be included, and the primary indication to perform the study should be clearly stated, e.g. 'patient with mass in the left upper lobe'; 'pathology reported non-small cell lung cancer (NSCLC)', or 'PET/CT requested for initial staging'.

Indications for FDG-PET/CT include, but are not limited to, the following:

— Differentiating benign from malignant lesions;
— Searching for an unknown primary tumour when metastatic disease is discovered as the first manifestation of cancer, or when the patient presents with a paraneoplastic syndrome;
— Staging known malignancies;
— Monitoring the effects of therapy on known malignancies;
— Determining whether residual abnormalities detected on physical examination or on other imaging studies after treatment represent tumour or post-treatment fibrosis or necrosis;
— Detecting tumour recurrence, especially in the presence of elevated levels of tumour markers;
— Selecting the region of a tumour most likely to yield diagnostic information for biopsy;
— Guiding RT planning.

2.2. RECOMMENDATIONS AND GUIDELINES

Several professional organizations such as the European Association of Nuclear Medicine (EANM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the National Comprehensive Cancer Network (NCCN) have published recommendations regarding the use of FDG-PET and PET/CT in oncology.

In 2010, the IAEA published Appropriate Use of FDG-PET for the Management of Cancer Patients (IAEA Human Health Series No. 9) [2.3]. It

included recommendations that were compiled following an expert consultancy meeting held in March 2009 and represents the state of knowledge at the time of writing regarding the utility of FDG-PET in some types of cancer. These broad recommendations cannot be rigidly applied to all patients in all clinical settings and will be periodically updated. It should be noted that recommendations regarding the use of FDG-PET and PET/CT in oncology are available from several professional organizations; however, to list them all is beyond the scope of this publication. Readers are therefore advised to seek the most recent reports pertinent to this particular area.

The following sections present selected examples of recommendations for some types of cancer included in Ref. [2.3]. It should be noted that this list is a summary and is not intended to replace the comprehensive review and detailed information included in Ref. [2.3].

2.2.1. Head and neck cancers

DIAGNOSIS

- *Characterization of mass lesion.* Recommendation: Inappropriate.
- *PET guided biopsy.* Recommendation: Inappropriate.
- *Cervical adenopathy with occult primary.* Recommendation: Appropriate.

STAGING — Recommendation: Potentially appropriate.
RESPONSE EVALUATION — Recommendation: Appropriate.
RESTAGING

- *End of therapy.* Recommendation: Appropriate.
- *Confirmed recurrence.* Recommendation: Potentially appropriate.

SUSPECTED RECURRENCE — Recommendation: Appropriate.
FOLLOW-UP — Recommendation: Inappropriate.
RT PLANNING — Recommendation: Potentially appropriate.

2.2.2. Thyroid cancer

DIAGNOSIS — Recommendation: Inappropriate.
STAGING — Recommendation: Inappropriate.
RESPONSE EVALUATION — Recommendation: Inappropriate.

RESTAGING AND SUSPECTED RECURRENCE

— *Differentiated thyroid cancers.* Recommendation: Appropriate.
  In patients with rising thyroglobulin (TG) levels and a negative ^{131}I whole body scan, FDG-PET provides useful data. Recombinant human thyroid-stimulating hormone (rhTSH) stimulation may increase sensitivity.
— *Medullary thyroid cancers.* Recommendation: Potentially appropriate.

FOLLOW-UP — Recommendation: Inappropriate.
RT PLANNING — Recommendation: Inappropriate.

2.2.3. Breast cancer

DIAGNOSIS — Recommendation: Inappropriate.
STAGING

— *Axilla.* Recommendation: Inappropriate.
— *Distant metastases.* Recommendation: Potentially appropriate.

RESPONSE EVALUATION — Recommendation: Potentially appropriate.
RESTAGING

— *End of therapy.* Recommendation: Inappropriate.
— *Confirmed recurrence.* Recommendation: Potentially appropriate.

SUSPECTED RECURRENCE — Recommendation: Potentially appropriate.
FOLLOW-UP — Recommendation: Inappropriate.
RT PLANNING — Recommendation: Possibly appropriate.

2.2.4. Non-small cell lung cancer (NSCLC)

DIAGNOSIS

— *Characterization of pulmonary nodules.* Recommendation: Appropriate.

STAGING

— *Regional lymph nodes.* Recommendation: Appropriate.
— *Distant metastases.* Recommendation: Appropriate.

RESPONSE EVALUATION

- — *Following neoadjuvant chemotherapy.* Recommendation: Potentially appropriate.
- — *Following definitive RT or chemoradiation.* Recommendation: Inappropriate.
- — *During definitive RT or chemoradiation.* Recommendation: Possibly appropriate.

RESTAGING

- — *End of therapy.* Recommendation: Inappropriate.
- — *Confirmed recurrence.* Recommendation: Possibly appropriate.

SUSPECTED RECURRENCE — Recommendation: Possibly appropriate.
FOLLOW-UP — Recommendation: Inappropriate.
RT PLANNING — Recommendation: Potentially appropriate.

2.2.5. Oesophageal cancer

DIAGNOSIS

- — *Characterization of mass lesion.* Recommendation: Inappropriate.
- — *PET guided biopsy.* Recommendation: Inappropriate.

STAGING — Recommendation: Appropriate.
RESPONSE EVALUATION — Recommendation: Potentially appropriate.
RESTAGING — Recommendation: Inappropriate.
SUSPECTED RECURRENCE — Recommendation: Potentially appropriate.
FOLLOW-UP — Recommendation: Inappropriate.
RT PLANNING — Recommendation: Potentially appropriate.

2.2.6. Colorectal cancer

DIAGNOSIS — Recommendation: Inappropriate.
STAGING — Recommendation: Potentially appropriate.
RESPONSE EVALUATION — Possibly appropriate.
RESTAGING — Recommendation: Appropriate.
SUSPECTED RECURRENCE — Recommendation: Appropriate.
FOLLOW-UP — Recommendation: Possibly appropriate.
RT PLANNING — Recommendation: Possibly appropriate.

2.2.7. Cancer of the uterus and cervix

DIAGNOSIS — Recommendation: Inappropriate.
STAGING — Recommendation: Appropriate.
RESPONSE EVALUATION — Recommendation: Possibly appropriate.
RESTAGING

— *End of therapy.* Recommendation: Potentially appropriate.
— *Confirmed recurrence.* Recommendation: Appropriate.

SUSPECTED RECURRENCE — Recommendation: Appropriate.
FOLLOW-UP — Recommendation: Inappropriate.
RT PLANNING — Recommendation: Potentially appropriate.

2.2.8. Melanoma

DIAGNOSIS — Recommendation: Inappropriate.
STAGING

— *Stages I and II, low pretest probability of metastases.* Recommendation: Inappropriate.
— *Stages I and II, high pretest probability of metastases.* Recommendation: Appropriate.
— *Stage III or potential stage IV.* Recommendation: Potentially appropriate.

RESPONSE EVALUATION — Recommendation: Inappropriate.
RESTAGING

— *End of treatment.* Recommendation: Inappropriate.
— *Confirmed recurrence.* Recommendation: Appropriate.

SUSPECTED RECURRENCE — Recommendation: Possibly appropriate.
FOLLOW-UP — Recommendation: Inappropriate.
RT PLANNING — Recommendation: Inappropriate.

2.2.9. Lymphoma

DIAGNOSIS — Recommendation: Inappropriate.
STAGING — Recommendation: Appropriate.

Owing to its superior sensitivity and specificity for most types of lymphoma, FDG-PET is appropriate for staging of Hodgkin's disease and aggressive non-Hodgkin's lymphomas, but not for non-follicular low grade lymphomas. Since diffuse bone marrow involvement and small disease foci may be missed, FDG-PET cannot be recommended to replace bone marrow biopsy at initial staging. A baseline FDG-PET scan is also indicated to assess the FDG avidity of the tumour if a subsequent evaluation of response to treatment with FDG-PET is planned.
RESPONSE EVALUATION — Recommendation: Appropriate.
RESTAGING — Recommendation: Appropriate.
SUSPECTED RECURRENCE — Recommendation: Appropriate.
FOLLOW-UP — Recommendation: Inappropriate.
RT PLANNING — Recommendation: Inappropriate. There are no data available to support the use of PET for RT planning.

Note: The above recommendations also apply to primary central nervous system lymphomas.

2.2.10. Definitions of the appropriateness criteria for the use of PET

The use of PET for clinical indications can be considered appropriate, potentially appropriate, possibly appropriate or inappropriate. The appropriateness criteria for the usefulness of PET are defined as follows:

Appropriate (all the conditions below must be met):

- There is evidence of improved diagnostic performance (higher sensitivity and specificity) compared with other current techniques.
- The information derived from the PET scan influences clinical practice.
- The information derived from the PET scan has a plausible impact on the patient's outcome, either through the adoption of more effective therapeutic strategies or through the non-adoption of ineffective or harmful practices.

Potentially appropriate (potentially useful): There is evidence of improved diagnostic performance (greater sensitivity and specificity) compared with other current techniques, but evidence of an impact on treatment and outcome is lacking.

Possibly appropriate (appropriateness not yet documented): There is insufficient evidence for assessment, although there is a strong rationale for clinical benefit from PET.

Inappropriate: Improved accuracy of tumour staging will not alter management, or the performance of PET is poorer than that of other current techniques.

2.3. PERTINENT CLINICAL INFORMATION

A medical history should be obtained from each patient. Any history of previous treatment with radiation, chemotherapy or other experimental therapeutics, including when those therapies were performed and completed, should be documented. In particular, the use of medications that may affect the uptake or biodistribution of FDG, such as marrow-stimulating cytokines or steroids, should be noted. This information is important in assessing the interval from the completion of a certain therapy to the time of the FDG-PET study in order to ensure that all relevant confounding clinical issues are identified.

Proper interpretation of PET and PET/CT images requires a thorough understanding of the normal physiological distribution of FDG in the body, along with knowledge of frequently encountered physiological variations in FDG distribution, and recognition of non-malignant causes of FDG uptake that can be confused with a malignant neoplasm. The interpreting nuclear medicine physician should be familiar with these pitfalls. The referring physician should be aware of these factors when deciding whether and when to request a PET/CT study and when interpreting the clinical significance of the PET/CT findings. Some of the most important factors affecting the FDG uptake and the timing between therapy or clinical conditions and a PET scan are presented in Table 2.2.

TABLE 2.2. CLINICAL SITUATIONS THAT AFFECT FDG UPTAKE AND FDG-PET/CT — TIMING AND RECOMMENDATIONS

Prior therapies and clinical issues	Recommended interval between therapy and PET/CT	Confounding factor	Other recommendations
Recent chemotherapy	2 weeks Interim PET 2−3 weeks from last cycle End of treatment 4−6 weeks	Marked increase in FDG uptake in the bone marrow	
Recent therapy with cytokines or growth factors	Short acting: 1 week Long acting: 3 weeks	Marked increase in FDG uptake in the bone marrow	
Inflammatory or infectious processes	Wait until inflammatory process resolved, if possible	Increase in FDG uptake in the infected or inflamed areas	
Radiation therapy	4−6 weeks	Focal increase in FDG uptake in the radiated area	
Recent surgery	4−6 weeks	Increase in FDG uptake in the surgical sites	
Granulomatous diseases such as sarcoidosis		Focal increase in FDG uptake in the affected area	
History of claustrophobia			Pretreatment

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[2.2] SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING, Physician Request Form for Oncologic PET/CT Imaging, PET Professional Resources and Outreach Source (PET PROS), Reston, VA, USA, http://interactive.snm.org/index.cfm?PageID=9273

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3. PRECAUTIONS, PATIENT PREPARATION AND SET-UP

3.1. PRECAUTIONS

3.1.1. Prior studies

The patient should bring with him or her prior studies, if possible, since this information will help to improve not only the quality of the report, but the acquisition parameters as well. With these studies, the nuclear medicine physician will be able to evaluate:

— The patient's imaging history, lesions seen using different imaging modalities and the response to treatment compared with prior PET/CT studies.
— The necessity, or not, for example, of acquiring a full dose, contrast enhanced CT scan. If the patient has already undergone such a scan within a short period of time, it is not necessary to perform another one.

Caution should be exercised if PET/CTs have been performed at other institutions with different types of equipment, since semi-quantitative indices of uptake such as SUV may show significant variability, in which case a qualitative (visual) assessment of the imaging findings would be more appropriate. For detailed information on the subject, see Sections 5 and 6.

3.1.2. Pregnant women

Pregnant women should avoid undergoing PET/CT studies. Therefore, women of reproductive age should be carefully screened for possible pregnancy, prior to administering FDG.

3.1.2.1. The foetus and radiation

The foetus is more sensitive to radiation than adults, and the radiation related risks differ according to the stage of the pregnancy and to the absorbed dose. A PET/CT study delivers radiation from the CT component as well as from the injected FDG dose. During early pregnancy, the dose to the foetus may be as high as 0.04 mGy/MBq of FDG [3.1]. The International Commission on Radiological Protection (ICRP) has published recommendations based on radiation risks, and although it is not intended as a complete reference work, it does provide a practical approach that can be used in relation to pregnancy and

medical radiation [3.2]. Also, the risk of malformation is significantly increased with doses higher than 150 mGy [3.3]. If the diagnostic procedure is medically justified and the risk of not performing the examination is greater than the potential risk to the foetus, the studied should be carried using a 'low dose CT'.

3.1.2.2. Acquisition and pregnancy

If the study is to be performed on a pregnant woman, the ALARA (as low as reasonably achievable) principle should be followed. The most effective ways to reduce the absorbed dose to the foetus are: (i) to encourage the woman to drink water and to void frequently after the injection of the lowest possible FDG dose (perform 3-D PET instead of 2-D); (ii) to use a 'low dose CT'; and (iii) to limit the scan area so that it covers only the region of interest [3.4]. For further information on the dose to be injected in adult patients, see Section 4.1.1.

3.1.3. Breastfeeding

Recent mothers may continue breastfeeding up until the injection of FDG. After the injection, complete interruption of breastfeeding is not necessary, but close contact between the mother and child should be avoided. If possible, a 3–4 h delay in breastfeeding will ensure that the radiation dose to the child is negligible.

Indeed, the FDG administered to the mother is excreted in breast milk, resulting in unnecessary exposure to the child who ingests it. Although the radioactivity in milk samples taken after the administration of FDG is a small fraction of less than 0.71% of the activity given to the mother [3.4], a delay in breastfeeding is always warranted (Fig. 3.1).

The FDG administered to the mother is also taken up by the uterus after delivery (Fig. 3.2).

3.1.4. Medical history

A detailed medical history of the patient should be obtained, including any history of claustrophobia, movement disorders and other diseases, as well as the dates and types of procedures previously performed. Careful assessment is recommended of the following comorbidities and any complications related to: diabetes, renal failure, prior infections, surgery and invasive diagnostic procedures, the use of steroids, RT and chemotherapy.

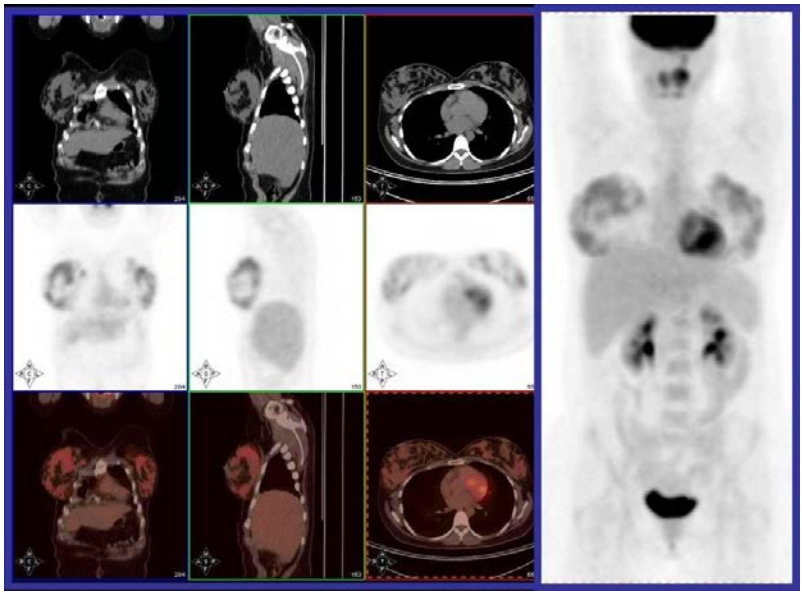

FIG. 3.1. FDG uptake in the breast of a breastfeeding woman.

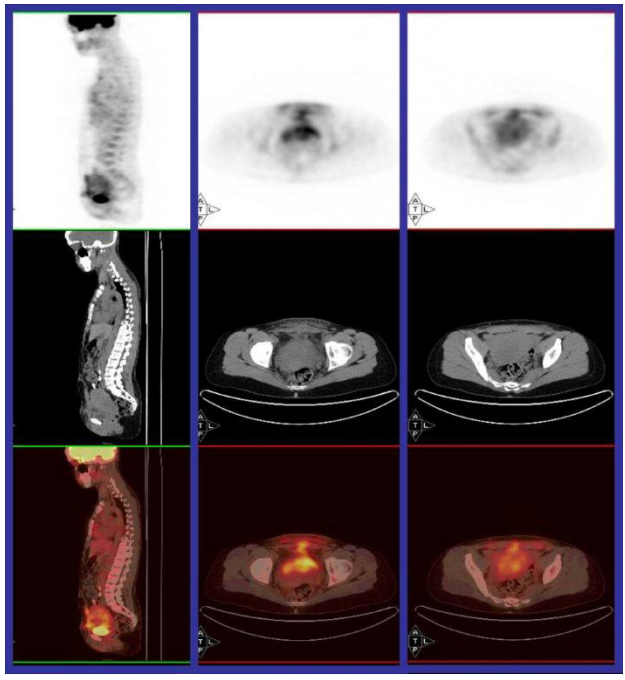

FIG. 3.2. Intense, heterogeneous FDG uptake in the uterus after delivery.

3.1.4.1. Claustrophobic patients and patients with movement disorders

The PET/CT acquisition may last from 5 to 30 min, depending on the type of PET/CT scanner and the protocol used, and the patient is required to lie still for the entire length of the study. Claustrophobia is usually treated with diazepam 1–2 mg po. On rare occasions, conscious sedation and/or anaesthesia may be used, both of which require additional qualified personnel.

3.1.4.2. Diabetes

The patient's blood glucose level should be controlled prior to the study in order to obtain the best possible image quality. The control of blood glucose levels is sometimes challenging, so that diabetic patients need special preparation prior to the study. It should be noted that metformin may markedly increase FDG uptake in the intestinal tract (see Section 3.2).

3.1.4.3. Allergies

If intravenous contrast material is to be used, the patient should be screened for a history of iodinated contrast material allergy, the use of metformin for the treatment of diabetes mellitus and a history of renal disease. Intravenous contrast material *should not* be administered when the serum creatinine level is above 1.6 mg/dL or above the normal limit for each institution [3.5].

3.1.4.4. Renal failure

Images of patients with renal failure are usually of poor quality due to reduced renal clearance. However, this should not be considered a study contraindication.

3.1.4.5. Surgeries and previous invasive diagnostic procedures

FDG accumulates in inflamed or infected tissue and in tumours. In patients with a prior history of surgery and/or invasive diagnostic procedures, FDG uptake can occur at the site of the intervention, such as in scar tissue, as well as in enlarged, reactive lymph nodes located in close proximity to the surgical site. It is not uncommon to observe a halo of diffuse, low grade uptake at the periphery of lesions treated with radiofrequency ablation, which can be differentiated from residual disease, and in turn may be characterized by focal/nodular intense uptake in the treated area. However, other complications from these radiofrequency

procedures may potentially cause false positive results, so that a detailed history is always needed in order to minimize erroneous reporting [3.6].

3.1.4.6. Radiation therapy

Tissue irradiation causes oxidative stress, which leads to inflammation and thus increased FDG uptake. This is especially important in head and neck tumours, in which altered metabolism in irradiated tissues may persist up to one year after RT [3.7].

3.1.4.7. Hematopoietic cytokines

Increased diffuse bone marrow uptake can also be seen in patients with hyperplasia and reactive hematopoietic stimulation from anaemia. Treatment with hematopoietic cytokines such as granulocyte colony-stimulating factor (CSF), hematopoietic growth factor or erythropoietin can also produce diffuse skeletal FDG uptake, which can persist for up to 3 weeks after the discontinuation of granulocyte CSF treatment. FDG-PET should be delayed for at least 1 week after administration of short acting cytokines and up to 3 weeks after administration of long acting cytokines or chemotherapy.

3.1.4.8. Chemotherapy

Chemotherapy will increase bone marrow and gastrointestinal tract toxicity, which may change radiotracer biodistribution, as well as tumour uptake. A careful history regarding the initiation and conclusion of chemotherapy cycles and the type of medication(s) used is needed. Most chemotherapeutic agents may cause a reduction of uptake in prior lesions, although a few drugs such as tamoxifen [3.8] and bevacizumab [3.9], in addition to standard chemotherapy, may cause a flare phenomenon due to inflammatory reactions in the lesions. Other immunotherapy agents may also cause inflammatory reactions and interim therapy scanning may be confounding, especially in lymphoma patients [3.10] (see Sections 5 and 6).

3.1.4.9. Infection and inflammation

Sites of inflammation and infection (bacterial, fungal, non-caseous granulomatous diseases or even inflamed arterial plaques) are well known to have different degrees of FDG avidity [3.11] (Fig. 3.3). Inflammatory or infectious processes are usually highly FDG avid, and differentiation with neoplastic processes may be difficult. Granulomatous diseases such as sarcoidosis are usually highly FDG avid. A controversial point is the waiting period between RT

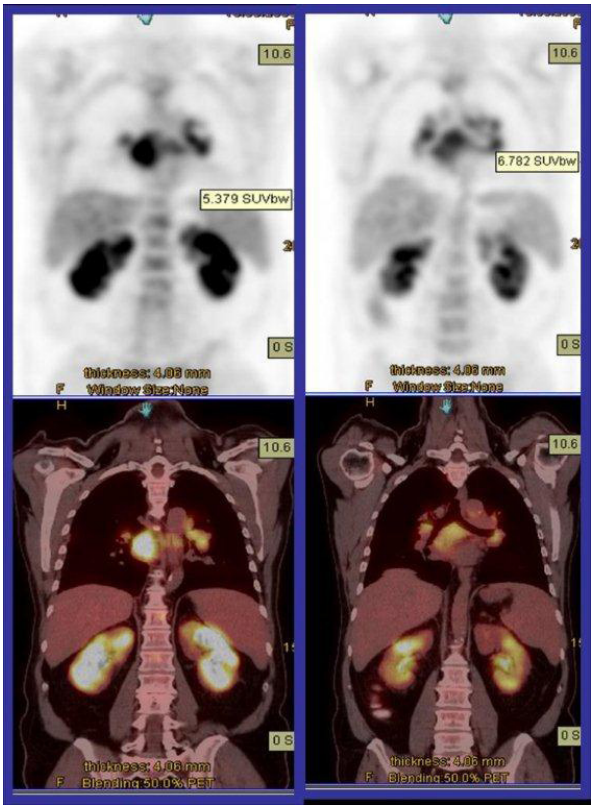

FIG. 3.3. FDG uptake in mediastinal lymph nodes in a patient with granulomatous disease.

and PET scanning, which should be 4–6 weeks in order to avoid misinterpretation due to inflammatory tissue increasing metabolic activity and FDG uptake in the areas treated with radiation. Recent surgery (within 6 weeks) can cause increased FDG uptake in the surgical incision, sutures and tube sites. Assessment for residual tumour is usually difficult. Some of the most important factors that affect FDG uptake and the timing between therapy or clinical conditions and a PET scan are presented in Table 2.2 (Section 2).

3.2. PATIENT PREPARATION

3.2.1. Patient arrival

Patients should be advised to arrive at the nuclear medicine laboratory at least 30 min prior to their scheduled appointment. This will allow a period of rest prior to FDG injection, normalization of the body temperature on cold days

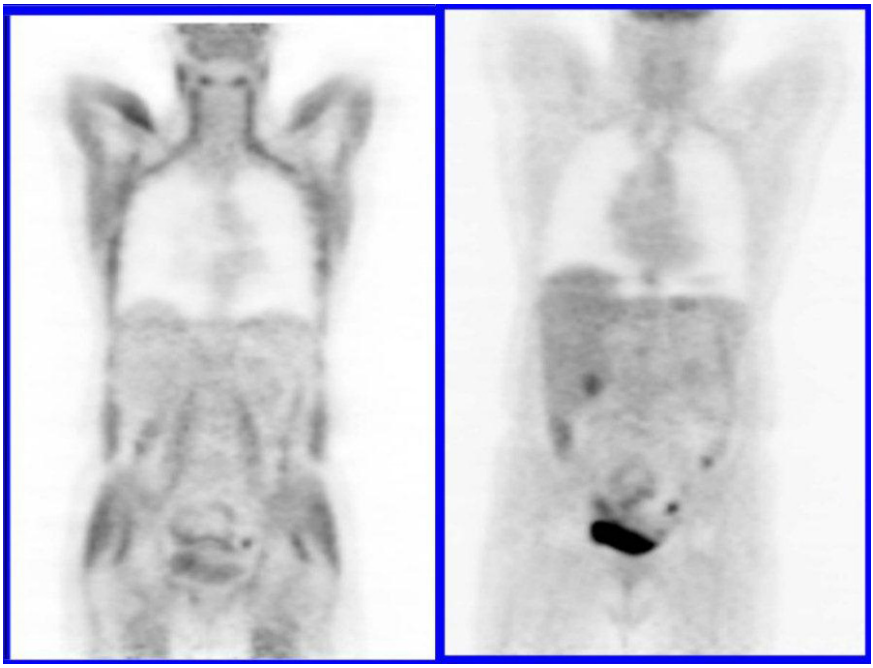

FIG. 3.4. The same patient shown in Fig. 3.3, with two different blood glucose levels at the time of radiotracer administration. Left: The patient with increased blood glucose levels. Note the marked FDG uptake in the muscles and reduced uptake in the liver and brain. Right: After fasting, there is no more FDG uptake in the muscles and increased uptake in the liver.

(minimizing uptake in brown fat), and history taking without delaying the start of the study and the patient's stay.

3.2.2. Fasting

Patients should fast for at least 4 h (preferably 6 h) prior to FDG injection in order to reduce muscle uptake (Fig. 3.4).

In children younger than 6 years of age, the period of fasting should not exceed 3 h, due to the fact that, by the time the PET/CT study is finished, they will not have eaten for more than 4.5 h.

It is recommended that all parenteral nutrition and intravenous fluids containing glucose be discontinued for 4−6 h prior to the study in order to reduce serum insulin to baseline, thus minimizing the shift of FDG uptake into muscle and fat. This will also permit the identification of fasting hyperglycaemia.

3.2.3. Hydration

Patients should be well hydrated to guarantee proper voiding. Hydration may be performed by oral ingestion or by administering a saline solution through a venous catheter.

3.2.4. Resting

All patients are to refrain from any strenuous activity or exercise for 24 h prior to the study. This will guarantee that FDG muscle uptake is reduced. FDG muscle uptake can be seen in the following sites:

— Diaphragm, due to hyperventilation (Fig. 3.5);
— Trapezius and paraspinal muscles, in anxious patients;
— Vocal cord and larynx, in patients who speak during the uptake phase (Fig. 3.6);
— Masticatory muscles, in patients who chew gum before and after radiotracer injection (Fig. 3.7).

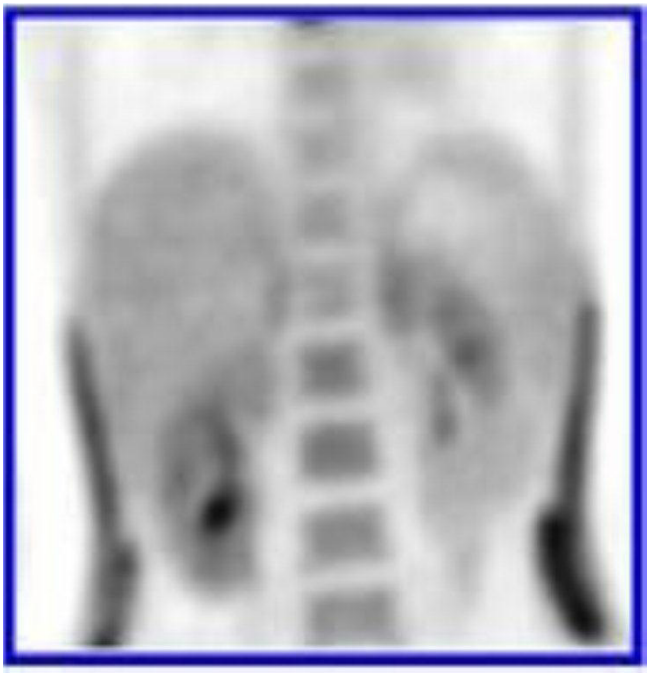

FIG. 3.5. FDG uptake in diaphragmatic muscle due to hyperventilation.

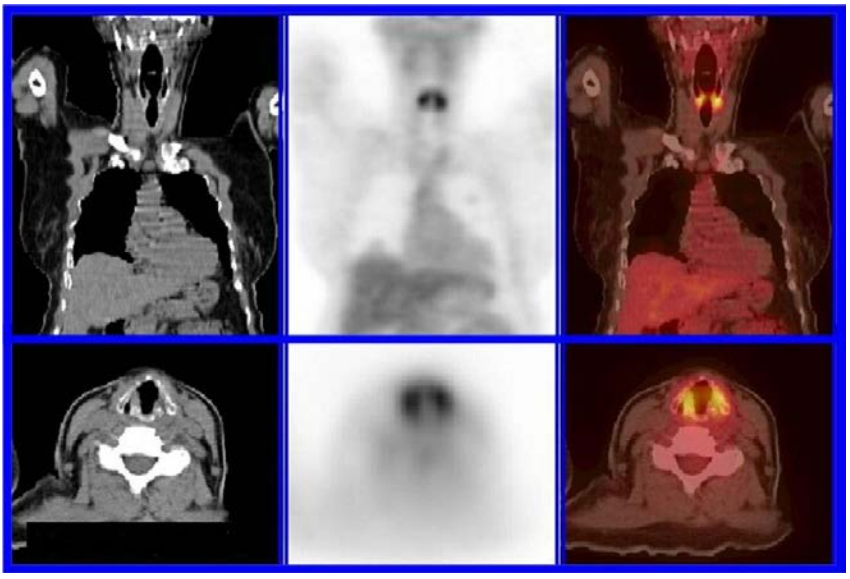

FIG. 3.6. FDG uptake in the vocal cords of a patient who had been speaking before and after radiotracer administration.

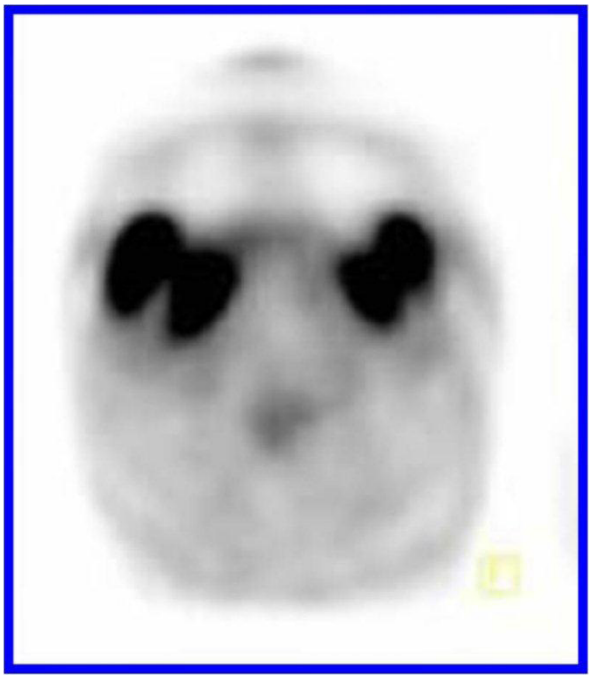

FIG. 3.7. FDG uptake in masticatory muscles (pterygoid and masseter) in a patient who had been chewing gum.

Benzodiazepines (5 mg) may be administered to obtain higher muscle relaxation and thus less uptake and to prevent/reduce brown fat FDG uptake. Brown fat uptake may also be reduced by using low dose beta-blockers such as oral propranolol (20 mg) 60 min prior to FDG injection [3.12].

3.2.5. Brain images

Patients undergoing brain PET/CT imaging should remain resting in a dark, quiet room for 15 min prior to radiotracer injection and for at least 30 min afterwards. This will reduce radiotracer uptake in brain areas that, when stimulated, show a higher level of uptake, such as the visual cortex.

3.2.6. Blood glucose levels

The patient's blood glucose level should be checked prior to radiotracer injection. Increased blood glucose levels cause increased insulin levels, altering the FDG biodistribution by shifting its uptake to muscle and fat. Therefore, if the glucose level is above 200 mg/dL or below 50 mg/dL, the nuclear medicine physician should be consulted before proceeding with the radiotracer injection.

— Among *non-diabetic* patients, plasma glucose levels should not exceed 130−150 mg/dL. In *diabetic* patients, these levels should be no higher than 180–200 mg/dL.
  • FDG tumour uptake is reduced in hyperglycaemic conditions (Fig. 3.8).
— Those patients whose blood glucose levels exceed the recommended values should be rescheduled. If a patient cannot be rescheduled for some specific reason, the following procedures are acceptable:
  • Administer an intravenous dose of 1−2 U of 'regular' insulin. Check blood glucose levels every 30 min. Blood glucose levels should drop. When blood glucose levels begin to increase again, FDG may be injected. If blood glucose levels are below 60 mg/dL, serum glucose 50% should be injected and the test suspended and rescheduled.
  • Administer an intravenous dose of 0.03–0.05 U/kg of 'regular' insulin. Check blood glucose levels every 15 min. Blood glucose levels should drop. When blood glucose levels begin to rise again, FDG may be injected. If blood glucose levels are extremely reduced, serum glucose 50% should be injected and the test suspended and rescheduled.

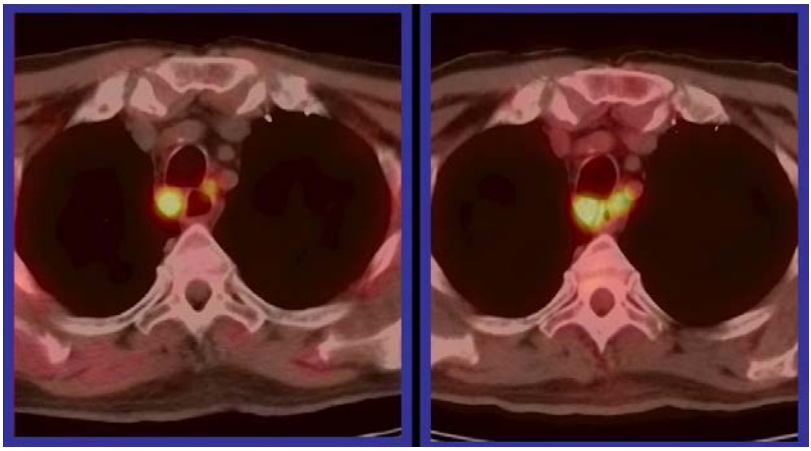

FIG. 3.8. FDG uptake in mediastinal lymphadenopathy in a patient with lymphoma. Left: Image obtained with the patient in a hyperglycaemic state. Right: Images obtained 2 days later of the same patient in the normal glycaemic state. Note how the same lymph nodes exhibited increased uptake after proper patient preparation.

3.2.7. Diabetic patient protocol

Diabetic patients should adhere to their normal dietary and insulin schedule (eat a light meal early in the morning and take their medication). If possible, these patients should be scheduled for injection after 12 noon. The study is not recommended when blood glucose levels are above 200 mg/dL. Insulin may be administered to reduce blood glucose levels prior to radiotracer injection:

— With 'regular' insulin, a dose of 1–2 U should reduce blood glucose levels. If the blood glucose reaches adequate levels, a radiotracer may be injected 90 min after the insulin injection. If blood glucose levels are extremely low, serum glucose 50% should be injected and the study suspended and rescheduled [3.13, 3.14].

3.3. PATIENT SET-UP

Before beginning the study, patients should be prepared as follows:

(1) Patients should be questioned regarding:
— Whether they have fasted prior to the study (Fig. 3.9).
— Female patients of child-bearing age for possibility of pregnancy.

— Female patients of child-bearing age for possibility of breastfeeding.
— Prior surgery, especially mastectomy and lymphadenectomy. The radiotracer should be injected in the arm contralateral to a mastectomy, and, in the case of a bilateral mastectomy, in the foot.

(2) Patients should be asked to wear a gown and remove all metal objects.
— Metallic objects will interfere with the CT portion of the study, causing artefacts and overcorrecting the PET emission images.

(3) The height and weight of the patient should be recorded using a scale.
— This will guarantee precision when calculating the uptake values.

(4) Insert an IV catheter (22 or 24 gauge) contralateral to the side of the surgery. Do not remove the IV line until the end of the study.

(5) If indicated (mainly for abdominal lesion detection), have the patient drink the oral contrast. Allow 15 min for the patient to drink the contrast from the time of arrival; if the patient does not finish contrast, inject the FDG. Have patient drink half a cup of water to remove the barium from the pharynx.

(6) Patients should void just prior to imaging.

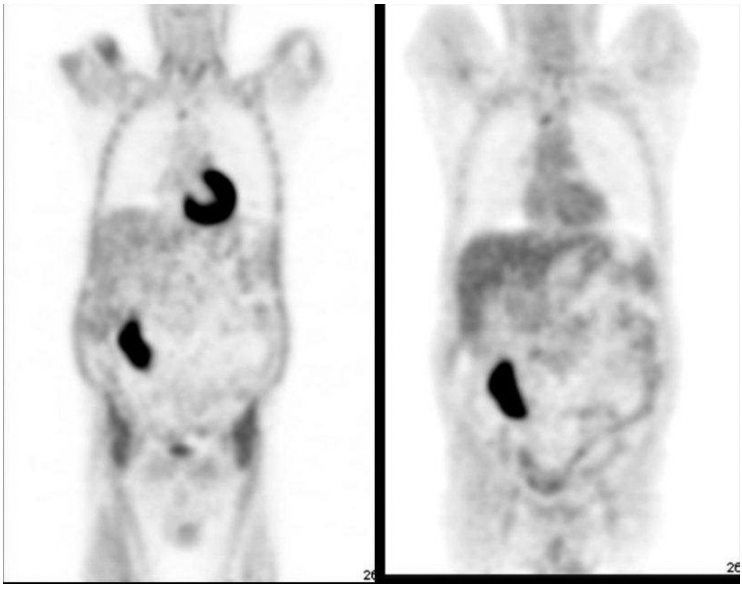

FIG. 3.9. Fasting prior to study will alter the FDG biodistribution. Left: Image acquired after FDG was administered in the hyperglycaemic state, showing increased radiotracer uptake in muscles (especially in the thorax and pelvis) and reduced uptake in the liver. Right: Image acquired after fasting, showing reduced FDG uptake in the muscles and increased uptake in the liver.

3.4. RADIATION SAFETY

Hybrid imaging imparts a higher radiation dose to the patient, typically in the range of 10–20 mSv of effective dose. Every effort should therefore be made to apply the principles of radiation protection. Also there is a potential for relatively high radiation exposure of staff.

The principles of radiation protection are well established. The ICRP provides recommendations on these principles, which are addressed in its two main publications [3.15, 3.16]. The operational aspects of the principles include justification and optimization. Justification is achieved by using appropriateness criteria developed by professional societies in order to avoid unnecessary examinations, and optimization through use of the ALARA principle (taking into account other factors such as image quality or clinical purpose and cost) to perform imaging with diagnostic quality at minimum radiation dose to patient.

The IAEA has developed standards for radiation safety, the BSS [3.17], which national organizations use to frame their own regulations. The BSS and associated guidance documents [3.17–3.19] are intended to help users to achieve a good standard of protection and to develop a consistent national approach to licensing and inspection. Since PET/CT is a relatively new area, most countries do not yet have specific national guidance, so the IAEA publications can play an important role. The internationally harmonized guidance from the IAEA regarding radiation protection is of recognized importance in Member States.

In PET/CT facilities, situations in which there is a potential for radiation exposure are reasonably well known. The levels of radiation dose that can be encountered by staff and patients have been estimated in a number of publications and have been reviewed in earlier IAEA publications [3.19, 3.20].

3.4.1. Protection of patients

There are no dose limits prescribed by any international or national organizations for patients. This does not mean that any amount of radiation dose can be delivered to a patient in medical examinations and procedures. The concept of diagnostic reference levels (DRLs) provides guidance on appropriate activity. DRLs are not dose limits, as they are established based on contemporary technology and practice. They should be applied with flexibility, allowing higher doses where indicated by sound clinical judgement. DRLs are provided in measureable quantities, such as administered activity for PET and volume computed tomography dose index (CTDIvol) for CT. DRLs are not given in effective dose, which is estimated rather than measured. Unlike with CT, there are no DRLs for PET examinations, but guidelines from professional societies are available [3.21].

In hybrid imaging, a typical dose from a diagnostic CT scan can be in the range of 5−10 mSv of effective dose, a low dose CT may give 2−4 mSv, and a typical PET or single photon emission computed tomography (SPECT) may be in the range of 5−10 mSv. Thus, a PET/CT or SPECT/CT scan with diagnostic CT may impart 10−20 mSv, and with low dose CT, 7−14 mSv. Some organs, such as the bladder, heart wall and brain, may receive more than 10 mGy of absorbed dose. Further information is available on the Radiation Protection of Patients (RPOP) pages of the IAEA web site [3.22].

3.4.2. Protection of staff

A significant part of the radiation exposure to staff accrues from the handling of radiopharmaceuticals and, in particular, the syringes containing the injections. For an injection syringe with 10–15 mCi (370−560 MBq) of ^{18}F-FDG, for example, the resulting finger doses can be as high as 30 μSv or higher per patient procedure [3.20]. The localized exposure to hands and fingers does not become evident in effective dose calculations, so that talking about effective dose alone may be totally misleading where localized exposure to areas with low tissue weighing factors (hands and fingers) is prominent. The effective dose is not useful for estimating tissue reaction (deterministic risk) to fingers, as it is primarily an index developed for stochastic risk estimation. The exposure to hands and fingers can result in tissue reaction to skin. For this reason, dose limits are also specified for hands (500 mSv/a), and are based on tissue reaction relative to a threshold for erythema. Similar dose limits have also been specified for the lens of the eye (cataract) and for the thyroid (based on the stochastic risk of thyroid cancer). For the staff of the PET/CT facility, the main sources of radiation exposure include:

— Unshielded radiopharmaceuticals (present during preparation and dispensing).
— Patients injected with PET radiopharmaceuticals.
— The toilet for patients.
— Sealed calibration sources, quality assurance phantoms.
— The CT scanner. Some staff in nuclear medicine may have difficulty in realizing that they need to remain at a distance/outside the room when the CT is being taken. For the PET part, there is no difference in staff exposure whether the PET scanning is ON or OFF (e.g. during the patient's adjustments), whereas, for the CT part, the radiation appears only when the scan is being taken (X ray tube ON).

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4. DOSE, ACQUISITION, INTERVENTIONS, PROCESSING AND DISPLAY

4.1. INJECTED ACTIVITY OF FDG

4.1.1. Injected activity in adults

When deciding what activity should be injected into the patient, the physician should bear in mind the ALARA (as low as reasonably achievable) principle. Injected activity must guarantee good quality images and also be reduced to guarantee minimal patient and staff exposure. Several factors are to be taken into consideration, including: (i) patient related factors (e.g. age, weight, body mass), and (ii) scanner related factors (e.g. crystal type (LSO, LYSO, BGO, GSO), acquisition mode (2-D, 3-D), bed overlap (25%, 50%) and acquisition time per bed position).

— Generally accepted activity: 185−555 MBq (5–14 mCi) [4.1].
— The injected activity may vary according to the acquisition mode (2-D versus 3-D):
  • Whole body protocol in 3-D mode with less than 25% bed overlap for a 70 kg patient and 3 min scanning time per bed position. Generally accepted dose: 322 MBq (9 mCi).
  • Whole body protocol in 3-D mode with 50% bed overlap for a 70 kg patient and 3 min scanning time per bed position. Generally accepted dose: 161 MBq (4.3 mCi).
— Maximum recommended activity: 529 MBq (14 mCi) for patients over 90 kg (198 lb).

4.1.2. Injected activity in children

— Generally accepted activity for whole body studies: 3.7–5.2 MBq/kg (0.10–0.14 mCi/kg) [4.2].
— Brain: 3.7 MBq/kg (0.10 mCi/kg).
— Minimum dose: 37 MBq (1.0 mCi).

4.1.3. Precautions

— The injection must be in the arm contralateral to a primary tumour in the thorax, breast or arm.

— Records needed: net injected dose, dose remaining in the syringe and the time of injection. This will ensure proper calculation of tracer uptake (SUV).

4.2. DOSES OF OTHER NECESSARY MEDICATIONS

All medications being taken by the patient should be recorded for legal reasons and to ensure proper patient preparation in follow-up studies.

4.2.1. Furosemide

— For renal/pelvis delayed imaging [4.3] (Fig. 4.1).
— Furosemide dose: from 2 mg/kg to 40 mg.
— Furosemide is best given after initial whole body images. Patient must be hydrated for at least 30 min and void prior to acquisition.

4.2.2. Diazepam

— Benzodiazepines may be administered to obtain higher muscle relaxation and lower brown fat uptake [4.4]:

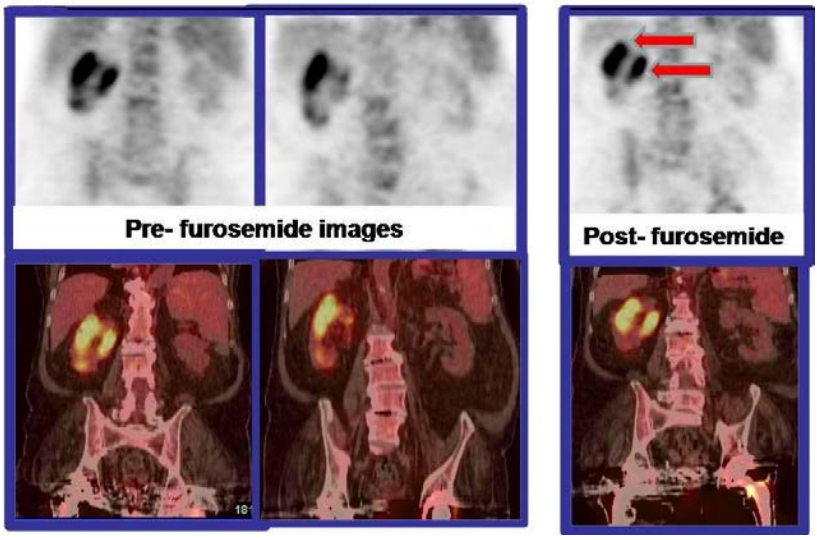

FIG. 4.1. FDG images of the kidneys showing renal tracer excretion. After furosemide injection, hyperhydration and voiding, delayed renal imaging showed focal areas of FDG uptake in the right kidney, suspicious for infection, indicated by the red arrows. Biopsy revealed renal tuberculosis.

- Brown fat uptake will occur mainly in children, adolescents and young women, and during cold weather (Fig. 4.2).
- Muscle uptake will occur mainly in anxious patients and in patients undergoing head and neck surgery.

— Per os (po) diazepam dose: 1–2 mg.
— Intravenous dose: 5 mg (adult dose) or 0.06 mg/kg.
— Diazepam is best given 30 min prior to radiotracer injection:
  (i) If diazepam has to be given after whole body images have been performed, reschedule the patient for another day and administer diazepam prior to imaging.
  (ii) If the imaging is to be performed on the same day, the patient should be instructed to discontinue fasting, and to return in the afternoon after fasting for 4 h. Administer diazepam prior to imaging.

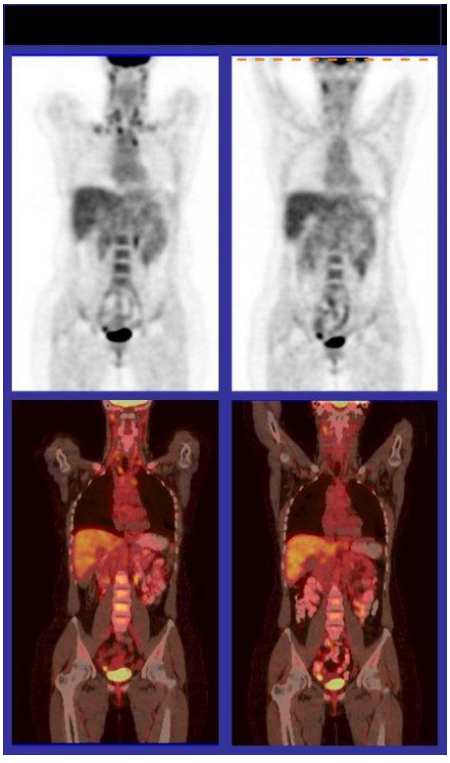

FIG. 4.2. FDG images on the left show brown fat uptake. FDG images on the right do not show brown fat uptake after administration of benzodiazepines.

4.2.3. Beta-blockers

Beta-blockers such as propranolol may be administered to obtain higher muscle relaxation and lower brown fat uptake [4.5, 4.6].

— Oral propranolol dose: 10–40 mg (adults).
— Administer 30−60 min prior to radiotracer injection.
— Precautions should be taken when administering propranolol in the following situations:
  • Liver or renal failure;
  • Glaucoma;
  • History of anaphylaxis due to beta-blockers;
  • Cardiac failure and patients with slow heart rate;
  • Diabetes;
  • Asthma.

4.2.4. Insulin administration

If the patient cannot be rescheduled and insulin has to be administered to reduce blood glucose levels, the following procedures are acceptable:

— Intravenous dose of 1–2 U of 'regular' insulin. Check blood glucose levels every 30 min. Blood glucose levels should drop. When blood glucose levels begin to increase again, FDG may be injected. If blood glucose levels are extremely low, serum glucose 50% should be injected and the test suspended and rescheduled.
— Intravenous dose of 0.03−0.05 U/kg of 'regular' insulin. Check blood glucose levels every 15 min. Blood glucose levels should drop. When blood glucose levels begin to rise again, FDG may be injected. If blood glucose levels are extremely low, serum glucose 50% should be injected and the test suspended and rescheduled [4.7, 4.8].

4.2.5. Oral contrast

An intraluminal gastrointestinal non-caloric contrast agent may be administered to provide adequate visualization of the gastrointestinal tract, unless it is medically contraindicated or unnecessary for the clinical indication. This may be a positive contrast agent (such as dilute barium), an oral iodinated contrast agent or a negative contrast agent (such as water). Collections of highly concentrated barium or iodinated contrast agents can result in attenuation correction artefacts that can lead to significant overestimation of the SUV [4.9].

Other dilute positive and negative oral contrast agents cause less overestimation and do not affect the PET image quality [4.10–4.12]. Water is useful for visualization of the stomach and proximal small bowel, although it is absorbed at the distal ileum and does not allow good visualization of the colon. A low attenuation 0.1% barium sulphate suspension has been shown to provide excellent gastrointestinal tract distension and superb visualization of mural features.

4.2.6. Intravenous contrast

— If an intravenous contrast material is to be used, a careful assessment of the patient's history of allergies to iodinated contrast material is necessary, as well as the patient's renal condition.
— When an IV contrast agent (iopamidol 61%, 30% organically bound iodine) is given, the timing of the IV contrast bolus can be optimized using automated triggering with serial low dose CT. IV contrast material (150 mL) is injected at 3 mL/s and is followed by a 30 mL saline flush [4.13].
— If it is planned to use IV contrast in diabetic patients treated with biguanides (such as metformin), the medication will have to be stopped before the scheduled date of the PET/CT scan according to the guidelines of individual institutions. In the case of these patients, it may be necessary to use insulin, using the criteria explained above, in order to control the serum glucose level.

4.3. IMAGE ACQUISITION

4.3.1. Routine image acquisition

— The time to image post-injection should be strictly followed for every patient to ensure proper patient follow-up (see Section 5).
— The recommended time to image after radiotracer injection is 60 min to ensure a higher tumour to background ratio.
— The patient should void prior to image acquisition.
— It is standard practice in CT to position patients with their arms raised above their head. If the arms are left parallel to the patient's body, beam artefacts from the long bones of the arms and forearms will degrade the quality of images of the chest and abdomen. The overall radiation exposure to the subject needs to be increased.
— Patients should be supported with adequate positioning aids (e.g. knee, head and neck, and arm supports) to limit involuntary motion that may lead to general or local misalignment during the combined examinations [4.14].

— Routine images: from the base of the skull to the proximal third of the thighs (standard body study).

4.3.2. Patient instructions prior to start of the acquisition

— Breathe normally: hyperventilation may cause increased diaphragm uptake and lung nodule artefacts (Fig. 4.3).
— Do not move: motion will cause misregistration artefacts.

4.3.3. Brain image acquisition

— For brain tumours or suspected metastases, note that CT images are no substitute for MRI images for detection and assessment of primary tumours or metastases.
— The images should have high resolution (longer acquisition times, e.g. 15 min per bed position).

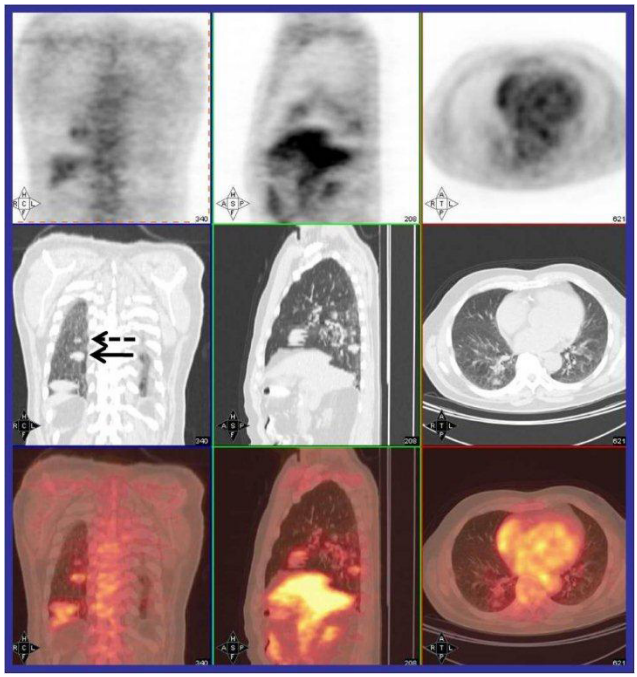

FIG. 4.3. Images of the lung of a hyperventilating patient. Note the lung nodule (full arrow) and, immediately above (dotted arrow), a lung nodule artefact, caused by hyperventilation. Note also the artefact in the dome of the liver.

— Brain FDG-PET images can be acquired 30−45 min after radiotracer injection.
— For primary brain tumours, obtaining a delayed set of FDG-PET images 4−6 h after radiotracer injection will increase the tumour to background contrast considerably.

4.3.4. Additional image acquisition

4.3.4.1. Whole body study (melanoma protocol): Images from top of the skull to the feet

For tumours with a high probability of metastases to the head, brain or lower limbs, such as lymphomas, melanomas, neuroblastomas and osteosarcomas (Fig. 4.4), the patient's arms should be positioned outside the field of view.

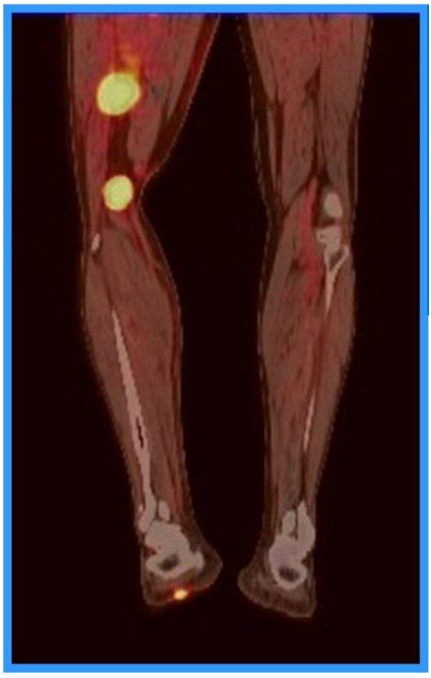

FIG. 4.4. Lower extremity coronal image in a patient with melanoma showing metastatic lesions in the right thigh and foot.

4.3.4.2. Head and neck lesions

These images can be delayed until approximately 2 h post-injection to ensure a higher lesion to background ratio.

— High resolution images only of the head and neck regions (after the routine images have been acquired) (Fig. 4.5).
— Consider IV contrast.
— Oral contrast is not recommended in patients being evaluated for head and neck tumours because swallowing may cause FDG uptake in the oropharynx, obscuring the visualization of this region.

4.3.4.3. Dedicated lung image acquisitions

After the routine images have been performed, additional delayed and dedicated high resolution images only of the lungs may be acquired.

— Consider the acquisition of a respiratory synchronized study — respiratory 4-D (gated) imaging [4.15].

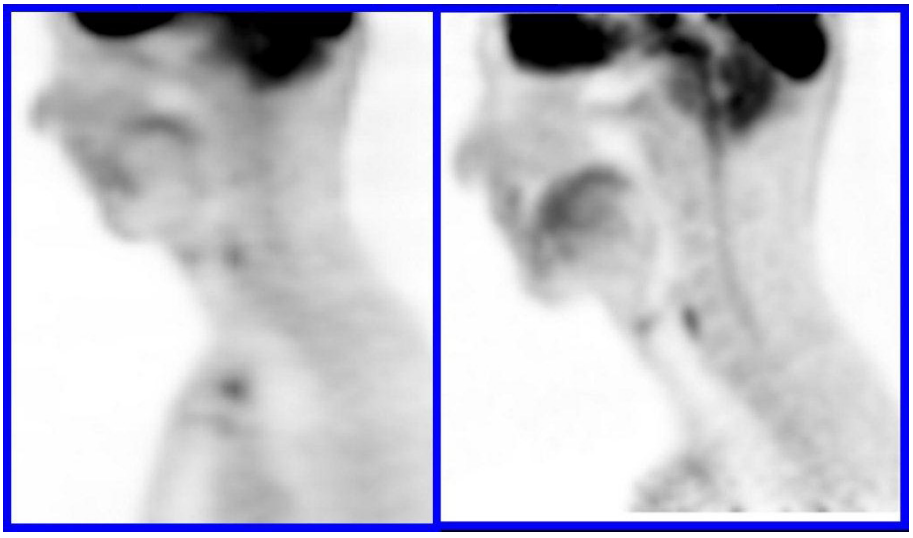

FIG. 4.5. Images of the head and neck acquired using 3 min per bed (left) and delayed, 8 min per bed (right). Note the improved quality of the images on the right. There is a clear view of the spinal cord, tongue and the lesion posterior to the trachea.

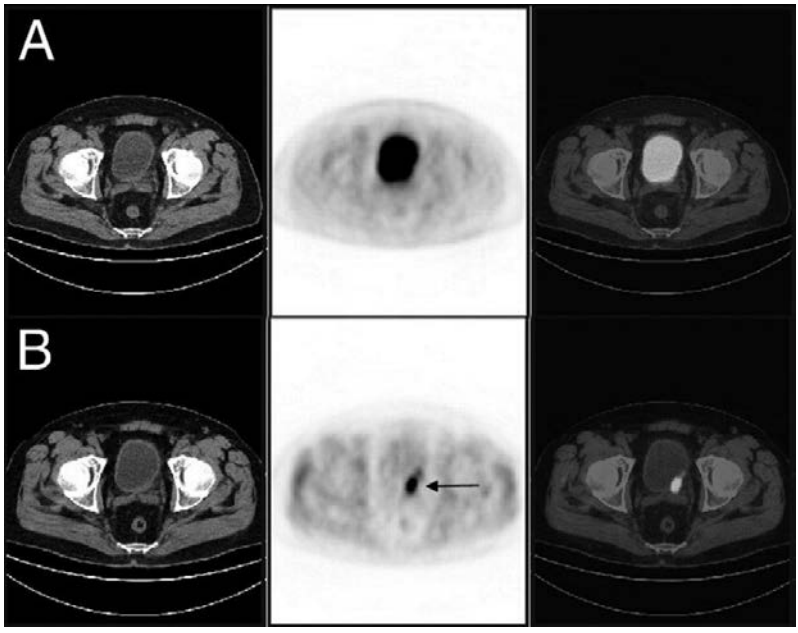

FIG. 4.6. (A) FDG in the bladder. (B) Additional delayed high resolution images of the pelvic region (following the acquisition of routine images) after furosemide injection, hydration and voiding show a hypermetabolic lesion in the posterior wall of the bladder and wall thickening consistent with malignancy. Biopsy diagnosed bladder cancer.

4.3.4.4. Pelvic lesions

After the routine images have been performed, additional delayed high resolution images only of the pelvic region may be acquired following furosemide injection, hydration and voiding (Fig. 4.6) [4.3].

4.3.4.5. Abdominal lesions

After the routine images have been performed, additional delayed high resolution images only of the abdomen may be acquired to detect peritoneal carcinomatosis. Furosemide injection, hydration and voiding may be needed to increase detection of nodes in the pelvic region (Fig. 4.7) [4.16].

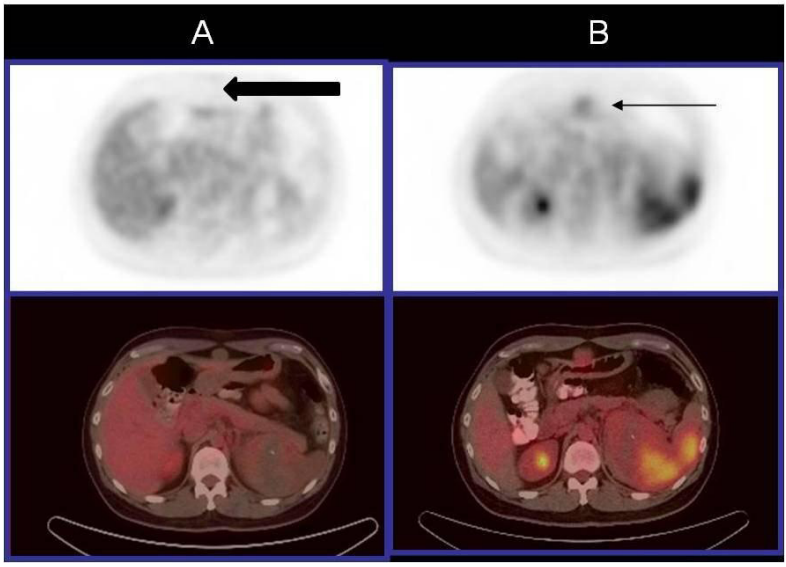

FIG. 4.7. (A) Peritoneal nodule seen on CT without FDG uptake. (B) Additional delayed images only of the abdomen show increased uptake in the peritoneal nodule, consistent with malignancy. Biopsy confirmed peritoneal carcinomatosis.

4.3.5. Estimation of lesion uptake

Lesion uptake is measured by the SUV, which is calculated based on radioactivity in the lesion, the injected activity and the patient's body weight. If quantifying the average of all pixels within the region of interest (ROI), the result will be SUV_{avg}, whereas with the maximum the result is expressed as SUV_{max}:

$$SUV = \frac{\text{Mean ROI activity (mCi/mL)}}{\begin{array}{c}\text{Injected activity (mCi)/body weight (g)}\\ \text{or lean body mass (LBM)}\\ \text{or body surface area (BSA)}\end{array}}$$

4.4. IMAGE ACQUISITION AND PROCESSING

Tables 4.1–4.3 present accepted parameters for image acquisition (note that these references may not apply to all PET systems).

TABLE 4.1. ACCEPTED PARAMETERS FOR IMAGE ACQUISITION

	Whole body	Brain	Head and neck
Reconstruction method	Iterative (cranial/caudal)	Iterative (cranial/caudal)	Iterative (cranial/caudal)
Interactions	2	6	4
Subsets	16	16	16
Image size (pixels)	128/168	256	256
Filter	Gaussian	Gaussian	Gaussian
FWHM (full width at half maximum)	4.0	4.0	4.0
Zoom	1	2	1
Normalization	Yes	Yes	Yes
Scatter correction	Yes	Yes	Yes
Minutes per bed	2	2	4

TABLE 4.2. CT IMAGING OPTIONS IN PET/CT

	Contrast	Indication	Breathing	Advantages	Disadvantages
CT ONLY for attenuation correction and anatomical mapping	Oral No IV	Initial staging Restaging	Breath holding in quiet end-expiration	Low radiation dose Complete metabolic information	Limited anatomical information
PET combined with CT of diagnostic quality with IV contrast	Oral IV	Initial staging Restaging	Breath holding in quiet end-expiration	Complete metabolic information Complete anatomical information	Increased radiation dose Requires IV contrast Risk of missing small pulmonary nodules
PET combined with CT of diagnostic quality without IV contrast	Oral No IV	Initial staging Restaging	Breath holding in quiet end-expiration	Complete metabolic information Complete anatomical information	Increased radiation dose Risk of missing small pulmonary nodules
PET/CT with special interest in the chest	Oral No IV	Initial staging Restaging: Lung cancer Oesophageal cancer	Breath holding in quiet end-expiration followed by breath holding at end of full inspiration	Complete metabolic information Complete anatomical information in the chest	Limited evaluation of hilar regions Limited evaluation of the abdomen and pelvis

TABLE 4.3. PARAMETERS FOR CT AQUISITIONS

Parameter	Parameters for CT scan for attenuation correction and anatomical localization, 3-D PET/CT	Parameters for CT scan for attenuation correction and anatomical localization for patients with head and neck tumours, 3-D PET/CT		Parameters for CT scan for attenuation correction and diagnostic parameters, 3-D PET/CT
Protocol	Standard body study	Standard body study	Neck	Standard body study
Coverage	From base of the skull to upper thighs	From base of the skull to upper thighs	Frome top of the skull to aortic arch	From base of the skull to upper thighs
Patient positioning	Arms up	Arms up	Arms down	Arms up
Scout	120 mV – 10 mA	120 mV – 10 mA	120 mV – 10 mA	120 mV – 10 mA
Scan type	helical	helical	helical	helical
Rotation time	0.6 s	0.6 s	0.5 s	0.5 s
Rotation length	Full	Full	Full	Full
Detector coverage	40 mm	40 mm	40 mm	40 mm
Helical thickness	3.75 mm	3.75 mm	3.75 mm	3.75 mm
Pitch	0.984:1	0.984:1	0.984:1	0.984:1
Table speed	39.37 mm/rotation	39.37 mm/rotation	39.37 mm/rotation	39.37 mm/rotation

TABLE 4.3. PARAMETERS FOR CT AQUISITIONS (cont.)

Parameter	Parameters for CT scan for attenuation correction and anatomical localization, 3-D PET/CT	Parameters for CT scan for attenuation correction and anatomical localization for patients with head and neck tumours, 3-D PET/CT		Parameters for CT scan for attenuation correction and diagnostic parameters, 3-D PET/CT
Coverage speed	65.62 mm/s	65.62 mm/s	78.74 mm/s	65.62 mm/s
Tube potential	120 kV	120 kV	120 kV	120 kV
Tube current	Smart mA (auto mA) mA range: minimum 50–maximum 100	Smart mA (auto mA) mA range: minimum 50–maximum 100	Smart mA (auto mA) mA range: minimum 30–maximum 100	Smart mA (auto mA) mA range: minimum 120–maximum 650
Noise index	12.35	12.35	12.35	12.35

4.4.1. Protocol for CT imaging during the acquisition of PET/CT

CT uses an external source of radiation to provide 3-D images of the density of tissues in the body. CT is used for attenuation correction of the PET data and provides information about the size and shape of organs and abnormalities within the body. Combined PET/CT scanners provide the metabolic information from FDG-PET coregistered with the anatomical information from CT in a single examination [4.17, 4.18]. With technological improvements, current PET/CT scanners now provide state of the art PET combined with state of the art CT.

The CT scan can be acquired using different protocols depending on the needs of the patient, the clinician's request and the training of the interpreting physician. The PET/CT examination can be performed either as a diagnostic PET/CT scan with the CT scan obtained for attenuation correction and anatomical correlation, or as a diagnostic PET scan and an optimized CT scan, with or without contrast. If a diagnostic CT scan is requested, the CT protocol appropriate for the body region(s) under study should be used. If the CT scan is obtained for attenuation correction and anatomical correlation, the CT parameters should be set to minimize the radiation dose to the patient, while still ensuring that the CT images are of sufficient quality to allow for accurate anatomical correlation of PET findings [4.19].

There are several options for the use of CT images, and the appropriate protocol should be defined by the interpreting nuclear medicine physician based on the referring physician's clinical question and the patient's needs. The most frequently used options are displayed in Table 4.1.

— *PET/CT with CT for attenuation correction and anatomical mapping only.* This is the most common scenario. The CT is used as a transmission scan for attenuation correction. All patients receive oral negative contrast with the exception of patients with head and neck tumours. No IV contrast is given. The radiation dose is low. The patient is instructed to hold his or her breath in quiet end-expiration to match the PET emission scan obtained with shallow breathing. The CT scan is acquired. The CT findings are reviewed and correlated with the PET findings but are not formally reported. CT findings of potential significance are included in the PET report. The majority of these patients will have already undergone a recent diagnostic CT examination.
— *PET combined with thoracic, abdominal and pelvic CT performed with oral and IV contrast enhancement.* The CT is of diagnostic quality and may be used for attenuation correction. The patient is instructed to hold his or her breath in quiet end-expiration to match the PET emission scan obtained with shallow breathing. In this case, there will be separate PET

and CT reports, or one report that thoroughly describes the CT and PET findings. The PET portion is interpreted by the nuclear medicine physician and the CT portion by a nuclear radiologist or a radiologist. This option is most appropriate when both PET and diagnostic CT studies are indicated. Referring oncologists frequently request PET/diagnostic CT with contrast enhancement for initial staging studies and for the evaluation of diseases and conditions such as liver lesions in which IV contrast material is needed for accurate assessment.

— *PET combined with thoracic, abdominal and pelvic CT of diagnostic quality with oral contrast but without IV contrast.* The CT may be used for attenuation correction. The patient should be instructed to hold his or her breath in quiet end-expiration to match the PET emission scan obtained with shallow breathing. This option is used when the referring physician believes that IV contrast is not necessary or is contraindicated. The referring clinician is given PET and CT reports.

— *PET/CT with special interest in the lungs.* This option can be used for patients with lung or oesophageal cancers. PET/CT with CT for attenuation correction and anatomical localization. The CT is used as a transmission scan for attenuation correction. All patients receive oral negative contrast with the exception of patients with head and neck tumours. No IV contrast is given. The radiation dose is low. The patient is instructed to hold his or her breath in quiet end-expiration to match the PET emission scan obtained with shallow breathing. The CT scan is acquired. The CT findings are reviewed and correlated with the PET findings but are not formally reported. The CT scan for attenuation correction is followed by a CT scan of the chest with the patient holding his or her breath in full inspiration. The referring physician is given a PET report and a chest CT report.

— *Scout scan or topogram.* PET/CT examinations start with the acquisition of a topogram or scout scan that is an X ray image overview of the anatomical area of interest. The scout scan is acquired during continuous table motion, typically with the X ray tube/detector assembly locked in the frontal position, generating an anatomical overview image that is similar to a conventional X ray at a given projection. The scout scan is used to define the axial examination range of the PET/CT study. The axial extent of the CT portion and that of the PET portion of the combined examinations are thereby matched to ensure fully quantitative attenuation and scatter correction of the emission data. Visual markers for the measured transverse field of view of the CT (typically 50 cm) and the PET (typically 60 cm) are displayed on the topogram. These markers guide the technologist to ensure that all body parts are positioned inside the smaller transverse field of view of the CT. Patients should be repositioned before the CT scan when

truncation of the anatomy is predicted by the scout scan. Remember that body parts not included in the CT field of view will not be attenuation corrected in the PET scan, leading to streak artefacts.

— *Image registration between PET and CT.* PET images are acquired over several minutes per bed position with the patient breathing quietly. To minimize motion artefacts, CT scans should be obtained with the patient in suspended respiration. The best image registration between CT and PET images is obtained when the patient suspends respiration at the end–tidal volume (quiet end-expiration), because the diaphragm spends the most time in this position during quiet respiration. To obtain properly registered PET/CT images, it is important that patients fully understand the breathing instructions. Many patients have undergone previous CT and need to unlearn the conventional CT instructions of full inspiration. The patient must instead be instructed carefully to hold his or her breath in quiet end-expiration. Scanning should proceed only after the patient has successfully practised the breathing manoeuvre. Accurate alignment of the PET and CT images requires that the patient remain still throughout the study. Comfort is important, and the patient is held securely on the scanning table with blankets and Velcro straps. The patient is then positioned on the scanner with both arms up. A set of handles on the scanner table above the patient's head is useful to help the patient comfortably maintain the arms-up position and eliminate motion during PET and CT acquisitions [4.20].

— *Diagnostic CT with IV contrast.* When indicated, the CT scan can be performed with IV contrast material using appropriate injection techniques. High intravascular concentrations of IV contrast agents may cause an attenuation correction artefact on the PET image, but the impact is limited. When an IV contrast agent (iopamidol 61%, 30% organically bound iodine) is given, timing of the IV contrast bolus is optimized using automated triggering with serial low dose CT. IV contrast material (150 mL) is injected at 3 mL/s and is followed by a 30 mL saline flush.

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5. RESPONSE EVALUATION IN FDG-PET/CT

5.1. BACKGROUND

5.1.1. Why we need response evaluation

Greater understanding of cancer cell biology has translated into several novel strategies in the treatment of cancer in recent times. The ultimate goal of such treatments is to cure cancer. In disseminated solid tumours, however, this goal is rarely achieved. Instead, the aim is to prolong survival. Demonstrating improvements in survival often takes years. Survival trials can also be complicated by deaths due to non-malignant causes, especially in older patients in whom comorbidities are common. Additional complexities can include patients who progress on a clinical trial but who go on to have one of several non-randomly distributed follow-up therapies, which can confound survival outcomes.

For individual patients, most cancer treatments are associated with significant side effects and costs. Thus, it is important to assess the effectiveness of a treatment early in the course of the therapy so that drug regimens can be changed and tailored for an individual. On the other hand, in the rapidly progressing world of drug development it is imperative to have surrogate end points to survival that provide earlier answers about the efficacy of therapy. Determining which innovative cancer therapeutics should be advanced to pivotal large phase III trials can therefore be unacceptably delayed if survival is the sole end point for efficacy. There is therefore a need for some surrogate metrics for survival after treatment.

5.1.2. Tumour shrinkage as a response criterion

Tumour shrinkage in response to therapy is one such parameter that has served as the standard of response evaluation in oncology. Many studies have demonstrated that a reduction in the size of a tumour following chemotherapy as measured on CT correlates well with the long term survival of the patient. Various guidelines have utilized different methodological tools for the measurement of tumour size. The measurements may be bidimensional, as recommended by the older World Health Organization (WHO) criteria, or unidimensional, as recommended by the Response Evaluation Criteria in Solid Tumours (RECIST). Reviewing the detailed methodologies of these criteria and each of their relative merits and demerits is beyond the purview of this section. However, as PET/CT studies replace PET studies around the world, it is imperative that nuclear medicine physicians are conversant with these methodologies.

5.1.3. Limitations of anatomical methods of response evaluation

While tumour shrinkage in response to therapy makes intuitive sense as a measure of response, there are many fundamental limitations to this concept. Interobserver variability in tumour size measurements is still high because of difficulties in delineating tumour tissue from secondary changes in the surrounding tissues. CT is inaccurate in differentiating viable tumour from surrounding necrotic or fibrotic tissue; consequently, the degree of response may be underestimated on CT. Conversely, if tumour shrinkage is short lived and followed by rapid tumour regrowth, CT may overestimate the beneficial effects of a treatment. Finally, CT is limited in its ability to characterize responses in tumours that do not change in size during therapy. Because the growth rate of untreated human tumours may vary tremendously, an unchanged tumour size after some weeks of therapy may represent a drug effect, but it may also indicate a slowly growing indolent tumour that has not responded to the applied therapy. Some chemotherapeutic agents are cytostatic rather than cytocidal and, therefore, do not result in profound changes in tumour size despite their effectiveness [5.1, 5.2].

Many tumours, such as lymphomas, sarcomas, mesotheliomas and gastrointestinal stromal tumours (GISTs), do not shrink even in response to effective therapy. In some situations, no tumour shrinkage may be evident on radiological follow-up but a clear histological response can be seen. In certain situations, the size of a tumour may first increase as a consequence of internal necrosis. CT attenuation, contrast enhancement patterns and changes in MRI intensity may be better indicators of response in many such situations. However, most of the response evaluation criteria do not take these parameters into consideration, possibly because they are difficult to quantify objectively, especially in follow-up studies.

5.2. RESPONSE EVALUATION BY PET/CT

Response evaluation by anatomical methods alone has been found to have several limitations. Hence, there is a growing need to incorporate biologically relevant functional and prognostic information in the response evaluation criteria. PET with FDG is one of the most powerful biomarkers that has been used to date in clinical trial settings as well as for individual patients. The basic justification for using ^{18}F-FDG-PET in oncology is that there appears to be a strong relationship between FDG uptake and the number of viable cancer cells in a substantial number of studies across a variety of tumours. As a consequence, it is reasonable to expect that reductions in tumour FDG uptake would be seen with a loss of viable cancer cells with each progressive treatment in the responding

patients, often preceding changes in tumour size. By contrast, it is widely accepted that the non-responding patients do not show significant reductions in SUVs in a wide range of tumours. Abundant data are now available showing that PET is a useful tool for response assessment in a variety of diseases, at the end of treatment, at mid-treatment and when performed soon after treatment is initiated, and that increases in tumour glucose use and the volume of tumour cells can be expected in progressive tumours.

5.2.1. Advantages of using PET/CT in response evaluation

Evaluation of tumour response with FDG-PET has several advantages over anatomically based criteria. By reflecting changes in tumour metabolism, FDG-PET imaging can provide a method by which tumour response can be measured in the absence of marked anatomical changes. A reduction in FDG uptake has been shown to indicate treatment response and/or improved survival in patients with solid tumours such as breast cancer [5.3], oesophageal cancer [5.4], lung cancer [5.5], osteosarcomas [5.6] and others. FDG-PET has also been shown to provide more rapid response data than anatomical measurements. FDG-PET/CT has also been successfully used to modify disease management by preventing futile thoracotomies in patients with lung cancer [5.5] and in stratifying patients with colorectal cancer into surgical versus palliative groups.

5.3. THE USE OF PET IN RESPONSE EVALUATION: METHODOLOGICAL CONSIDERATIONS

While quantitative FDG-PET is increasingly recognized as an important tool for response monitoring in oncology, it is important to remember that quantification in PET may be affected by countless technical and physiological factors. Standardization of acquisition and assessment parameters is thus of great importance, especially where serial studies are being performed for response assessment.

5.3.1. Visual interpretation versus quantitative measurement of tumour FDG uptake

For staging of malignant disease and evaluation after the completion of chemotherapy or RT, visual assessment of tumour FDG uptake is considered to be sufficient and quantitative analysis of FDG-PET scans is generally not required. At these time points, focally increased FDG uptake not explained by the normal biodistribution of FDG suggests residual viable tumour tissue. In various solid tumours, including non-small cell lung, oesophageal and cervical cancer,

persistent focal FDG uptake after completion of chemoradiotherapy has also been shown to be an indicator of a poor prognosis.

If PET scans are performed during treatment to predict subsequent tumour response in solid tumours, quantitative assessment of tumour metabolism becomes necessary, because at this time point there still is considerable residual FDG uptake, even in patients who respond to treatment.

5.3.2. Quantitative measurement of FDG uptake in follow-up studies

Full kinetic modelling has been used infrequently for the evaluation of malignancy in clinical practice because of the complexity of such an approach, including patient compliance issues and the requirement for arterial blood sampling or dynamic imaging of a blood-pool structure to obtain a precise input function [5.7]. The advantages of a full kinetic quantitative analysis, however, are that it yields an absolute rate for FDG metabolism, is independent of imaging time and provides insights into various components of glucose metabolism such as transport and phosphorylation. Other techniques such as graphical or Patlak analysis have also been used where the influx rate constant of the FDG can be determined from a graphical approach without the non-linear optimization inherent in the full kinetic approach. The potential value in absolute quantitative PET studies is the ability to determine metabolic rate and the greater robustness of the approach to variations that may affect semi-quantitative studies, such as the time from injection to scanning. However, both absolute quantification with dynamic imaging and Patlak analysis are technically challenging and are difficult to implement routinely in patients with cancer or, indeed, in large phase II and phase III clinical trials. One advantage of FDG-PET is the ability to easily image whole body distribution of the tracer and to look for new metastatic lesions. This advantage would be compromised with the full kinetic and Patlak approaches, which image only one body section and require monitoring of arterial FDG plasma concentration and, consequently, can be difficult for patients and PET centre personnel.

To avoid placing an arterial catheter to obtain the arterial input function, investigators have used various surrogate approaches, including dynamic scanning over the heart or a major artery. In addition, techniques have been developed for arterializing venous blood. However, these are fraught with technical difficulties, particularly in patients with poor venous access, as is typical in patients with cancer. Several ‘simplified kinetic’ methods have been proposed and represent a compromise between full kinetic analysis and simple static imaging [5.8]. These methods might prove useful in monitoring changes in FDG metabolism with therapy in select phase I or phase II clinical trials but may have limitations in their wider use.

5.4. THE STANDARDIZED UPTAKE VALUE

5.4.1. SUV_{BW} versus SUV_{LBM}

The SUV is the semi-quantitative method that is most commonly used to determine FDG uptake in attenuation corrected PET images. With this technique, the tumour FDG concentration is normalized to the amount of injected activity and total volume of distribution. Numerous indices have been used to represent the volume of distribution, such as body weight, lean body mass and body surface area [5.9]. When corrected only for body weight, SUV does not take into account the relatively lower FDG accumulation in fatty tissues. Normalization to body surface area or lean body mass potentially reduces the effect of weight loss, which may occur during therapy, on subsequent SUV determinations. Lean body mass may be the better method because of the availability of sex specific corrections. SUV normalized to lean body mass (also called SUL) can be calculated using the following formula [5.10]:

$$\text{SUV (LBM)} = \frac{\text{Tissue activity (mCi/mL)}}{\text{Injected activity (mCi)/LBM (kg)}}$$

LBM (kg) = 45.5 + 0.91 × [height (cm) – 152] for females

LBM (kg) = 48.0 + 1.06 × [height (cm) – 152] for males

5.4.2. SUV_{max} or SUV_{peak}

Although SUV_{max} is a commonly used value when reporting PET/CT scans for initial strategy decisions, it has been found that single-pixel measurements of this kind may be compromised when images have high levels of noise. Mean SUV values within a fixed-size region of interest located in the most metabolically active part of the tumour are a more robust measure, especially when used in comparative studies. The use of the SUV_{peak} value is recommended by the PERCIST criteria (see also Section 5.4.10). Even though the use of SUVs for quantitative assessment of tumour glucose use has been severely criticized, it should be noted that there is a fundamental difference between measuring absolute metabolic rates and measuring changes in metabolic rates for treatment monitoring. In the first situation, tumour glucose metabolism generally is quantified to compare different groups of patients. The dependence of SUVs on body composition and plasma FDG clearance is a known limitation of this technique compared with non-linear regression or the Patlak–Gjedde analysis. In the second situation, however, only an intra-individual comparison of metabolic

rates before and after treatment is made. As long as the treatment does not result in significant changes in renal function and body weight, the relative changes in SUVs should be identical.

5.4.3. Determining the region of interest

Determining accurate and reproducible ROIs is critical to obtaining accurate SUVs. With therapy, alterations in the shape and size of the tumour and heterogeneity of uptake within the tumour mass may occur and must be considered when drawing the ROI. There are many prescribed methodologies for drawing the ROIs. Freehand held drawings are frequently used. On the other hand, many commercially available software packages can create user-generated threshold-based ROIs. There is now mounting interest in creating volumes of interest (VOIs), as these have been shown to better sample the distribution of FDG within the tumour and also to provide a more accurate representation of the heterogeneity of response within the tumour. Many of the newer PET/CT systems that are capable of accurately registering these PET volumes to CT-derived anatomical volumes incorporate technically difficult algorithms developed to create evaluation volumes. The choice of method should depend on the technical support staff, expertise and image processing capabilities of an individual PET centre. However, in each clinical trial, the ROI technique should be specified (e.g. whether necrotic areas are included or not) and used consistently in subsequent FDG-PET studies to ensure quantitative consistency.

5.4.4. Time from injection to scanning

In most malignant tumours, FDG uptake increases continuously for at least 90 min after FDG injection, and is usually significantly higher at later time points. Stahl et al. [5.11] demonstrated a 50% higher tumour FDG uptake 90 min after FDG injection, compared with 40 min post-injection (SUV = 12.0 ± 4.0 versus 8.2 ± 2.0, respectively) in 43 patients with locally advanced gastric carcinomas. FDG uptake usually plateaus after about 2 h but may plateau earlier following therapy. Thus, when comparing SUVs from a baseline scan of a patient with SUVs from a follow-up scan after treatment, it becomes unreliable to compare SUVs obtained at different time points after injection. Therefore, every effort should be made to keep the range of variations in the uptake period to within <5–10 min.

5.4.5. Correcting for plasma glucose levels

Since FDG and glucose compete with each other for intracellular transport and phosphorylation, plasma glucose levels have a significant influence on tumour FDG uptake. Thus, FDG uptake tends to be lower in diabetic patients because of elevated plasma glucose levels. The SUV may be corrected for plasma glucose by the following formula:

$$SUV_{glu} = SUV \times \text{glucose concentration in mg/dL}/100 \text{ mg/dL}$$

assuming a normal blood glucose level of 100 mg/dL = 5.55 mmol/L.

5.4.6. Common errors in response evaluation

— *FDG dose extravasation.* A paravenous injection of FDG decreases the amount of tracer available for uptake by the tumour and can result in incorrectly low SUVs.
— *Failure to apply decay correction.* If the injected activity is not decay corrected, SUVs will be markedly underestimated. ^{18}F decays to roughly 49.93% of the initial activity over a period of 110 min.
— *Poor calibration of counting equipment.* In order for the counting rates of the scanner to be correctly converted to activity concentrations, the PET scanner needs to be precisely calibrated. This is usually done using the PET scanner to measure the counts from a cylinder with a known dose of ^{18}F. Errors in the calibration process can lead to incorrectly high or low SUVs. The quality control of instruments is beyond the scope of this section; complete information on this subject can be found in IAEA Human Health Series No. 1, Quality Assurance for PET and PET/CT Systems [5.12].
— *Partial volume effects.* With the progressive shrinkage of tumours in response to therapy, partial volume effects on determinations of FDG uptake may be significant. If a significant decrease in tumour size is evident from anatomical imaging studies (which are typically available throughout therapy), this information should be documented because subsequent analysis may require partial volume corrections of the FDG-PET data. Further data analysis and research are required to improve the definition of how the assessment of response can be adjusted to account for partial volume effects, tumour heterogeneity and other confounding variables.
— *Different reconstruction methods across vendors.* With a plethora of different kinds of PET/CT equipment available, it is important to understand that the type of equipment, acquisition protocols, filters, image reconstruction techniques and application of attenuation maps can all make

a difference in the calculation of semi-quantitative metrics like SUV. The use of contrast CT images as the attenuation maps tends to overestimate SUV as compared with those protocols using non-contrast-enhanced CT scans as the attenuation maps. As the specifications of PET cameras are variable and manufacturer specific, every attempt should be made to use the same scanner (ideally at the same centre) or the same scanner model for serial scanning of the same patient. In those cases where different equipment or techniques are employed, comparisons of the estimated lesion SUVs may not be reliable.

5.4.7. Optimal imaging time point for treatment assessment with FDG-PET scanning

Regarding the prediction of therapy response after completion of treatment, the most challenging issue is to determine the optimal timing for performing FDG-PET during the post-therapy follow-up period. Immediately after the completion of treatment, FDG-PET can present false positive results due to the tissue healing process, or false negative results due to alterations of FDG kinetics, particularly when RT is involved. It has been seen that persistent FDG uptake after therapy is a sign of therapy failure. In contrast, the rapid disappearance of FDG uptake early in the course of therapy usually indicates a good prognosis.

When FDG-PET is performed after completion of potentially curative chemotherapy or RT, one has to consider that only small amounts of residual viable tumour may be present. In this case, differentiating between ‘responders’ and ‘non-responders’ using FDG-PET can be a challenge. In order to achieve the highest sensitivity for detection of residual tumour tissue, FDG-PET should be performed as late as possible after the completion of therapy in order to enhance the detection of residual tumour tissue. Usually, waiting for about 4–6 weeks after the end of treatment provides optimal results. In interim PET scans, the scans should be timed as close to the next cycle of therapy as is possible (optimally about 2–3 weeks from the last cycle). It is important to remember that the post-RT and post-immunotherapy (e.g. rituximab for lymphoma) inflammatory changes may persist for longer periods of time, sometimes even up to 6 months after completion of RT, and this should be kept in mind when reporting post-RT response. The absence of an obvious mass lesion on CT with just residual thickening and stranding on the corresponding CT images should alert the reading physician to the FDG uptake being the consequence of inflammatory changes in a post-radiation scenario. Follow-up scans or a pathological correlation may be made in areas of doubt.

5.4.8. Visual assessment of response

A side by side visual evaluation comparing the baseline and follow-up studies can help detect errors in SUV measurements. For a visual comparison of changes in tumour FDG uptake, it is advisable to set the maximum intensity of the display no lower than the maximum tumour SUV. Otherwise, quite significant changes in tumour FDG uptake may be missed. If both studies are normalized to the same maximum FDG uptake, normal tissues should show approximately the same intensities in both studies. Because SUVs of the normal liver remain relatively stable over time, the intensity of FDG uptake in the liver provides a helpful orientation [5.13]. The presence of marked differences in liver FDG uptake may alert the reading physician to an error in the calculation of the SUVs.

5.4.9. Using the criteria

Uniformity of technique and the reproducibility of measurements are of great importance when incorporating PET as a tool to assess cancer response criteria. In view of the wide variability in acquisition parameters and equipment types in use across the world, there have been many attempts to standardize the use of PET in clinical trials, such as those in the guidelines published by EORTC [5.14], the Netherlands Society of Nuclear Medicine [5.15] and the National Cancer Institute [5.16]. PERCIST [5.17] represents the most recent effort to create standardized criteria that accurately reflect response in the largest number of malignancies.

5.4.10. The PERCIST criteria

The PERCIST criteria utilize the concept of tumour response as a continuous variable. Because tumour response is an inherently continuous, discrete categorization — e.g. complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD) — may result in the loss of important information. Therefore, PERCIST specifies that the percentage change in metabolic activity from baseline and the number of weeks from the initiation of therapy be recorded in order to provide a continuous plot of metabolic activity within the tumour (Table 5.1).

TABLE 5.1. PET RESPONSE CRITERIA IN SOLID TUMOURS (PERCIST 1.0)

Response category	Criteria
Complete metabolic response	Normalization of all lesions (target and non-target) to SUL less than mean liver SUL and equal to normal surrounding tissue SUL
	Verification with follow-up study in 1 month if anatomical criteria indicate disease progression
Partial metabolic response	>30% decrease in SUL peak; minimum 0.8 unit decrease
	Verification with follow-up study if anatomical criteria indicate disease progression
Progressive metabolic disease	>30% increase in SUL peak; minimum 0.8 unit increase in SUL peak
	>75% increase in total lesion glycolysis (TLG) of the five most active lesions
	Visible increase in the extent of FDG uptake
	New lesions
	Verification with follow-up study if anatomical criteria indicate complete or partial response
Stable metabolic disease	Does not meet other criteria

	RECIST	PERCIST
Characteristics	Size criteria for assessment of response	Functional response criteria reflecting tumour metabolism
Advantages	Common use allows direct comparison of the results of different studies	Allows response determination regardless of the location of the metastasis
Disadvantages	Limited to ‘measurable’ soft tissue metastases or unequivocal progression of immeasurable disease	Limited to FDG avid metastases

The primary determinant of response using PERCIST is the standardized uptake value (SUV), a semi-quantitative measure of activity that is most commonly calculated by dividing the measured tumour activity by injected activity/body weight. Among the many variants of SUV (e.g. maximum SUV, mean SUV), SUV corrected for lean body mass (SUV_{LBM} or SUL) was selected

for use with PERCIST, because SUL has been shown to be less susceptible to variations in patient body weight than the other SUV metrics [5.18]. PERCIST specifies that the SUL peak is to be obtained on the single most active lesion on each scan. The SUL peak is the average of the activity within a spherical region of interest measuring 1.2 cm in diameter (for a volume of 1 cm^3) centred on the most active portion of the tumour. The SUL peak may be located in a different lesion on a follow-up scan because the current most avid lesion is to be measured. Using a concept similar to RECIST, it is also recommended that the sum of the activity of up to five target lesions (no more than two per organ) be measured as a secondary determinant of response.

5.4.11. Quantifying response by the PERCIST criteria

In addition to plotting tumour response as a continuous function in the weeks from initiation of therapy, the PERCIST criteria define four response categories:

(1) *Complete metabolic response* is defined as the disappearance of metabolic tumour activity in both target and non-target lesions. Since residual FDG uptake may be noted within the residual lesion due to inflammatory changes post-treatment, a decline in uptake to a value equal to or less than that of surrounding tissue is considered adequate for definition of complete response.
(2) *Partial metabolic response* is defined as a decline of >30% in SUL peak with at least a 0.8 unit decline in SUV.
(3) *Progressive metabolic disease* includes an increase of >30% in SUL peak with at least a 0.8 unit visible increase in the extent of FDG uptake (increase in the colour field representing FDG uptake), or the development of new lesions. In the absence of clear evidence of disease progression on the fused CT image, new FDG avid foci are to be verified on a follow-up scan 1 month after discovery.
(4) *Stable metabolic disease* is the absence of change or mild changes that do not meet the minimum qualifications of the other categories.

A change in tumour (morphological) size remains an important factor under PERCIST and is to be measured according to RECIST 1.1. If a lesion increases or decreases in size without a corresponding change in metabolic activity, disease progression or response is to be verified on a follow-up scan.

5.4.12. Measuring global metabolic response

A major difficulty with whole body FDG-PET is that the patient may have numerous lesions, including both the primary tumour and metastatic lesions spread throughout the body. An alternative index that can be used to measure global changes in tumour glycolysis is the total glycolytic volume (TGV), which is calculated by multiplying the mean SUV by the total tumour volume (mL) [5.19], and is the volume of the lesions determined from the PET-FDG images by an adaptive thresholding technique. Another index, the total lesion glycolysis (TLG), may be obtained by multiplying the tumour volume on CT by the FDG uptake on PET [5.20]:

TGV = mean SUV × total tumour volume (mL)

The percentage response is computed by expressing the change in TLG in the post-treatment PET as a percentage of the TLG in the pretreatment PET-FDG images. TLG has been tested in several malignancies with mixed results in comparison with SUV metrics. TLG has been shown to have a weaker correlation with response in bone metastases in breast cancer patients [5.21] and in sarcomas [5.22], but equal or better in oesophageal, lung, gastric and rectal cancers. PERCIST suggests that SUL peak and TLG can be measured simultaneously in order to evaluate the efficacy of TLG. For further specifics regarding PET scanning, such as information regarding patient preparation and scan acquisition parameters, see Ref. [5.17].

Although there may be some variability in the optimal criteria for assessing tumour response, and predicting patient outcomes will be dependent on the tumour type and the specific treatment used, the results of FDG-PET for monitoring tumour response in different tumour types have been fairly consistent, and justify the definition of common response criteria. Such general criteria will not be as accurate as response criteria defined for specific clinical situations, but the ability to pool data in meta-analyses and to compare response rates across different studies will almost certainly outweigh this limitation.

5.5. SOME SPECIAL CONSIDERATIONS

5.5.1. Lymphoma

In 2007, the International Harmonization Project (IHP) subcommittee developed consensus recommendations on the use of FDG-PET in patients with lymphoma, based on the literature and the collective expertise of its members [5.23].

Visual assessment alone was considered adequate for FDG-PET reading after the completion of therapy. Mediastinal blood pool activity is recommended as the reference background activity to define FDG-PET positivity for a residual mass ≥2 cm in the greatest transverse diameter, regardless of its location. A smaller residual mass or a normal sized lymph node should be considered positive if its activity is above that of the surrounding background. Specific criteria for defining FDG-PET positivity in the liver, spleen, lung and bone marrow were also proposed. The use of attenuation corrected PET was strongly encouraged.

5.5.2. Response evaluation in interim PET/CT

The above criteria were developed for interpretation of FDG-PET at the end of treatment and not specifically for interim FDG-PET. Although the basic concepts of response remain unchanged, interim PET/CT in lymphoma is done both for assessing chemosensitivity and for individual response-adapted treatment modifications. In 2009, at an international workshop in Deauville, France, a group of experts reached consensus on simple and reproducible criteria for interim FDG-PET. For classical Hodgkin's lymphoma, the experts proposed that (i) a baseline FDG-PET/CT be performed prior to therapy initiation, and (ii) a visual analysis using a five point scale be applied (Table 5.2).

For the therapeutic decision, the cut-off should be determined according to the strategy. An international validation study of a selected cohort of ABVD-treated[1] Hodgkin's lymphoma is currently in progress with the aim of validating the proposed criteria.

TABLE 5.2. VISUAL ANALYSIS OF FDG UPTAKE IN INTERIM FDG-PET FOR RESPONSE EVALUATION

Five point scale	
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately more than liver uptake, at any site
5	Markedly increased uptake at any site and new site of disease

Source: Adapted from Ref. [5.24].

[1] ABVD: adriamycin, bleomycin, vinblastine and dacarbazine.

5.5.3. Non-haematological solid tumours

Treatment monitoring in solid tumours other than lymphomas is more challenging than response evaluation in lymphomas. These tumours are more resistant to chemotherapy and RT than are malignant lymphomas, and changes in tumour glucose metabolic activity are smaller and occur more slowly than in lymphomas. Therefore, quantitative analysis of FDG-PET scans is used much more frequently in solid tumours. Furthermore, very few patients with solid tumours have a pathological complete response to chemotherapy or RT. Even patients whose FDG-PET scans performed after completion of treatment show a nearly complete disappearance of FDG uptake will frequently have microscopic residual disease that will eventually lead to tumour recurrence.

Neither PET/CT nor conventional imaging procedures can assess the extent of residual microscopic disease as accurately as histopathology. Therefore, studies of lung, colorectal and breast cancer have focused on detecting non-responding tumours early rather than on identifying patients who are cured by chemotherapy or RT. In this context, the goal of FDG-PET is to guide decisions in order to intensify or change treatment for non-responding patients. Ultimately, predictions of therapeutic effectiveness using PET and PET/CT could help to individualize treatment and to avoid ineffective chemotherapies, with their associated toxicities.

5.5.4. Bone metastases

One of the areas of interest in assessing treatment response in solid tumours is in patients with bone metastases. Bone metastases are a common manifestation of advanced disease, with autopsy studies showing an incidence of 33–36% in patients with lung cancer [5.25], 68% with prostate cancer and 73% with breast cancer [5.26]. Bone metastases have, however, been regarded as non-measurable lesions by the RECIST criteria. Cancer patients with no measurable disease (e.g. individuals with bone-only metastases following the resection of a primary tumour) are often ineligible for clinical trials, which may be the only available source of therapy. Therefore, the absence of measurable tumours can significantly affect patient disease management, with the exception of bone metastases with soft tissue components.

Progressive sclerosis of a lytic lesion has been regarded as an index of response in some studies. The reduction in FDG uptake in bony lesions in response to therapy can be considered a sensitive indicator of response. Conversely, progressive osteolysis with increasing FDG uptake may be considered as disease progression. The only warning is the initial metabolic flare that is seen in response to hormonal therapy in patients with breast cancer, which may actually indicate a better response to treatment.

5.5.5. Response evaluation in cytostatic therapy

While FDG has been used extensively for the evaluation of cytoreductive therapies, there is only limited experience in using FDG as a marker of response in cytostatic therapies. The initial experience of using FDG in response evaluation of cytostatic therapies came from the use of imatinib in gastrointestinal stromal tumours. Other commonly used cytostatic agents include the epidermal growth factor receptor (EGFR) kinase inhibitors such as gefitinib, erlotinib, cetuximab and, more recently, the EGFR/HER2 dual kinase inhibitor lapatinib. The anti-angiogenic agents such as bevacizumab, the endocrine therapies including oestrogen receptor (ER) antagonists, such as tamoxifen and fulvestrant, and the aromatase inhibitors have also been studied.

Although the basic patient preparation, acquisition, reconstruction and image analysis protocols in clinical trials using cytostatic agents remain similar to those for cytoreductive therapies, the key difference is in the optimal time selected for performing the PET scans after treatment with cytostatic agents. The time courses of changes in FDG uptake differ among therapeutic classes. Some of the effects are related to pharmacodynamics, while others are associated with reduced tumour cell viability (e.g. the assessment of responses to cytoreductive therapies). For example, imatinib mesylate decreases tumour FDG uptake within hours to days after the commencement of treatment, whereas endocrine therapies, such as tamoxifen, increases FDG uptake within the same time frame. In general, effects occurring from hours to days after the initiation of treatment reflect pharmacodynamics (e.g. a direct effect on glucose transporter expression or hexokinase activity). Effects occurring after approximately 2–3 weeks or after 1–3 cycles of treatment are more characteristic of reduced cell viability.

The other issue in using PET for response evaluation in cytostatic therapies is to resolve the magnitude of changes in uptake that can be considered significant. While the guidelines for assessing partial response in cytoreductive drugs have been reasonably standardized at 30%, it is not known whether the same response criteria will be appropriate for all classes of targeted therapeutic agents, particularly in the early assessment of pharmacodynamics, as these changes may not predict clinical outcomes.

Several new therapeutic agents may affect glucose transporter expression or hexokinase activity directly, in contrast with cytoreductive therapies, where the change is largely attributable to a reduction in cell viability. The different mechanisms of action may lead to differences in the correlation of changes in FDG uptake with clinical outcomes. For most targeted therapies, a baseline scan followed by an early post-treatment scan, within 1 week (pharmacodynamic effects), and a scan after 1 or 2 cycles of therapy (cell viability effects) is

recommended. However, more research is required to optimize the timing for post-treatment scanning for cytostatic agents.

Few studies have demonstrated that 3′-deoxy-3′-^{18}F-fluorothymidine (FLT) PET is a better marker of therapeutic responses than FDG-PET in cytostatic agents. In addition to assessing glycolytic metabolism, it may be desirable to examine the impact of therapy on other biological functions such as perfusion, proliferation and protein metabolism, at least in a subset of patients.

In conclusion, FDG-PET/CT is a useful end point for assessing response to targeted therapies. The biological basis of changes in FDG uptake may be more complex than those for traditional cytoreductive therapies, and this factor may affect the timing of post-treatment scans and the clinical significance of the magnitude of changes observed.

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6. PET/CT REPORTING IN ONCOLOGY

The PET/CT report is an essential part of every imaging procedure. It is a permanent document, in written or digital format, that summarizes important components of the study and the interpreting physician's analysis of the findings. The report communicates information to the referring physician, records that information for future use, and serves as the legal record for the episode of care. In addition to its clinical function, the PET/CT report may be used for billing, accreditation, quality improvement, research and teaching. It also serves as a means of communication with the patient.

The primary goal of the PET/CT report is to communicate the results of the imaging procedure to the referring physician. The report must be accurate, easily understood and appropriately thorough, and written in clear and unambiguous language. It is important that the report be concise and to the point; a long essay is unlikely to be read, with the risk that key information will be missed.

The PET/CT report is divided into five sections:

— Clinical history (indication);
— Technique;
— Comparison;
— Findings;
— Impression.

6.1. CLINICAL HISTORY

This section includes information regarding indication for the examination, relevant history and information needed for billing.

6.1.1. Indication

The indication is a concise statement based on the information provided by the referring physician that includes the specific reason why the PET/CT is being performed, such as 'Patient with newly diagnosed oesophageal cancer'; 'PET/CT for initial strategy planning (staging)' or, in the case that the PET/CT is being performed for routine follow-up, 'Patient with follicular lymphoma for subsequent therapy planning (restaging)'. It should also include specific reasons for performing the PET/CT, such as 'Patient with history of colon cancer and recent elevation in CEA [carcinoembryonic antigen]'.

The indications for PET/CT can be categorized as follows:

— Diagnosis;
— Search for an unknown primary tumour in the presence of metastatic disease or when the patient presents with a paraneoplastic syndrome;
— Initial therapy strategy planning (staging);
— Subsequent therapy strategy planning (restaging);
— Therapy monitoring;
— Evaluation for residual tumour;
— Detecting tumour recurrence, especially in the presence of elevated levels of tumour markers;
— Selecting the region of a tumour most likely to yield diagnostic information for biopsy.

The clinical indication for the study should be clearly addressed and answered at the end of the report. This is probably the most important of all the elements of the report. For example, if the referring physician has sent the patient to get an FDG-PET/CT study, it has been requested to answer a specific question. If the reason for doing the study is not clearly addressed in the impression section of the report, the report is unlikely to have any impact on patient management. For the referring physician, it is discouraging to receive a report that does not promote clinical understanding. Ultimately, this may lead the physician to order fewer PET/CT studies when the perception is that they do not contribute to the clinical management of patients.

— The tumour type should be mentioned (e.g. ‘66 year old patient with recently diagnosed right lower lobe NSCLC’). Avidity for FDG is variable depending on tumour histology. Some tumours, such as NSCLCs, are in general highly FDG avid, while others, such as adenocarcinomas, show minimal or no FDG avidity.
— If a specific abnormality is to be evaluated, this should be clearly stated (e.g. ‘Patient with history of colon cancer, new mass in the right lobe of the liver found in a surveillance CT scan’).
— The specific clinical question for which the PET/CT scan is being done should be included (e.g. ‘72 year old male with long history of smoking, with pulmonary nodule in the left upper lobe found in CT scan, search for malignancy’).
— The degree of FDG avidity in the lesion should be addressed in the body of the report and the clinical question should be answered at the end of the report.

6.1.2. Relevant history

This portion of the 'Clinical history' section of the PET/CT report should contain information regarding the patient that could impact the interpretation of the examination. The most common information pertains to histopathological results and previous treatments such as chemotherapy or radiation completed within 3 months prior to the PET/CT. Other pertinent information includes concurrent and ongoing therapy, such as granulocyte colony stimulating factors (G-CSF) and interleukins. Relevant surgeries, including dates, or a history of infections and systemic processes may modify FDG uptake in different tissues and lesions, and can potentially interfere with interpretation, as is the case of sarcoidosis, AIDS, tuberculosis and vasculitis.

Relevant history includes:

— *Biopsy* or surgical pathology results;
— *Chemotherapy,* including the date of completion;
— *Radiation therapy,* including the date of completion;
— *Treatments;*
— *Medical/surgical history* that may have relevance for PET/CT interpretation.

If requested, the form should provide information needed for billing, with a clear statement explaining the reason why PET/CT is being performed.

6.2. TECHNIQUE

6.2.1. PET procedure

The 'Technique' section of the PET/CT report must include the administered activity and the route of administration. Any significant dose infiltration should be reported. The areas of the body evaluated by the scan field should be described using appropriate anatomical nomenclature. For example, some protocols for imaging patients with cancers of the head and neck begin at the vertex of the skull and extend to the upper thighs. There is a dedicated head and neck protocol including scans from the sternal notch, followed by scans from the top of the head to the region of the aortic arch. Scans in patients with known malignant involvement of the mid-thigh may begin at the orbit and extend to the knees. Whole body scans for patients with melanoma should extend from the vertex to the feet. Additional dedicated acquisitions should be noted. These include: delayed views of the chest for solitary pulmonary nodule, delayed head and neck image acquisitions for head and neck cancer, or delayed images of the abdomen and pelvis after furosemide administration.

The uptake time — the time between injection and scanning — should be reported. In some cases, a range is appropriate, such as 60–90 min. If the uptake time is shorter or longer than the established time, it should also be reported because this may cause changes in the degree of FDG avidity.

Fasting blood glucose levels should be measured immediately prior to FDG administration in patients undergoing FDG-PET/CT. The results are relevant for the sensitivity of the study and should be included. The report should reflect the diagnostic uncertainties imposed by non-ideal blood glucose levels or when follow-up studies are being performed at different blood glucose levels.

Medications administered as part of procedure (i.e. anxiolytics, muscle relaxants, beta-blockers) are usually given to reduce FDG uptake in the muscles or in brown fat and may be required in future examinations. The use of furosemide to clear FDG from the collecting systems and urinary bladder, or premedication for contrast reaction, should be reported.

6.2.2. CT procedure

The CT portion of the report should include a description of the protocol used, especially the use of IV or oral contrast. If oral contrast is used, the type of contrast should be noted as positive or negative contrast. Positive contrast may cause artefactual elevations in FDG uptake and this should be explained in the report.

Because PET/CT involves two complementary but separate imaging techniques, there are added challenges associated with reporting and billing for the two examinations. For the CT portion of the examination to have reliable value as a source of anatomical localization for the FDG-PET interpretation, the image quality will render the CT images as diagnostic. Even without contrast, at one third the beam current of optimized CT scan protocols there is ample anatomical diagnostic information both complementary to the metabolic images of the PET scan and independent of the PET derived diagnostic information. Therefore, interpretation of a PET/CT examination always involves not just anatomical localization, but anatomical diagnosis as well. A PET/CT report, therefore, must always combine both PET and CT findings and render an integrated interpretation that merges the anatomical and metabolic findings.

If the CT scan was requested and performed as a diagnostic examination, then the CT component of the study may be reported separately to satisfy regulatory, administrative or reimbursement requirements. In that case, the PET/CT report may refer to the diagnostic CT scan report for findings not related to the PET/CT examination.

6.2.3. Additional information

Any details regarding allergic reactions or adverse reactions to contrast should include the signs and symptoms, and treatment and response. Special measures required by the patient such as oxygen administration, IV fluids, and/or any significant modification of the standard protocol should all be noted in the report.

6.3. COMPARISON

Comparisons with previous examinations and reports should be part of the current PET/CT report. PET/CT studies are more valuable when correlated with previous diagnostic CT, PET, PET/CT and MRI. All appropriate imaging studies and clinical data and results are relevant. The dates of prior PET or PET/CT studies used for comparison should be given. If prior studies were performed using a different scanner or different facility, or acquired using a different technique (e.g. 2-D or 3-D), this information should be included in the report. If no previous PET studies are available, this should be stated as well.

6.4. FINDINGS

6.4.1. Quality of the study

The PET/CT report should indicate any factors that may have affected the quality of the study. For example, the quality may be limited because of motion or misregistration, muscular uptake or hyperglycemia.

6.4.2. Limitations

When appropriate, the report should identify factors that could limit the sensitivity and specificity of the examination, such as with small lesions or an inflammatory process.

6.4.3. Description

The report should indicate the location, extent and intensity of abnormal FDG uptake in relation to the uptake in normal comparable tissues, and describe the relevant morphological findings related to PET abnormalities on the CT images. An estimate of the intensity of FDG uptake can be provided in a semi-quantitative manner by the SUV. However, the intensity of uptake should be described as either mild, moderate or intense, or described in relation to

the background uptake in normal hepatic parenchyma (average SUV: 2.0–3.0; maximum SUV: 3.0–4.0). The integrated PET/CT report should include any detected incidental findings on the CT scan that are relevant to patient care. If the CT scan was requested and performed as a diagnostic examination, then the CT component of the study may be reported separately to satisfy regulatory, administrative or reimbursement requirements. In that case, the PET/CT report may refer to the diagnostic CT scan report for findings not related to the PET/CT examination.

6.4.4. Clinical issues

This section of the report should address or answer any pertinent clinical questions raised in the request for the imaging examination.

When PET/CT is performed for monitoring therapy, a comparison of the extent and intensity of uptake may be summarized as metabolic progressive disease, metabolic stable disease, metabolic partial response or metabolic complete response. The EORTC has published criteria for these categories, although they have not yet been validated in outcome studies. A change in the intensity of uptake with semi-quantitative measurements, expressed in absolute values and percentage changes, may be appropriate in some clinical scenarios. However, the technical protocol and analysis of images need to be consistent in the two sets of images. The FDG uptake time should be constant whenever possible and certainly when two studies are being compared by use of semi-quantitative parameters, especially the SUV.

There are different ways to report PT/CT studies. The two most common styles are ‘focused’ and ‘anatomical site’.

6.4.4.1. Focused

These findings should be described in the order of importance to the clinical issues of the patient. This type of report follows the tumour, node, metastasis (TNM) classification and begins by describing the metabolic activity in the primary tumour or the largest site of recurrent disease. This is followed by the description of metabolic activity in the regional lymph nodes and an evaluation for metabolically active metastatic lesions.

The findings should be described according to the abnormalities that are not FDG avid, like pertinent negatives, and are followed by unexpected findings in PET or CT. Critical, unexpected findings, such as pneumothorax and abdominal aortic aneurysms, should be communicated immediately to the referring physician. Normal physiological FDG uptake in muscle, bowel and other organs should also be described.

6.4.4.2. Anatomical site

With this approach, the PET and CT findings are described and organized by anatomical region. The report is divided into three regions: head and neck, chest, and abdomen and pelvis. For each region, the report should begin with a description of positive PET and CT findings or CT abnormalities with significant metabolic activity. This should be followed by CT-only and unexpected findings, with separate descriptions of the musculoskeletal findings for each level. In this style of reporting, the findings on both PET and CT are grouped by region of the body, with a separate section describing musculoskeletal findings.

6.5. IMPRESSION (CONCLUSION OR DIAGNOSIS)

The impression is the final and most important section of the PET/CT report because it answers the clinical question. Some digital reports present the impression first. Many referring physicians read the impression first and may not read the rest of the report.

The impression should be concise and answer the clinical question. For example: 'Hypermetabolic mass in the right lower lobe is consistent with malignancy. Hypermetabolic right hilar and right paratracheal lymph nodes are consistent with metastasis, without distant metastasis.'

- When possible, a precise diagnosis should be given.
- When appropriate, a differential diagnosis should be given.
- When appropriate, follow-up and additional diagnostic studies needed to clarify or confirm the impression should be recommended.
- If a precise diagnosis cannot be given, a differential diagnosis should be given.
- If appropriate, follow-up and additional diagnostic studies needed to clarify the impression should be recommended.

Two sample PET/CT reports are presented in the Appendix to this publication.

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7. FUTURE DIRECTIONS OF PET

7.1. INTRODUCTION

FDG-PET and PET/CT imaging have revolutionized the care of cancer patients over the past 20 years. It is now widely recognized that FDG-PET and PET/CT are superior techniques that may perform better than conventional imaging. The list of current indications has grown over the years as understanding of this imaging modality has improved, including its advantages and limitations in defining and characterizing malignant disease. From their initial use in staging, restaging cancer and characterization of indeterminate pulmonary nodules, FDG-PET and later PET/CT have also been applied with great success in assessing response to therapy, determining the recurrence of disease and evaluating patients with elevated tumour markers. In addition, they are also being used, although is not yet considered a standard indication, in RT planning of certain types of cancer, early assessment of response to therapy, such in lymphomas, and prognostication of disease.

7.2. ADVANTAGES AND LIMITATIONS OF FDG-PET OR PET/CT IMAGING

PET/CT represents a significant advance over stand-alone PET in many ways. Not only is the duration of the study at least half what it used to be, but, probably more important, it provides superior anatomical detail from the multislice CT scanner incorporated into the system. This additional morphological information can characterize with great accuracy the abnormal signal detected on the PET scanner and, through the superb quality fused images, can pinpoint the location of disease with high precision. Occasionally, an abnormal PET signal can come from an anatomical structure that, on the basis of the image provided by the multislice CT, appears to be completely normal or is non-diagnostic. Therefore, there is now a clear understanding/agreement within the medical community of the benefits of combining metabolic and morphological information in a single imaging modality such as PET/CT.

Although FDG is an outstanding radiotracer with many advantages, it also has some limitations. First, it is of rather limited use in tumours with low metabolic rates, such as prostate cancer, in those that are well differentiated, as is the case with many hepatocellular carcinomas, or in very mucinous tumours like signet ring cell type tumours. PET/CT imaging using other radiotracers can further characterize the tumour cell to obtain a non-invasive insight into the phenotype of the malignant process, while serving as a surrogate for biomarker

assessment. In addition, FDG is a well recognized cause of false positives, and there can be prominent FDG uptake in patients with inflammatory and infectious diseases. While this could provide an important source of new indications for FDG-PET/CT imaging in benign conditions, for cancer patients it can complicate substantially the interpretation of the scans.

7.3. FUTURE OF PET AND PET/CT IMAGING

The future of PET/CT imaging resides in two main developments. First, technological advances in imaging technology and computer science mean that future scanners will be able to acquire the PET signal and the CT X rays in the same imaging detectors, allowing for true hybrid imaging. In addition, the increased signal sensitivity, faster electronics and better reconstruction algorithms will translate into better image quality carried out in shorter imaging time and/or with a lower activity of radiotracer, and therefore less radiation dose to the patient. Moreover, the technology and the market are becoming mature enough for the introduction of new, dedicated imaging devices, such as PET/MRI or PET mammography (PEM).

The second major development has been the introduction into clinical use of new non-FDG-PET radiopharmaceuticals, which could exploit the limitations of FDG and take advantage of the deeper knowledge of cancer cell biology.

Over the past few years, there have been enormous advances in the understanding of cancer cell biology at the molecular level. These have brought the opportunity for the recognition of many different therapeutic targets. Molecular imaging has exploited this knowledge to develop a battery of different 'tumour cell signal-specific' PET radiopharmaceuticals that can characterize both genotypic and phenotypic signatures of tumour cells. The deeper understanding of the specific biological features for each different type of cancer, and the present widespread use of molecular targeted therapy, has prompted the development of patient-specific individualized cancer management and therapy. Therefore, there is a growing clinical need for the non-invasive characterization of different functions in the biology of cancer cells, besides the glycolytic pathway.

Over the past 10–15 years, many alternative non-FDG-PET tracers have been developed and evaluated in preclinical and clinical studies with different degrees of success. Although labelling of new PET tracers has been done on many occasions with ^{11}C, its short half-life of only 20 min has limited its use to hospitals and imaging centres with an on-site cyclotron. Therefore, other radionuclides with longer half-lives, such as ^{18}F with almost two hours, or even ^{68}Ga with 68 min, have become more attractive options. The list of non-FDG-PET

tracers is long (Table 7.1). However, this section describes the current status of those that could have a potential effect in medical oncology.

TABLE 7.1. NON-FDG-PET TRACERS IN ONCOLOGY

PET radiopharmaceuticals	Biochemical process	Applications in oncology[a]
^{18}F-sodium fluoride	Hydroxyapatita — bone turnover and flow	Detection of bone metastasis
^{18}F-choline or ^{11}C-choline	Membrane−lipid metabolism (choline)	Prostate cancer, HCC
^{18}FLT	Tumour cell proliferation	Early assessment of response
^{18}F-DOPA	Amino acid	Brain, NET, MTC, insulinoma, FCH
^{68}Ga-DOTA-SSA	Receptor binding somatostatin receptor (SSR)	NET
F-MISO, F-AZA, F-EF5, Cu-ATZM	Hypoxia	HN, lung
^{11}C-methionine	Amino acids	Brain
^{18}FES	Receptor binding	Breast
^{18}F-FDHT	Receptor binding	Prostate
F-galacto-RGD	Angiogenesis	Oncology (preclinical stages)
^{124}I-annexin V, ^{64}Cu annexin V	Apoptosis	Oncology (preclinical stages)
^{124}I-cG250	Tumour antigen binding	Renal cancer

[a] HCC, hepatocellular carcinoma; NET, neuroendocrine tumour; MTC, medullary thyroid cancer; FCH, focal congenital hyperinsulinism; HN, head and neck cancer; oncology (preclinical stages) are studies carried out in small animals.

7.4. TECHNOLOGICAL ADVANCES IN PET AND PET/CT IMAGING

Advances in computer science, including immensely improved computer power, faster scintillators and advanced electronics, have enabled shorter scanning times and lower injected radioactivity doses, which translate into a lower radiation dose to the patient.

Advances in standard and newly developed electronics, including new detectors, have considerably improved the resolution of PET images (to date, on the order of 4 mm). The requisites for a PET detector are both high spatial resolution and high sensitivity to minimize both the duration of the scan and the injected radioactivity dose. The three most widely used scintillator crystals, namely bismuth germanate (BGO), lutetium oxyorthosilicate (LSO) and lutetium yttrium oxyorthosilicate (LYSO), especially the last two, provide fast coincidence timing, thereby reducing random events and improving image quality.

In the design of a PET scanner, higher sensitivity often compromises spatial resolution, and vice versa. Most commercial clinical and small animal PET scanners still use photomultiplier tubes (PMTs) as light detectors. Nevertheless, much of PET research is focused on replacing these bulky and relatively expensive PMTs with novel semiconductor based light detectors. Over the past 15 years, avalanche photodiodes (APDs) have been intensively researched; as a result, their reliability and robustness have improved considerably, and current models are capable of operating for many years without performance degradation. Since APDs are semiconductor devices, they have the potential to become less expensive as production volumes increase. Moreover, APDs are not only compact but also insensitive to magnetic fields and are therefore ideal as PET light detectors in combined PET/MRI scanners. An alternative to current APDs is the new generation of Geiger-mode APDs, or silicon photomultipliers (SiPMs), which could drastically change current PET detector technology. Because they can detect both PET photons and CT X rays, SiPMs are likely to become the technology of choice for combined PET/MRI scanners, and potentially also for PET/CT scanners.

Time of flight (TOF) methods increase the signal to noise ratio (SNR) of the PET images by including more accurate information about the location of the annihilation event. TOF PET is now commercially available following recent improvements in PET detector technology, electronics, computational performance and image processing that can measure the arrival time of a photon in the scintillator to within a few hundred picoseconds (ps). Current clinical TOF PET systems can achieve time resolutions of about 500 ps. The most important advantage of TOF PET is its ability to produce higher resolution PET scans with higher SNRs of obese patients, whereas the gain in SNR is modest for scans of slim or normal weight patients.

Advances in reconstruction algorithms have provided newer iterative reconstruction methods, and the improvement in image quality is most noticeable in 3-D PET data, especially in whole body applications.

Clinical MRI/PET systems that utilize the newest APDs have become available very recently. These systems benefit from the exquisite soft tissue contrast and resolution provided by MRI, even in whole body applications, and from the picomolar range sensitivity of the PET scanner as well.

To date, there are two basic designs for clinical MRI/PET systems: (i) a PET/CT-like combination in which images are obtained serially, using the same couch for PET and MRI scanners, and (ii) a true integrated MRI/PET system that permits simultaneous use of both scanners with the benefit of shorter scanning times and true fused imaging. The latter system allows for cross-correlation studies in which the same physiological or functional parameter is evaluated by both PET and MRI.

The specific clinical indications for MRI/PET imaging in oncology are currently unknown, but the independent and especially the combined capabilities of the scanners will need to be taken into account. MRI provides high resolution structural definitions of tumour volume and the extent of local disease. This definition is particularly useful in the evaluation of primary tumours that originate from anatomical sites that are suboptimally depicted on CT (e.g. the brain, head and neck, spinal cord, pelvic organs, breasts or musculoskeletal system), as PET provides complementary information through molecular detection and characterization of suspicious lesions as benign or malignant. For instance, PET/MRI has recently been shown to be feasible for use in patients with head and neck cancers and to provide greater spatial resolution and image contrast compared with PET/CT. Regarding the detection of distant metastases (M staging) in organs such as the liver and bone marrow, PET and MRI are also complementary to varying degrees depending on the underlying tumour biology, the sizes of the metastases and the specific anatomical sites involved. Compared with standard mammography, PET/MRI mammography may better detect and characterize breast cancer and help assess breast cancer treatment response. In addition, hepatobiliary MRI contrast agents can be applied to improve the detection of metastatic disease to the liver and may aid the pretransplant evaluation of patients with hepatocellular carcinoma. Advanced functional MRI techniques such as diffusion-weighted imaging (DWI) and dynamic contrast enhanced (DCE) MRI can also be used with PET to further enhance the detection and characterization of malignant lesions for prognostic assessment, biopsy and pretreatment planning, patient selection for certain therapeutic agents, and treatment response prediction and assessment.

7.5. DEVELOPMENT OF NON-FDG-PET TRACERS

Just as important as the technological advances in PET devices has been the development of new PET radiotracers for oncology (Table 7.1). Their clinical uses vary greatly from country to country, in part due to the different regulatory agencies involved in the control of these tracers.

7.5.1. ^{18}F-sodium fluoride

^{18}F-sodium fluoride is the oldest of all the non-FDG-PET tracers. In fact, its use in nuclear medicine started in the 1960s with the rectilinear scanners for bone imaging. However, in the 1970s, it was completely replaced by conventional bone scanning with ^{99m}Tc-diphosphonate imaging. Nevertheless, both tracers are metabolized in similar ways, although with some important differences. Sodium fluoride behaves in the body in a similar way to calcium ion, and is deposited in the hydroxyapatite crystal of the bone matrix in a proportion directly related to bone turnover and blood flow. The advantage of sodium fluoride over the diphosphonates is that it is less bound to the proteins in the blood, and a higher fraction is taken/retained in the skeleton (80% versus 60%). Therefore, with sodium fluoride, imaging can be initiated earlier than 1 h after injection, whereas with ^{99m}Tc-diphosphonates there is a minimum waiting time of 2 h.

As an imaging technique, sodium fluoride PET or PET/CT imaging is clearly superior to standard bone scintigraphy (Fig. 7.1), even when SPECT is used. Not only is it faster than a conventional bone scan and provides sharper images of the skeleton with similar radiation dosages to patients, but it is also considerably more sensitive for the detection of osteoblastic and even osteolytic bone metastases. In addition, using PET/CT the specificity and accuracy of the technique further improve through precise localization and characterization of skeletal lesions.

7.5.2. ^{11}C-choline or ^{18}F-choline

^{11}C-choline and ^{18}F-choline take advantage of the overexpression of choline kinase found in many cancer cells. Choline is a natural blood constituent and penetrates cell membranes through low affinity sodium independent transport systems or high affinity sodium dependent systems. There is also a choline specific transporter protein. Once inside the tumour cell, it accumulates rapidly, and is eventually phosphorylated by choline kinase to phosphocholine. Phosphocholine constitutes a substrate for the formation of phosphatidylcholine, which is a major constituent of cell membranes.

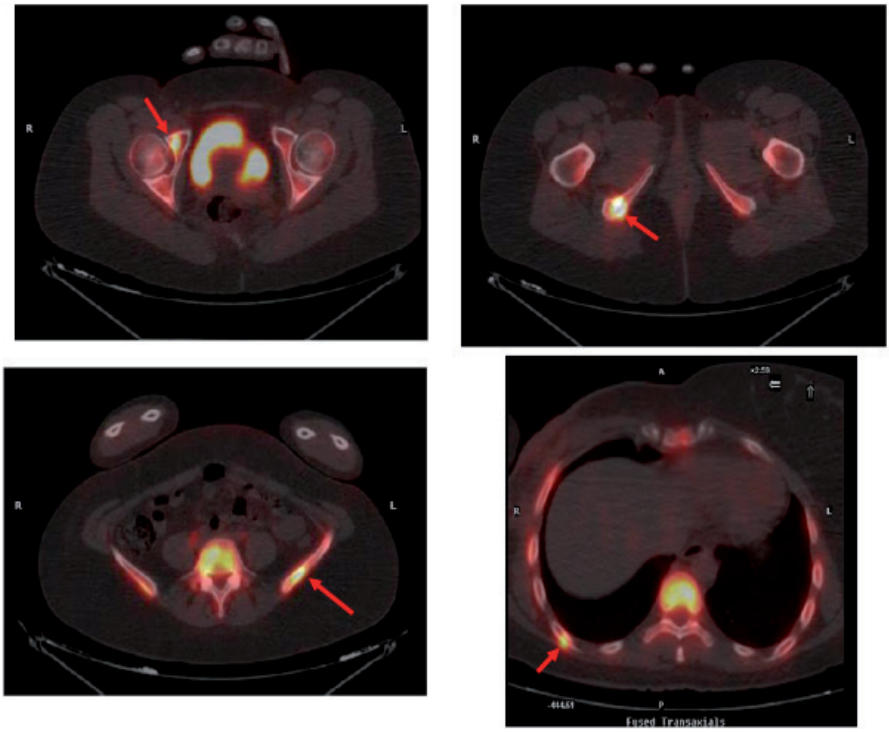

FIG. 7.1. Axial images of the pelvis and chest (right lower images) of a ^{18}F-sodium fluoride PET/CT scan in a breast cancer patient. The arrows point to osseous metastases not detected on a conventional bone scan done a few days before.

Although not yet commercially available in many countries, there is growing scientific evidence of the clinical utility of this new non-FDG-PET tracer in prostate cancer. Since the initial publication in 2001 by DeGrado using ^{18}F-choline, there have been many papers demonstrating the clinical benefits of this PET probe in prostate cancer.

By far, the main indication for ^{11}C-choline is in the evaluation of patients with biochemical recurrence of disease. In this regard, it outperforms conventional imaging, with sensitivities that increase as the prostate-specific antigen (PSA) levels rise (Fig. 7.2).

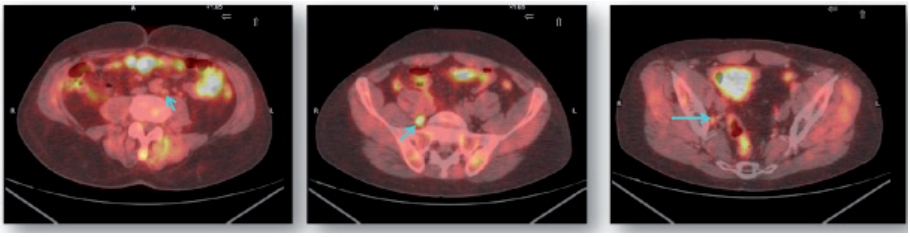

FIG. 7.2. Axial images of a ^{18}F-choline PET/CT scan in a 72 year old man with prostate cancer, initially treated with radical prostatectomy, followed by RT. Later, the patient showed evidence of biochemical recurrence of the disease with a PSA of 3.15 ng/mL. The arrows point to the left lower paraortic and two right common iliac nodes, representing metastatic lesions. The size of the second smaller right common iliac node (right image) was 0.8 cm × 0.6 cm with an SUV_{max} of 1.7.

7.5.3. ^{18}F-FLT

Since uncontrolled cell growth is one of the hallmarks of cancer, proliferation imaging could potentially improve the diagnosis, staging and grading of malignant tumours. The most studied non-FDG-PET tracer to assess proliferation is 3′-deoxy-3′-fluorothymidine (FLT), which was originally synthesized as an antineoplastic and antiretroviral agent, and was first used as an anti-HIV agent without a radioactive label.

FLT imaging takes advantage of the pyrimidine salvage pathway of DNA synthesis, and enters tumour cells both via a nucleoside transporter and partly via passive diffusion. Once inside the cell, FLT is phosphorylated by the enzyme thymidine kinase 1 (TK1), and is thereby trapped in the cell. Subsequently, following the salvage pathway it is phosphorylated twice, to form FLT-triphosphate. However, it differs from the natural pyrimidines in that it does not become incorporated into the growing DNA strand as thymidine does. Nevertheless, FLT accumulates in the tumour cells in proportion to TK1 activity. The activity of TK1 is greatly overexpressed in tumour cells and up-regulated just before and during the S-phase, with greatly reduced concentrations in the G0/G1 phases of the cell cycle. Therefore, in practice, TK1 activity is representative of cellular proliferation.

The most promising clinical indication of FLT PET imaging is for monitoring tumour response to therapy.

7.5.4. F-DOPA

^{18}F-deoxiphenilalanine is a radiolabelled amino acid precursor of dopamine. It was originally synthesized several decades ago for the evaluation of the dopamine transporter system in the striatum. Since then, it has found applications in the assessment of various diseases and conditions. Besides being very useful for the initial assessment of patients with Parkinson's disease, and monitoring the patient's condition, it has also found application in the imaging of brain tumours. Over the past decade, F-DOPA has been more widely used in tumours derived from the neural crest tissue, which on many occasions are difficult to detect, stage and follow up with conventional imaging. In medullary thyroid cancer, the experience with F-DOPA PET is more limited. However, the preliminary results are very encouraging, complementing and sometimes improving staging over other imaging modalities. In focal congenital hyperinsulinism in infants, F-DOPA PET has quickly become an invaluable diagnostic aid, with sensitivities in the 90–100% range, accurately guiding curative surgical resection. For the detection of insulinomas, F-DOPA is a promising, potentially very useful molecular probe, although its performance in the detection of adult islet cells tumours has not been completely characterized.

7.5.5. ^{68}Ga-DOTA somatostatin receptor analogue

^{68}Ga is a PET tracer with a half-life of 68.3 min that has the advantage of being produced in a generator, meaning there is no need for an expensive on-site cyclotron. It has been successfully labelled using the DOTA quelator to different somatostatin analogues. The three most used so far have been ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-TATE and ^{68}Ga-DOTA-NOC, which target the somatostatin subtype (SST) receptors 2, SSTr3 and SSTr5. However, it is still not clear which of these different ^{68}Ga somatostatin receptor peptides provides better clinical results. It may very well be that for some particular types of neuroendocrine tumours (NETs) one of them may be better than the others. Although somatostatin receptor scintigraphy (SRS) has been used for many years, ^{68}Ga PET imaging with one of the available somatostatin analogues has proven to be a superior imaging modality in several comparative studies. It offers not only increased spatial resolution but also the ability to perform whole body imaging with a short uptake time of 60 min (compared with 24 h for SRS), and relatively easy synthesis and labelling. Moreover, it has the added information of the fused PET/CT image, with the resultant increase in diagnostic accuracy.

7.5.6. Hypoxia imaging

Tumour hypoxia develops from the failure of tumour vessels to keep pace with the rather fast rate of growth of malignant tissue. The resulting adaptive changes in the proteome and genome of the tumour cells are believed to lead to more aggressive clones that are better adapted to survive in their compromised environment. In this respect, tumour hypoxia has been associated with an aggressive tumour phenotype, poor response to RT and chemotherapy, increased risk of invasion and metastasis, and worse prognoses in patients with advanced squamous cell carcinoma of the cervix, head and neck, and soft tissue sarcomas.

The first PET studies for in vivo imaging of tumour hypoxia were done with ^{18}F-fluoroimidazole (F-MISO), dating back to 1992. Since then, several other tracers have also been evaluated for this purpose, including ^{18}F-FAZA, Cu(II)-ATSM labelled with either ^{60}Cu or ^{64}Cu, and ^{18}F-EF5. Although none of the currently available tracers has all the properties of an ideal hypoxia imaging agent, F-MISO remains the most extensively studied agent.

F-MISO enters cells by passive diffusion, where it is reduced by nitroreductase enzymes to become trapped in cells with reduced tissue oxygen partial pressure. By contrast, in normally oxygenated cells when oxygen is abundant, the parent compound is quickly regenerated by reoxidation and metabolites do not accumulate. In hypoxic cells, however, the low oxygen partial pressure prevents reoxidation of F-MISO metabolites, resulting in tracer accumulation in hypoxic cells. Because F-MISO accumulates only in hypoxic cells with functional nitroreductase enzymes, it only accumulates in viable cells and not in dead necrotic cells.

7.5.7. Amino acid and protein imaging

The most widely used amino acid for PET tumour imaging has been ^{11}C-methionine. The mechanism of uptake into tumour cells is poorly understood, although it is probably dependent on amino acid transport. Unlike FDG, ^{11}C-methionine uptake does not seem to be affected by hypoxia. This non-FDG-PET tracer has been used mostly for brain tumours. In the normal brain, there is very little uptake of ^{11}C-methionine, and conditions such as oedema, fibrosis and necrosis do not exhibit any uptake. However, although it is not able to distinguish between benign and malignant tumours, it can determine with great accuracy whether there is tumour recurrence versus necrosis even in patients with low grade brain tumours, an area where FDG is notoriously not very helpful. Such important differentiation is difficult to obtain with FDG, due to the fact that inflammatory changes secondary to treatment can produce a

prominent uptake with this tracer. The reported sensitivities and specificities for this purpose are 87% and 89%, respectively.

7.5.8. Receptor imaging (FES, FDHT)

^{18}F-fluoroestradiol (FES) has been available for a few decades and is therefore the best known PET receptor tracer. It binds to the oestrogen receptors, and thus can provide an in vivo map of the oestrogen receptor status of tumour lesions in breast cancer patients. FES has been used to accurately predict responses to breast cancer treatment, whereby up to a third of patients with positive uptake may respond to hormonal therapy, compared with a less than a quarter if there is no uptake.

Dihydrotestosterone (DHT) is the primary ligand of the androgen receptor (AR). Fairly recently, 16β-^{18}F-fluoro-5α-dihydrotestosterone (^{18}F-FDHT), an androgen analogue, has been synthesized. Although only a few studies in prostate cancer patients have been published to date, it has already been demonstrated that metastatic and recurrent prostate cancer lesions can be detected with this PET tracer. ^{18}F-FDHT PET can potentially characterize the evolving phenotype of prostate cancer cells, through the non-invasive assessment of AR status in all metastatic sites of this often heterogeneous tumour. This information could prove to be invaluable for patient selection and prediction of response to therapy.

7.5.9. Angiogenesis, apoptosis and immuno-PET

Most of the PET imaging studies to assess tumour angiogenesis have been carried out on animals. A few radiolabelled anti-VEGF antibodies have been reported. HuMV833, a humanized anti-VEGF monoclonal antibody (MAb), has been labelled with ^{124}I and investigated in a phase I clinical trial. Recently, bevacizumab has been labelled with ^{89}Zr for PET imaging in mice. ^{64}Cu has been used with the quelator DOTA to label VEGF121 for small animal studies, in which it has exhibited rapid, specific and prominent uptake in highly vascularized small tumours with prominent levels of VEGFR-2 expression.

Among all the integrins discovered to date, the most widely studied is α5β3, which binds to arginine-glycine-aspartic acid (RGD)-containing components of the extracellular matrix, found to be significantly up-regulated in tumour vasculature. Selective PET tracer agonists to this receptor now exist, including ^{64}Cu-DOTA-PEGEcRGDyK2 and ^{18}F-galacto-RGD. Promising results of human studies with ^{18}F-galacto-RGD are starting to become available.

Cells undergoing apoptosis expose their cell membrane phosphatidilserine, which is the target most frequently selected to image this process. Annexin V is an endogenous human protein with a high affinity for phosphatidilserine found

on the outer leaflet of the cell membrane. Animal studies have evaluated annexin V labelled with PET tracers such as ^{124}I or ^{18}F annexin V or ^{64}Cu-labelled streptavidin, after pretargeting with annexin V.

Immuno-PET is based on the labelling of MAbs or its fragments with PET tracers, to allow imaging on a PET or PET/CT scanner. Chimeric G250, which is a MAb that targets clear-cell renal cancer, has proven to have a very good sensitivity for detection of disease. A proof of concept study of ^{124}I-labelled cG250 has demonstrated a specificity of 100% and a sensitivity of 94% for correctly characterizing suspicious kidney lesions as clear-cell renal cancer. Clinical trials are well under way and will eventually allow its commercialization for the pre-surgical diagnosis of clear-cell renal cancer.

7.6. CONCLUSIONS

Technological advances in computer science, coupled with the rapid developments in detector technology and scanner electronics, with more sophisticated reconstruction algorithms, are allowing considerable improvements in the quality of PET imaging, with studies acquired faster. An added benefit of these developments is that they deliver a lower radiation dose to the patient as well as cost savings in PET radiopharmaceuticals. At the same time, the continuous advances in CT technology, and the merging of MRI and PET, are opening up new possibilities in molecular imaging.

Although FDG-PET and PET/CT imaging have proven to be very useful for a large number of tumours and a growing list of indications, the broad clinical experience accumulated with FDG has at the same time allowed an understanding of its limitations. In addition, with the now routine use of targeted therapy, there is a pressing clinical need to prognosticate, predict and assess early responses to therapy in cancer patients. The deeper knowledge of tumour biology and recent advances in radiochemistry offer opportunities to characterize malignant tumours non-invasively and to obtain a deeper insight into many of its functions with PET imaging. Therefore, non-FDG-PET and PET/CT are contributing to achieving the goal of personalized cancer therapy. There is a long list of non-FDG-PET tracers at different stages of development, some of which will probably be commercially available in the near future.

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8. TAKE HOME MESSAGES

8.1. THE MOLECULAR BASIS BEHIND THE FDG IMAGE

— Cancer cells use glucose anaerobically to produce lactic acid in non-hypoxic tissues, rather than relying on the supposedly more efficient tricarboxylic acid (TCA) cycle of oxidative phosphorylation to drive ATP synthesis in the mitochondria.
— Aerobic glycolysis in cancer cells provides for a growth advantage in the tumour microenvironment and for the production of lactic acid, which in turn may facilitate cancer progression by degrading the extracellular matrix of the affected host organ. Finally, this increase in glucose metabolism can lead to the immortalization of cancer cells by diminishing the generation of reactive oxygen species in the mitochondria by decreasing the rate of cellular senescence.
— This principle by which tumour cells take up glucose under aerobic conditions constitutes the basis for the detection and staging of human cancers with ^{18}F-FDG and PET.
— FDG-PET imaging has evolved into a technique of proven clinical value and substantial clinical potential by addressing important aspects of the daily management of cancer patients. Its inherent ability to interrogate the biological behaviour of neoplastic molecular pathways in one whole body scan has made it a very important, and in some cases an indispensable, diagnostic and staging tool for cancer patients.
— Newly introduced hybrid imaging systems, e.g. PET/CT and PET/MRI, provide better assessment of disease processes by coupling the pathophysiological findings with their anatomical landscape, therefore allowing for better characterization of the physiological or pathological nature of a particular imaging finding. This is the reason that anatomo-metabolic imaging with FDG-PET/CT has become one of the imaging modalities of choice for the daily clinical assessment of cancer patients.

8.2. FDG PHARMACOKINETICS AND PHARMACODYNAMICS

— FDG is a structural analogue of 2-deoxyglucose, and is used as a tracer of glucose metabolism.
— FDG's distribution is not only limited to malignant tissue. Inflammatory and infectious processes can be FDG avid.
— FDG is delivered to cells via blood flow and then internalized through the same transport mechanism as plasma glucose (*GLUT* transporters).

— Hexokinase is the first enzyme in both the glycolytic and the oxidative phosphorylation pathways of glucose metabolism. It is responsible for cytoplasmic localization and phosphorylation of FDG to FDG-6-phosphate.
— FDG-6-phosphate is then trapped intracellularly because further catabolysis is not possible.
— FDG-PET yields functional information based on altered tissue metabolism and is useful for both diagnosing and staging cancer.
— To interpret FDG tumour images properly, one must be familiar with the normal distribution of the probe, as well as with all the variables influencing its uptake to include benign conditions that may be FDG avid. An educated understanding of all these variables is essential for the accurate interpretation of PET images.

8.3. THE PET/CT REQUEST

— Before the PET/CT scan is approved and performed, there is clinical information that the interpreting nuclear medicine physician needs to know. The written or electronic request for an FDG-PET/CT examination should provide sufficient information to demonstrate the medical necessity of the examination and allow for its proper performance and interpretation.
— The PET/CT request form should simplify pertinent patient information, both personal and clinical. The Society of Nuclear Medicine and Medical Imaging (SNMMI) has published a generic form that is easy for each PET/CT facility to adapt to its particular needs.
— Indications for FDG-PET/CT include, but are not limited to, the following:
  (a) Differentiating benign from malignant lesions;
  (b) Searching for an unknown primary tumour when metastatic disease is discovered as the first manifestation of cancer, or when the patient presents with a paraneoplastic syndrome;
  (c) Staging known malignancies;
  (d) Monitoring the effects of therapy on known malignancies;
  (e) Determining whether residual abnormalities detected on physical examination or on other imaging studies after treatment represent tumour or post-treatment fibrosis or necrosis;
  (f) Detecting tumour recurrence, especially in the presence of elevated levels of tumour markers;
  (g) Selecting the region of a tumour most likely to yield diagnostic information for biopsy;
  (h) Guiding RT planning.

8.4. CLINICAL FACTORS THAT AFFECT FDG BIODISTRIBUTION AND THE INTERPRETATION OF PET/CT STUDIES

— Recent chemotherapy or anaemia;
— Recent cytokine therapy (granulocyte colony-stimulating factor, hematopoietic growth factor or erythropoietin);
— Inflammatory or infectious processes;
— RT, which can be a source of inflammation;
— Recent surgery, which can cause linear uptake along the incision and surgical sites;
— Granulomatous disease;
— Claustrophobia or anxiety.

8.5. PRECAUTIONS, PATIENT PREPARATION AND SET-UP

— The patient should bring prior studies when possible.
— Pregnant women should avoid undergoing PET/CT studies. Therefore, women of reproductive age should be carefully screened for possible pregnancy prior to administering FDG. If the diagnostic procedure is medically justified and the risk of not performing the exam is greater than the potential risk to the foetus, the studies should be carried out following the ALARA (as low as reasonably achievable) principle.
— The most effective ways to reduce the absorbed dose to the foetus are:
  (i) Encourage the mother to drink water;
  (ii) Encourage the patient to void frequently after the injection of the FDG activity;
  (iii) Use a ‘low dose CT’;
  (iv) Limit the scan area to cover only the region of interest.
— A thorough medical history should be obtained, including any history of claustrophobia, movement disorders and other diseases, and the dates and types of procedures previously performed. Careful assessment is recommended of the following comorbidities and any complications regarding: diabetes, renal failure, prior infections, surgeries and invasive diagnostic procedures, use of steroids, RT and chemotherapy.
— *Allergies*. If IV contrast material is to be used, patients should be screened for a history of iodinated contrast material allergy, use of metformin for the treatment of diabetes mellitus, and a history of renal disease. IV contrast material should not be administered when the serum creatinine level is above 1.6 mg/dL or above the normal limit for each institution.
— Patients should arrive at the nuclear medicine laboratory at least 30 min prior to their scheduled appointment.

— Patients should fast for at least 4 h prior to injection. In children younger than 6 years, fasting should not exceed 3 h, due to the fact that, by the time the PET/CT study is finished, the child will not have eaten for more than 4.5 h.
— Patients should be well hydrated to guarantee proper voiding.
— All patients are to refrain from any strenuous activity or exercise for 24 h prior to the study.
— Patients undergoing brain PET/CT imaging should remain resting in a dark, quiet room prior to radiotracer injection and for at least 30 min afterwards.
— Blood glucose levels should be checked prior to radiotracer injection. Plasma glucose levels among non-diabetic patients should not exceed 130–150 mg/dL. In diabetic patients, these levels should be no higher than 180–200 mg/dL. Those patients whose blood glucose levels exceed the recommended values should be rescheduled if possible.

8.6. DOSE, ACQUISITION, INTERVENTIONS, PROCESSING AND DISPLAY

— *Injected activity in adults.* Generally accepted activity: 185–555 MBq (5–14 mCi), which may vary according to the acquisition mode (2-D versus 3-D).
— *Injected activity in children.* Generally accepted activity for whole body studies: 3.7–5.2 MBq/kg (0.10−0.14 mCi/kg). Minimum dose is 37 MBq (1.0 mCi).
— The recommended time to image after radiotracer injection is 60 min to ensure a higher tumour to background ratio.
— *Estimation of lesion uptake.* Lesion uptake is measured by SUV and is based on radioactivity in the lesion, injected activity and the patient's body weight. If quantifying the average of all pixels within the ROI, the result will be SUV_{avg}, whereas with the maximum the result will be expressed as SUV_{max}:

$$SUV = \frac{\text{Mean ROI activity (mCi/mL)}}{\begin{array}{c}\text{Injected activity (mCi)/body weight (g)}\\ \text{or lean body mass (LBM)}\\ \text{or body surface area (BSA)}\end{array}}$$

8.7. TREATMENT RESPONSE EVALUATION WITH PET/CT

— Most cancer treatments are associated with significant side effects and costs. Thus, it is important to assess the effectiveness of a treatment early in the course of the therapy so that drug regimens can be changed and tailored for each individual. On the other hand, in the rapidly progressing world of drug development, it is imperative to have surrogate end points to survival that will provide earlier answers about the efficacy of therapy.
— Tumour shrinkage in response to therapy is one such parameter that has served as the standard of response evaluation in oncology. Many studies have demonstrated that a reduction in the size of a tumour following chemotherapy as measured on CT correlates well with the long term survival of the patient. Different methodological tools have been utilized in various guidelines for measuring tumour size. The measurements may be bidimensional, as recommended by the older WHO criteria, or unidimensional, as recommended by the RECIST criteria.
— While tumour shrinkage in response to therapy makes intuitive sense as a measure of response, there are many fundamental limitations to this concept. There is therefore a growing need to incorporate biologically relevant functional and prognostic information in the response evaluation criteria.
— The basic justification for using FDG-PET in oncology is that there appears to be a strong relationship between FDG uptake and the number of viable cancer cells in a substantial number of studies. Consequently, it is reasonable to expect that reductions in tumour FDG uptake would be seen with a loss of viable cancer cells with each progressive treatment in the responding patients, often preceding changes in tumour size. By contrast, it is widely accepted that the non-responding patients do not have a significant decline in their SUV in a wide range of tumours.
— There are now abundant data confirming that PET is a useful tool for response assessment in a variety of diseases, at the end of treatment, at mid-treatment, and when performed soon after treatment is initiated, and that increases in tumour glucose use and the volume of tumour cells can be expected in progressive tumour.
— FDG-PET scanning can provide a method by which tumour response can be measured in the absence of marked anatomical changes. A reduction in FDG uptake has been shown to indicate treatment response and/or improved survival times in patients with solid tumours such as breast cancer, oesophageal cancer, lung cancer, osteosarcoma and others. FDG-PET has also been shown to provide more rapid response data than anatomical measurements. FDG-PET/CT has been successfully used to

modify disease management by preventing futile thoracotomies in patients with lung cancer and stratifying patients with colorectal cancer into surgical versus palliative groups.

— While quantitative FDG-PET is increasingly recognized as an important tool for response monitoring in oncology, it is important to remember that the quantification in PET may be affected by a myriad of technical and physiological factors. Standardization of acquisition and assessment parameters is therefore of paramount importance, especially where serial studies are being performed for therapeutic response assessment.
— For staging of malignant disease and evaluation after the completion of chemotherapy or RT, visual assessment of tumour FDG uptake is considered to be sufficient and quantitative analysis of FDG-PET scans is generally not required (especially in lymphoma cases). Treatment monitoring in solid tumours is more challenging than response evaluation in lymphomas. These tumours are more resistant to RT and chemotherapy than are malignant lymphomas, and changes in tumour glucose metabolic activity are smaller and occur more slowly than in lymphomas. Therefore, quantitative analysis of the FDG-PET scan is much more frequently used in solid tumours.
— If PET scans are performed during treatment to predict subsequent tumour response in solid tumours, quantitative assessment of tumour metabolism becomes necessary, because at this time point there still is considerable residual FDG uptake, even in patients responding to treatment.
— The goal of FDG-PET is to guide decisions on whether to intensify or change treatment in non-responding patients. Ultimately, the prediction of therapeutic effectiveness by PET and PET/CT could help to individualize treatment and to avoid ineffective chemotherapies, with their associated toxicities.

8.8. THE PET/CT REPORT

— The PET/CT report communicates information to the referring physician, records that information for future use, and serves as the legal record for the episode of care. In addition to its clinical function, the PET/CT report may be used for billing, accreditation, quality improvement, research and teaching. The report also serves as a means of communication with the patient.
— PET/CT reports should employ clear and unambiguous language. It is important that the report is concise and to the point; a long essay is unlikely to be read, with the risk that key information will be missed.
— The PET/CT report is divided into five sections: clinical history (indication), comparison, technique, findings and impression.

8.9. FUTURE DIRECTIONS OF PET

— FDG-PET and PET/CT have revolutionized the care of the cancer patients over the past 20 years.
— PET/CT represents a significant advance on stand-alone PET in many ways, including reduced study duration and superior anatomical detail from the multislice CT images.
— Despite being an outstanding radiotracer with many advantages, FDG has known limitations, including its rather limited use in several tumours with low metabolic rates, and false positives due to inflammatory and infectious diseases, etc.
— The future of PET/CT imaging resides in developments in two main areas. First, technological advances in imaging technology and scanner electronics (new detectors, time of flight, PET/MRI, etc.) and computer science (new reconstruction algorithms, etc.) could bring added benefits such as the delivery of lower radiation doses to the patient and cost savings in PET radiopharmaceuticals. The second development concerns the introduction into clinical use of new non-FDG-PET radiopharmaceuticals, which could exploit the limitations of FDG and take advantage of the deeper knowledge of cancer cell biology.
— The deeper understanding of the specific biological features of each different type of cancer, and the now widespread use of molecular targeted therapy, has prompted the development of patient specific, individualized cancer management and therapies. Therefore, there is a growing clinical need for the non-invasive characterization of different functions in the biology of cancer cells, besides the glycolytic pathway.
— To this end, alternative non-FDG-PET tracers have been developed and evaluated in preclinical and clinical studies with different degrees of success (^{18}F-sodium fluoride, ^{18}F-choline or ^{11}C-choline and 3′-deoxy-3′-fluorothymidine (FLT), among others).
— All of these developments will help considerably in achieving the goal of personalized cancer therapy.

Appendix

SAMPLE PET/CT REPORTS

A.1. SAMPLE REPORT 1 — SUSPICIOUS SOLITARY PULMONARY NODULE (SPN)

PATIENT NAME: Doe Joe

MEDICAL RECORD NUMBER: 000000-7

EXAMINATION: PET/CT Base of skull to mid-thigh

EXAM DATE: __/__/____

CLINICAL HISTORY: 70 year old male active smoker with 40 year history of smoking. CT scan showed enlarging 1 cm spiculated nodule in the right mid-lobe without lymphadenopathy. PET/CT requested to search for malignancy.

COMPARISON STUDY: No prior PET exams. CT chest dated 12/31/2010.

TECHNIQUE:

Approximately 60 min after the IV administration of 10 mCi of ^{18}F-FDG, PET images were obtained from the orbits to mid-thighs using 3-D acquisition. The patient's fasting blood glucose level was 120 mg/dL. The patient was positioned in the PET/CT scanner approximately 60 min after injection of the radiopharmaceutical. A CT scan from the orbits to upper thighs was obtained for attenuation correction and anatomical localization. Images were displayed in the axial, coronal and sagittal planes. Injection site was in the right antecubital fossa.

FINDINGS:

A 1 cm spiculated nodule is seen unchanged at the anterior aspect of the right middle lobe with intense FDG uptake (SUV_{max} 4.7). No other abnormalities are seen in the rest of the lung parenchyma. There is no FDG avid mediastinal or hilar lymphadenopathy.

No abnormal FDG uptake was demonstrated in the abdomen and pelvis.

There is normal physiological FDG uptake in the liver, spleen, adrenal glands, bone marrow, bowel, renal collecting systems and urinary bladder.

IMPRESSION:

Highly FDG avid enlarging spiculated 1 cm nodule in the right middle lobe is highly suspicious for malignancy. Biopsy is recommended. No evidence of metastatic disease.

A.2. SAMPLE REPORT 2 — TONSIL TUMOUR

PATIENT NAME: Doe Joe.

MEDICAL RECORD NUMBER: 000000-2

EXAMINATION: PET/CT Base of skull to mid-thigh with head and neck protocol

EXAM DATE: __/__/____

CLINICAL HISTORY: 72 year old male with left tonsilar mass, biopsy proven squamous cell carcinoma and lymphadenopathy in the left neck. PET/CT for initial strategy planning.

COMPARISON STUDY: No prior PET exams. CT neck dated 12/31/2010.

TECHNIQUE:

Approximately 60 min after the IV administration of 10 mCi of ^{18}F-FDG, PET images were obtained from the sternal notch to mid-thighs using 3-D acquisition. A CT scan from the sternal notch to upper thighs was obtained from the sternal notch to upper thighs for attenuation correction and anatomical localization. Subsequently, PET and CT images from the top of the skull to the aortic arch were obtained. Images were displayed in the axial, coronal and sagittal planes. No IV or oral contrast was given. The patient's fasting blood sugar was 110 mg/dL.

COMPARISON: There are no prior PET scans available for comparison. CT neck dated 12/31/2010.

FINDINGS:

Head and neck:

Previously demonstrated 1.5 cm mass in the left tonsil is highly FDG avid (SUV_{max} 7.5 on image 19). There is a 1.5 cm left level 2 highly FDG avid lymphadenopathy (SUV_{max} 4.5 on image 23). No other FDG avid lymphadenopathy was seen in the rest of the neck. Physiological FDG uptake is seen in the salivary glands and larynx.

Chest:

No FDG avid abnormalities are demonstrated in the lung parenchyma. There is no hilar or mediastinal adenopathy. There are no pleural or pericardial abnormalities. Physiological FDG uptake is noted in the heart. The diameter of the thoracic aorta is normal. The thyroid gland is normal.

Abdomen and pelvis:

There is no abnormal FDG uptake in the abdomen and pelvis. The liver, pancreas and spleen are normal. There are no adrenal masses. Physiological FDG uptake is seen in the kidneys and urinary bladder. There is an infrarenal abdominal aortic aneurysm measuring 5.1 cm × 4.8 cm × 6.2 cm without abnormal FDG uptake.

Musculoskeletal:

Normal FDG uptake is seen in the axial skeleton. No sclerotic or lytic lesions are seen on CT. Injection site is noted in the right antecubital fossa.

IMPRESSION:

(1) Highly FDG avid mass in the left tonsil secondary to known squamous cell carcinoma. Left level 2 highly FDG avid lymphadenopathy is highly suspicious for metastasis. No evidence of other metastatic lesions.
(2) Unexpected finding: 5.1 cm infrarenal abdominal aortic aneurysm.

The findings were forwarded to the referring physician.

ACRONYMS AND ABBREVIATIONS

ALARA	as low as reasonably achievable
APD	avalanche photodiode
AR	androgen receptor
ATP	adenosine triphosphate
BAT	brown adipose tissue
BGO	bismuth germanate
BSA	body surface area
CEA	carcinoembryonic antigen
CSF	colony-stimulating factor
CT	computed tomography
CTDIv	volume computed tomography dose index
DCE MRI	dynamic contrast enhanced MRI
DHT	dihydrotestosterone
DRL	diagnostic reference level
DWI MRI	diffusion-weighted imaging MRI
EANM	European Association of Nuclear Medicine
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
FCH	focal congenital hyperinsulinism
FDG	^{18}F-fluorodeoxyglucose
^{18}F-FDHT	16β-^{18}F-fluoro-5α-dihydrotestosterone
F-DOPA	^{18}F-deoxiphenilalanine
FES	^{18}F-fluoroestradiol
FLT	3′-deoxy-3′-^{18}F-fluorothymidine
F-MISO	^{18}F-fluoroimidazole
G-CSF	granulocyte colony stimulating factor
GIST	gastrointestinal stromal tumour
GLUT	glucose transporter
HCC	hepatocellular carcinoma
ICRP	International Commission on Radiological Protection
IHP	International Harmonization Project
IV	intravenous
LDHA	lactic dehydrogenase
LSO	lutetium oxyorthosilicate
LYSO	lutetium yttrium oxyorthosilicate
MIP	maximum intensity projection
MAb	monoclonal antibody
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer

NCCN	National Comprehensive Cancer Network
NET	neuroendocrine tumour
NSCLC	non-small cell lung cancer
PEM	PET mammography
PET	positron emission tomography
PETPROS	PET Professional Resources and Outreach Source
PKB	protein kinase B
PMT	photomultiplier tube
po	per os (by mouth)
PSA	prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumours
rhTSH	recombinant human thyroid-stimulating hormone
ROI	region of interest
RT	radiation therapy
SiPM	silicon photomultiplier
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SNR	signal to noise ratio
SPECT	single photon emission computed tomography
SPN	solitary pulmonary nodule
SRS	somatostatin receptor scintigraphy
SST	somatostatin subtype
SUL	SUV corrected for lean body mass
SUV	standardized uptake value
TCA	tricarboxylic acid
TG	thyroglobulin
TGV	total glycolytic volume
TK1	thymidine kinase 1
TLG	total lesion glycolysis
TNM	tumour, node, metastasis
TOF	time of flight
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VOI	volume of interest
WHO	World Health Organization

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