Guide on Clinical Standard Operating Procedures on the use of PET/CT

A PRACTICAL APPROACH IN ADULT ONCOLOGY
FOREWORD

Over the last 20 years, PET and PET/CT have revolutionized the care of cancer patients in the industrialized world. In fact, it has been and still is, one of the fields in medical imaging with the highest growth rate. There are several reasons for the rapid development of this imaging technology. As the population continues to age in many countries, cancer constitutes a major health problem world-wide, with an increase in incidence. In developed countries where heart diseases constitute the first cause of mortality, cancer is a close second one, and may eventually overtake the first place. Proper cancer management requires highly accurate imaging to properly characterize, stage, re-stage, assess response to therapy, prognosticate, and detect recurrence. This information is critical in a disease that oftentimes requires the correct initial treatment in order to improve the chance to succeed and cure the patient.

The ability to provide in a single image session detailed anatomical and metabolic/functional information, which has a powerful synergistic effect more so than the individual sum of both 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 quality of the imaging technique. This publication addresses this important aspect of PET/CT imaging, namely how to perform the $^{18}$F-FDG (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, we intended to offer a comprehensive overview that could be used either by a PET/CT centre that is in the process of starting, as well as for the updating of older protocols being used in an already established imaging centre. In fact the authors of this publication have many years of experience in PET and PET/CT imaging, and come from several different continents.

The aim was to write an-up-to-date, evidence-based, comprehensive and current overview of Operating Procedures for FDG-PET/CT imaging in adult oncology patients. We wrote the manuscript in consensus and agreement amongst the authors, following a systematic approach of relying on our 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 very well be that each PET/CT centre may have to accommodate the recommendations from this publication to their own particular circumstances, according to the type of scanner, patient population, use of intravenous contrast, availability of FDG, professional staff experience, local regulations and preferences of referring physicians, amongst others.

The information provided in this publication is felt to be important since there is a growing need to standardize and optimize the way PET/CT scans are performed, not only because trials using FDG-PET/CT in different institutions can be compared and correlated, but also, because it will allow for a more accurate comparison of scans performed at different time points in the same patient in a single institution. This is especially true when assessing response to cancer therapy, more so when this evaluation is frequently performed earlier and after using novel targeted treatments that very often only produce a change in metabolic activity and not in lesion/tumour size. This is the reason why strictly following a correct imaging protocol becomes 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 are viewed by the pharmaceutical industry as potentially useful biomarkers to shorten the clinical validation process of drugs. Moreover, although it is
not the subject of this publication, 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. The existing variability in cancer types, in PET radiotracers, in patient conditions, in PET/CT scanners, in published imaging protocols, and clinical scenarios, make this publication very relevant and necessary.

This publication is part of the IAEA Human Health Series Publications that include further reading on *Planning a Clinical PET Centre* and the *Appropriate Use of FDG-PET for the Management of Cancer Patients*. Technical officers in charge of this publication were Ms Diana Paez and Mr Maurizio Dondi from the Nuclear Medicine Section, Division of Human Health. We are indebted to the contributors whose names are provided in alphabetical order at the end of this book for sharing invaluable knowledge, time and effort.
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1. THE ROLE OF FDG-PET/CT IN ONCOLOGY

1.1. INTRODUCTION

The molecular basis behind the FDG image

In 1931 Doctor Otto Warburg described the effect that carried his name leading to the Nobel Prize. Warburg observed that tumoural tissue metabolized 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 used glucose anaerobically to produce lactic acid in non-hypoxic tissues, rather than relying on the supposedly more efficient TCA (tricarboxylic acid cycle) of oxidative phosphorylation to drive ATP synthesis in the mitochondria.

Different 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 isofrom II, which phosphorylates intra-cellular glucose. On the other hand, the MYC oncogene 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 that stimulates the expression of hundreds of genes including GLUT-1, GLUT-3 transporters, Hexokinase isofrom 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 results in increased metastatic potential and poor survival of patients with different cancer types. Last but not least, 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 contribute to the Warburg effect by stimulating glycolytic metabolism while in parallel they attenuate mitochondrial function, thereby decreasing the rate of oxidative phosphorylation taking place within the tumour cell (Fig. 1.1).

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 uptake 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).

In the past 20 years, FDG-PET imaging has evolved into a technique of proven clinical value and substantial clinical potential addressing important aspects in the daily management of cancer patients. Its inherent ability to interrogate the biologic 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 planning, monitoring results of cancer therapy, and determination of prognosis in some cancer types. Newly introduced hybrid imaging systems, e.g. PET/CT (Computed Tomography) and PET/MRI (Magnetic Resonance Imaging), provide better assessment of disease processes by coupling the pathophysiological findings with their anatomical landscape, and therefore, allowing for better characterization of the physiologic or pathologic nature of a particular imaging finding.

This is the reason for which 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 it is 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 into 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 receptors recognition, angiogenesis, and tumour hypoxia, amongst others.

1.2. FDG PHARMACOKINETICS AND PHARMACODYNAMICS

$^{18}$F-FDG is a structural analog of 2-deoxyglucose, and is used as a tracer of glucose metabolism (and of the Warburg effect). Its distribution is not only limited to malignant tissue. Once intravenously administered, FDG is delivered to cells via blood flow and 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 thirteen 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 trans-locates 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 diffusion of sugar molecules in both directions, based on a concentration gradient. Tumours express GLUT at higher levels than normal tissue, and therefore may uptake 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 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 bladder on PET/CT images. Once in the cytoplasm, $^{18}$F-FDG is phosphorylated to $^{18}$FDG-6-phosphate, a reaction which is catalysed by hexokinase (mainly isoforms II and I).
Hexokinase is the first enzyme in both the glycolytic and 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 also has anti-apoptotic action through its effect upon protein kinase B (PKB/Akt), and is unregulated in cancer cells (Fig. 1.1).

\(^{18}\text{F-} \text{FDG-6-phosphate is then trapped intra-cellularly because further catabolysis is not possible due to the absence of an oxygen atom on the molecule’s C-2 position (which holds }^{18}\text{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}\text{F-} \text{FDG-6-phosphate will not concentrate, resulting in poor visualization of tissues/tumours on PET imaging (i.e. hepatocellular carcinoma).}

\(^{18}\text{F-} \text{FDG-PET yields functional information based on altered tissue metabolism and is useful for both diagnosing and staging cancer. It should also be kept 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.}

To properly interpret FDG tumour images 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 accurate interpretation of PET images. Simplification is not uncommon and perhaps it could 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 like 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 can 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 less than 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 salivary glands. FDG is excreted by the salivary glands, therefore, with activities ranging from moderate to high, and should not be considered a positive focus of head and neck malignancy. The parotid and submandibular glands usually have a symmetric pattern of mild to moderate FDG avidity. On the other hand when in 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, uptake can be minimized by keeping the patient from speaking, drinking or chewing before and after FDG administration (the uptake period).

1.3.4. Thyroid gland

Uptake in the thyroid gland is variable, ranging from absent to low-moderate in intensity. Diffuse uptake can be normal or 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 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. Significantly higher uptake may be found in thymoma, thymic carcinoma or lymphoma in the list of differentials.

1.3.6. The 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 its energy source, but post-prandially, or after glucose loading, it preferentially uses glucose. Therefore, in the fasting state, with low insulin and blood sugar levels, FDG myocardial uptake is usually low or absent. However, this does not hold true for ischemic segments, which in the fasting state will uptake FDG with greater avidity than normal segments. Based on this, it is recommended that patients receive a glucose load before myocardial FDG scanning, where normal myocardial segmental uptake will be enhanced when compared to ischemic segments. In contrast, when FDG imaging is performed for tumour targeting, a long fasting state is recommended. This minimizes blood glucose levels that compete with FDG uptake as well as it will diminish, in the majority of the cases, cardiac activity by stimulating the shift of glycolytic metabolism to fatty acid metabolism in the myocyte, and 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 to 12 hours (Fig. 1.2).

If scans are corrected for attenuation, mediastinal activity tends to be higher than lung activity. On the contrary, in uncorrected images, 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 better target to background ratio when staging mediastinal structures. Activity in the blood pool decreases slightly over time, while 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 sub-acute phase of pulmonary emboli and infarcts mild-to-moderate uptake may be seen, which should be distinguished from malignancy.

1.3.7. Breast

Breast uptake 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 GLUT-1 as well as the fact that phosphorylated FDG becomes trapped intra-cellularly 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 falls below the 1 mSv recommended for breast feeding cessation. Please refer to section 3.1.3 for further information on breast feeding. Taking into consideration the above-mentioned facts, higher radiation dose is received by the infant from close contact with the breast rather than from ingestion of radioactive milk. Breast uptake has mild variation 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 does not have an effect on SUVavg or SUVmax (Standardized Uptake Value). Of note, 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 uptake which is mild to moderate in intensity, and the truth is that small lesions may be difficult to detect against this background. In fact small foci of FDG avidity, without CT correlate, 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 follow-up MRI or PET/CT scan is indicated to rule out metastasis. Liver uptake is most often slightly higher than spleen. However, it may be decreased 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 with the surrounding liver background.

Splenic uptake is mostly homogeneous, of mild-to-moderate 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 gastric-oesophageal junction. This may be either physiologic, or secondary to esophagitis due to gastro-oesophageal reflux. Activity in the small and large intestines vary from patient to patient. Bowel activity may be related to smooth muscle peristaltic function and/or bacterial uptake. Frequently, low to moderate uptake could be observed in the lymphoid tissue of Waldeyer’s ring as well as in the cecum (due to concentration of lymphoid tissue in Peyer’s patches). As mentioned before, 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 hours 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 hours prior to the exam. Low to moderate uptake of FDG is seen in the vertebral body’s bone marrow and even weaker uptake can be appreciated in the bone marrow of femur, pelvis, and ribs. More diffused bone marrow uptake is a frequent finding when patients have undergone chemotherapy with or without colony stimulating factors or in anaemic patients. Another source of increased bone marrow uptake is acute infection.

1.3.11. Kidneys and urinary collecting system

It is common to see kidneys, ureters, and bladder activity, 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 hour post injection; therefore, the renal parenchyma will no longer contain much of the injected activity by then. 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 this 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 the 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 post-menopausal 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 is moderate and symmetric. Asymmetric uptake may be due to tumour (hot), or 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. Of note, however, is that many prostate cancers do not uptake FDG. Fig. 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 to 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 aging, and/or the FDG activity in the macrophages present in the atherosclerotic plaque. In general, the abdominal aorta is usually seen less frequently compared to the pelvic and 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 hour 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 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 the colder weather. On PET/CT, the foci of uptake co-localize with areas of fat density, however, when uptake is very extensive, or in those cases with significant mis-registration between the CT and the 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 helps minimize BAT uptake. Other reported methods include pre-treatment with propranolol or other beta blockers, or with a fatty-meal protocol.

When armed with knowledge about proper acquisition and processing techniques, being familiar with the normal distribution and physiological variations of FDG uptake, will enable the observer to depict the presence of pathological findings with a high degree of confidence. Once accomplished, recognition of the extent and location of disease depends upon the type of information in the image, both 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 document is intending to do for its readers.

For a complete gallery of PET/CT cases please visit the Human Health Campus at http://humanhealth.iaea.org. The Human Health Campus is an educational resource website for health professionals in radiation medicine.
FIG. 1.1. FDG Metabolism

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 (upper row) and the moderate lung uptake in the non-corrected images (Bottom row).
FIG. 1.3: Normal distribution of FDG

Grey matter
Oropharynx
Oesophageal
Myocardium
Renal pelvis
Colon
Small bowel in midline
Urinary bladder
Urine in urethra
BIBLIOGRAPHY FOR CHAPTER 1


INTERNATIONAL ATOMIC ENERGY AGENCY, Planning a clinical PET centre, Human Health Series 11, IAEA, Vienna (2010).
2. INFORMATION FOR REFERRING PHYSICIANS

2.1. THE PET/CT REQUEST

There is a general recognition that FDG-PET/CT studies result in a significant change in management in 10%–30% of patients studied, with significant variation between different malignancies. This impact is based on the interpretation of the degree of FDG uptake in masses, lymph nodes and other organs which determine the presence of a metabolically active lesion and the extension 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 of the examination and allow for its proper performance and interpretation.

There are clear requirements for referring medical practitioner in the IAEA’s International Basis Safety Standards (BSS) that require registrants and licensees to ensure that no patient, whether symptomatic or asymptomatic, undergoes a 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;

Further, the justification process particularly for patients who are pregnant or breast-feeding or paediatric shall take into account following 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 simplify pertinent patient information, both personal and clinical. All PET/CT facilities should have request forms to simplify this. The Society of Nuclear Medicine (SNM) has published a generic form that is easy to adapt to each PET/CT facility individual needs. The SNM Physician Request Form for Oncologic PET/CT Imaging can be found online under the PET Professional Resources and Outreach Source (PETPROS) page.*

* The link to PETPROS: http://interactive.snm.org/index.cfm?PageID=9273
1) The first part of the form contains patient’s personal information, identification and medical record number. This facilitates the contacting of the patient for appointment dates and instructions on the procedure (Table 2.1).

2) The second part contains the referring physician’s contact information and information about prior PET/CT or other imaging studies and the facility in which these were performed. The actual images and report should be made available for comparison at the time of interpretation (Table 2.2). This information is necessary to know the morphologic characteristics of a lesion and correlate with the metabolic changes and if the patient had prior PET/CT scans to compare and determine if changes occurred between studies.

3) Part three includes information about diabetes, prior intravenous contrast use and some biometric data (Table 2.3).

   — History of diabetes: Hyperglycaemia or hyperinsulinemia can alter FDG biodistribution. Diabetic patients need monitoring before the day of the PET study. This monitoring will ensure that the glucose level is <180 - 200 mg/dL. This may require daily monitoring for a few days along with instructions to watch diet and follow exercise recommendations. Insulin administration within 2 hours of the FDG injection time or endogenous insulin secondary to hyperglycaemia, may cause increased glucose uptake in muscle or other soft tissue and compromise tumour uptake. If the 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 should be consulted.

   — If the request includes the use of IV contrast for the CT portion, the patient should be screened for 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 decreased when appropriate.

   — Height and body weight must be accurately recorded in the case of SUV measurements. With serial studies in the same patient, weight must be measured directly prior to each PET study because body weight often changes during the course of disease. Patient height, weight, and gender should be reported to allow for other SUV normalizations like (LBA) lean body weight and (BSA) body surface area. The latter is important to meet European Organization for Research and Treatment of Cancer (EORTC) recommendations and for response assessment studies, when large changes in body weight occur during the course of the treatment. Please refer to chapter 5 for extended information on Response Evaluation in FDG.

4) Part four indicates the type of study requested, this 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 for 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 for cervical lymph node metastasis and to assess the primary tumour.
— Whole-body study (skull vertex to toes) - also known as the Melanoma protocol. For known or suspected lower extremity tumours (including melanoma or cutaneous lymphoma (Table 2.4.).

— Standard PET/CT: PET combined with diagnostic CT with intravenous contrast. When a diagnostic CT scan is required.

5) Part five indicates specific reasons for the PET/CT study. This section should include information that could have an impact on the interpretation. The type of cancer, the histologic 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), PET/CT requested for initial staging (Table 2.5).

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 effect 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 radiation therapy planning.

2.2.RECOMMENDATIONS AND GUIDELINES

There are several recommendations available coming from different professional organizations such as, EANM, SNM and National Comprehensive Cancer Network (NCCN), regarding the use of FDG PET and PET/CT in oncology.

In early 2010 the IAEA published the Human Health Series No.9 on the Appropriate Use of FDG-PET for the Management of Cancer Patients; these recommendations were put together in light of 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 cancers types. These broad recommendations cannot be rigidly applied to all patients in all clinical settings and require periodic updating. We would like to emphasize to the reader that several recommendations are available regarding the use of FDG-PET and PET/CT in oncology from different professional organizations and yet to list all recommendations would be beyond the
scope of this publication, therefore the readers are advised to seek the most recent reports pertinent to this particular area.

Below we have selected examples of recommendations for some cancer types included in the above mentioned IAEA publication. Please note that the following list is just a summary and does not replace the comprehensive review found in the detailed information included in the Human Health Series No.9.

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 $^{131}\text{I}$ whole body scan, FDG-PET provides useful data. RThS 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


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 (HD) and aggressive non-Hodgkin’s lymphomas (NHLs), 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 FDG avidity of the tumour when 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 is no data available to support the use of PET for RT planning.

Note: The above recommendations also apply to primary central nervous system (CNS) 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 adoption of more effective therapeutic strategies or through 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 patients. Any history of previous treatment with radiation, chemotherapy, or other experimental therapeutics, including when these therapies were performed and completed, should be documented. In particular, the use of medications that may affect the uptake or bio-distribution 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 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 PET scan are included in table 2.6.
TABLE 2.1.
Physician Request Form for Oncologic PET/CT Imaging

<table>
<thead>
<tr>
<th>Patient Name____________________________</th>
<th>Date of Study__________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical record No._____________________</td>
<td>Gender_________</td>
</tr>
<tr>
<td>Patient’s Address_______________________</td>
<td></td>
</tr>
<tr>
<td>Patient’s Phone_______________________</td>
<td></td>
</tr>
<tr>
<td>Insurance information when applicable</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2.2.

<table>
<thead>
<tr>
<th>Requesting physician__________________</th>
<th>Phone_________</th>
<th>E-mail_________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous CT or MRI____ Where____________</td>
<td>Date__________</td>
<td></td>
</tr>
<tr>
<td>Previous PET Study____ Where____________</td>
<td>Date__________</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2.3.

<table>
<thead>
<tr>
<th>Diabetic No □ Yes □</th>
<th>Diabetic Medication:______________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latest fasting blood sugar__________</td>
<td></td>
</tr>
<tr>
<td>Allergy to contrast agents_________</td>
<td></td>
</tr>
<tr>
<td>Renal function__________</td>
<td>Creatinine level______________</td>
</tr>
<tr>
<td>Height (cm)______________</td>
<td>Body weight (kg)______________</td>
</tr>
</tbody>
</table>

TABLE 2.4.

<table>
<thead>
<tr>
<th>STUDY REQUESTED (Check One)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Standard body study (skull base to proximal thigh)</td>
<td></td>
</tr>
<tr>
<td>□ Special (non-standard) body study</td>
<td></td>
</tr>
<tr>
<td>□ Whole-body study (skull vertex to toes) for known or suspected lower extremity tumours (including melanoma)</td>
<td></td>
</tr>
<tr>
<td>□ Head and neck cancer study (skull vertex to thighs) or dedicated head and neck protocol</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2.5. Specific Reason for PET Study

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>□ Histologically Proven □ Suspected</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Diagnosis:</td>
<td>To determine if suspicious lesion is cancer</td>
</tr>
<tr>
<td>□ Diagnosis:</td>
<td>To detect an occult primary tumour:</td>
</tr>
<tr>
<td></td>
<td>□ Initial Staging of confirmed, newly diagnosed cancer</td>
</tr>
<tr>
<td></td>
<td>□ Monitoring Response during treatment</td>
</tr>
<tr>
<td></td>
<td>□ Chemotherapy ______ Radiotherapy ______ Other (type) __________________</td>
</tr>
<tr>
<td></td>
<td>□ Other (specify) _____________________________</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
# Table 2.6. Clinical Situations That Affect FDG Uptake and FDG-PET/CT Timing and Recommendations

<table>
<thead>
<tr>
<th>Prior therapies and clinical issues</th>
<th>Recommended interval between therapy and PET/CT</th>
<th>Confounding factor</th>
<th>Other recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent chemotherapy</td>
<td>2 weeks</td>
<td>Marked increase in FDG uptake in the bone marrow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interim PET 2-3 weeks from last cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>End of treatment 4-6 weeks (p.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent therapy with cytokines or growth factors</td>
<td>Short acting: 1 week</td>
<td>Marked increase in FDG uptake in the bone marrow</td>
<td></td>
</tr>
<tr>
<td>Inflammatory or infectious processes</td>
<td>Long acting: 3 weeks</td>
<td>Increase in FDG uptake in the infected or inflamed areas</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>4-6 weeks</td>
<td>Focal increase in FDG uptake in the radiated area</td>
<td></td>
</tr>
<tr>
<td>Recent surgery</td>
<td>4-6 weeks</td>
<td>Increase in FDG uptake in the surgical sites</td>
<td></td>
</tr>
<tr>
<td>Granulomatous diseases like sarcoidosis</td>
<td></td>
<td>Focal increase in FDG uptake in the affected area</td>
<td></td>
</tr>
<tr>
<td>History of claustrophobia</td>
<td>Pre-treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INTERNATIONAL ATOMIC ENERGY AGENCY, Appropriate use of FDG-PET for the management of cancer patients, IAEA Human Series 9, IAEA, Vienna (2010).


3. PRECAUTIONS, PATIENT PREPARATION AND SET-UP

3.1. PRECAUTIONS

3.1.1. Prior studies

The patient should bring prior studies when possible since this will not only improve the quality of the report, but the acquisition parameters as well.

— The nuclear medicine physician will be able to evaluate the patient imaging history, lesions seen on different imaging modalities, and compare with prior PET/CT studies for evaluation of response to treatment.

— The nuclear medicine physician will be able to evaluate the necessity or not, for example, of acquiring a full-dose contrast-enhanced CT scan. If the patient has already performed this scan in a short period of time, it is not necessary to perform another scan.

Caution should be exercised when PET/CTs are performed in other institutions with different types of equipment since semi-quantitative indices of uptake such as SUV may have significant variability, in which case a qualitative (visual) assessment of the imaging findings is more appropriate. Please refer to chapter 5- Response evaluation in FDG-PET/CT and chapter 6- PET/CT reporting in oncology for detailed information on the subject.

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. Fetus and radiation

The fetus 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. The dose to the fetus during early pregnancy may be as high as 0.04 mGy/MBq of FDG [3.1]. The International Commission on Radiological Protection (ICRP) provides certain recommendations based upon radiation risks, and though 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. To this effect, the ICRP advises that termination of a pregnancy is only justified if the fetal whole body dose has been higher than 100 mGy and based on individual circumstances [3.2]. Also, the risk of malformations 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 exam is greater than the potential risk to the fetus, the studied should be carried using a ‘low-dose CT’.

3.1.2.2. Acquisition and pregnancy

If the study is to be obtained on a pregnant woman, the ALARA principle of “as low as reasonably achievable” should be followed. The most effective ways to decrease the absorbed dose to the fetus are 1) to encourage the mother to drink water, 2) to void frequently after the injection of the lowest possible (perform 3D PET instead of 2D) FDG dose, 3) to use a ‘low-
dose CT’ and 4) to limit the scan area to cover only the region of interest [3.4]. For further information on the dose to be injected in adult patients please refer to section 4.1.1.

3.1.3. Breast feeding

Breast feeding may continue up until the injection of FDG. After the injection of FDG, complete interruption of breast feeding is not necessary. However, close contact of the mother with the child should be avoided and, if possible, a 3 to 4 hour delay in breast feeding will ascertain that the radiation dose to the child will be negligible.

— The FDG administered to the mother is excreted in breast milk resulting in an unnecessary exposure to the child who ingests it. Although the radioactivity in milk samples taken after the administration of FDG shows a total fraction of less than 0.71% of the activity given to the mother [3.4], a delay in breast feeding should be 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 thorough medical history should be obtained, including history of claustrophobia, movement disorders, as well as other diseases and 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, radiotherapy and chemotherapy.

3.1.4.1. Claustrophobic patients and patients with movement disorders

The PET/CT acquisition may last from 5 to 30 minutes, depending on the type of PET/CT scanner and the protocol used with patients required to lie still for the entire length of the study. Claustrophobia premedication is usually treated with diazepam 1 to 2 mg P.O. In rare occasions conscious sedation and/or anaesthesia are used, both requiring additional qualified personnel.

3.1.4.2. Diabetes

The 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, therefore, these patients need special preparation prior to the study. Of note, Metformin may markedly increase FDG uptake in the intestinal tract. Please see section 3.2. Patient preparation.

3.1.4.3. Allergies

If intravenous 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. 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 inflammation, infection and in tumours. In patients with a prior history of surgery and/or invasive diagnostic procedures, FDG uptake can be present in 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. Not uncommon is the presence of a halo of diffuse, low-grade uptake in the periphery of lesions treated with radiofrequency ablation, which can be differentiated from residual disease, which in turn may be characterized by focal/nodular intense uptake in the treated area. However, other complications from these radiofrequency procedures may cause potential false-positive results and thus a careful history is always needed to minimize erroneous reporting [3.6].

3.1.4.6. Radiotherapy

Tissue irradiation causes oxidative stress which leads to inflammation and therefore, increased FDG uptake. This is especially important in head and neck tumours in which altered metabolism in irradiated tissues may persist up to 1 year after radiotherapy [3.7].

3.1.4.7. Hematopoietic cytokines

Increased diffuse bone marrow uptake can also be seen 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 GI 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, however, 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 reaction in the lesions. Other immunotherapy agents may also cause an inflammatory reaction and interim therapy scanning may be confounding, especially in lymphoma patients [3.10]. Please refer to chapter 5- Response evaluation in FDG-PET/CT and chapter 6- PET/CT reporting.

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 like sarcoidosis are usually highly FDG avid. A controversial point is the waiting period between
radiation therapy and PET scanning that 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 tubes sites. Assessment for residual tumour is usually difficult. Table 2.6 includes some of the most important factors affecting the FDG uptake and the timing between therapy or clinical conditions and PET scan.

3.2. PATIENT PREPARATION

3.2.1. Patient arrival

Patients should arrive to the Nuclear Medicine laboratory at least 30 min prior to their scheduled appointment. This will guarantee resting prior to FDG injection, normalization of the body temperature on cold days (minimizing uptake in brown fat), and history taking without delaying the start of the study and the patient stay.

3.2.2. Fasting

Patients should fast for at least 4 (preferably 6 hours) hours prior to injection. Fasting will reduce muscle uptake (Fig. 3.4).

— In children below 6 years of age fasting should not exceed 3 hours, due to the fact that by the time the PET/CT study is finished, the child will have fasted for more than 4½ hours.

— Discontinuation of all parenteral nutrition and i.v. fluids containing glucose for 4 - 6 hours is recommended to reduce serum insulin to baseline, thus minimizing the shift of FDG uptake into muscle and fat. In addition this will 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 hours 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 para-spinal muscles in anxious patients.
- Vocal cord and larynx: in patients that speak during the uptake phase (Fig. 3.6).
- Masticator muscles: in patients that are chewing gum before and after radiotracer injection (Fig. 3.7).
— 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 minutes 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, 15 minutes prior to radiotracer injection and for at least 30 minutes afterwards.

— This will reduce radiotracer uptake in brain areas which, when stimulated, become very intense, such as the visual cortex.

3.2.6. **Blood glucose levels**

This should be checked prior to radiotracer injection. Increased blood glucose levels cause increase in insulin levels, altering 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, consult the nuclear medicine physician before proceeding with the 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.

- FDG tumour uptake is reduced in hyperglycaemic conditions (Fig. 3.8).

— Those patients in whom blood glucose levels exceed the recommended values should be rescheduled. If the patient cannot be re-scheduled for some specific reason, the procedures that follow are acceptable:

- Intravenous dose of 1-2 U of ‘regular’ insulin. Check blood glucose levels every 30 minutes. 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 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 minutes. 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.

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, radiotracer may be injected after 90 minutes of the
insulin injection. If blood glucose levels are extremely low, serum glucose 50% should be injected and the study suspended and re-scheduled [3.13, 3.14].

3.3. PATIENT SET-UP

Before beginning the study, patients should be questioned regarding:

1) Fasting prior to study (Fig. 3.9).
   — Female patients of child-bearing age for possibility of pregnancy.
   — Female patients of child-bearing age for possibility of breast feeding.
   — Prior surgeries especially mastectomy and lymphadenectomy. Inject the radiotracer in the opposite arm to the mastectomy. If bilateral mastectomy, inject in the foot.

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

3) Record height and weight of the patient using a scale.
   — This will guarantee precision when calculating the uptake values.

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

5) If indicated (mainly for abdominal lesion detection), have the patient drink the oral contrast. Allow 15 minutes to drink the contrast from the time of arrival, if patient does not finish contrast, inject the FDG. Have patient drink ½ a cup of water to remove the barium from the pharynx.

6) Patients should void just prior to imaging.

3.4. RADIATION SAFETY

Hybrid imaging imparts higher radiation dose to patient typically in the range of 10-20 mSv of effective dose. Therefore every effort should be made to use the principles of radiation protection. Also there is potential for relatively higher radiation exposure of staff.

The principles of radiation protection are well established. The International Commission on Radiological Protection (ICRP) is responsible for establishing these principles and are addressed in their 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 so as to avoid unnecessary examinations and optimization through use of ALARA (as low as reasonably achievable - 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 develops standards for radiation safety called BSS-Basic safety standards [3.17]. The national organizations use the BSS to frame their regulations. The BSS and associated guidance documents [3.17-3.19] help users to achieve a good standard of protection and 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. IAEA documents [3.18, 3.19, 3.20] thus 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 level of radiation doses that can be encountered by staff and patients have been estimated in a number of publications and have been reviewed in an earlier publication of IAEA [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, to allow higher doses where indicated by sound clinical judgment. DRLs are provided in measureable quantity 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 CT, there is lack of DRLs for PET examinations but guidelines from professional societies are available [3.21].

In hybrid imaging, 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 a typical PET or 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 like urinary bladder, heart wall and brain may receive more than 10 mGy of absorbed dose. Further information is available on RPOP website of IAEA [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 and thus 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/year), and are based on tissue reaction relative to a threshold for erythema. Similar dose limits have also been specified for the lens of eye (cataract) and for the thyroid (based on stochastic risk of thyroid cancer). The main sources of radiation exposure for staff in the PET/CT facility include:

- Unshielded radiopharmaceuticals (present during preparation and dispensing);
- Patients injected with PET radiopharmaceuticals;
- The patient toilet;
- Sealed calibration sources, quality assurance phantoms;
The CT scanner, as staff in nuclear medicine may have difficulty in realizing that they need to be away (at a distance/outside the room) when the CT is being taken. For the PET part, there is no difference in staff exposure when 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).
REFERENCES TO CHAPTER 3


LEGENDS FOR ILLUSTRATIONS

- Fig. 3.1: FDG breast uptake in a breast feeding woman.
- Fig. 3.2: Intense, heterogenous FDG uptake in uterus after delivery.
- Fig. 3.3: FDG uptake in mediastinal lymph nodes in a patient with granulomatous disease.
- Fig. 3.4: The same patient as above shown with two different blood glucose levels at the time of radiotracer administration. The image on the left side shows the patient with increased blood glucose levels. Note the marked FDG uptake in the muscles and reduced uptake in the liver and brain. After fasting (image on the right) there is no more FDG uptake in the muscles and increased uptake in the liver.
- Fig. 3.5: FDG uptake in diaphragmatic muscle due to hyperventilation.
- Fig. 3.6: FDG uptake in vocal cords in a patient that had been speaking before and after radiotracer administration.
- Fig. 3.7: FDG uptake in masticatory muscles (pterigoid and masseter) in a patient that had been chewing gum.
- Fig. 3.8: FDG uptake in mediastinal lymphadenopathy in a patient with lymphoma. The image on the left was obtained with the patient in a hyperglycaemic state, and the images on the right (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.
- Fig. 3.9: Fasting prior to study will alter FDG biodistribution. The same patient shown on two different settings. The image on the left, acquired after FDG was administered in the hyperglycaemic state show increased radiotracer uptake in muscles (especially in the thorax and pelvis) and reduced uptake in the liver. After fasting (image on the right) there is reduced FDG uptake in the muscles and increased uptake in the liver.
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 in the patient, bear in mind the ALARA principle (as low as reasonably achievable). Injected activity must guarantee good quality images and also be reduced to guarantee reduction of patient and occupation exposure. Several factors are to be taken into consideration including: 1) Patient-related factors, e.g. Age, weight, body mass, 2) Scanner-related factors e.g. Crystal type (LSO, LYSO, BGO, GSO), acquisition mode (2D, 3D), bed overlap (25%, 50%) and acquisition time per bed position.

— Generally accepted activity: 185-555 MBq (5 - 14 mCi) [4.1].

— May vary according to the acquisition mode (2D versus 3D).

• Whole-body protocol in 3D mode with less than 25% bed overlap for a 70 Kg patient and 3 minute scanning time per bed position.
  
  i) Generally accepted dose 322 MBq (9mCi).

• Whole-body protocol in 3D mode with 50% bed overlap for a 70 Kg patient and 3 minute scanning time per bed position.
  
  ii) Generally accepted dose 161 MBq (4.3mCi).

— Maximum recommended activity is 529 MBq (14 mCi) for patients over 90 kg (198 lbs).

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 is 37 MBq (1.0 mCi).

4.1.3. Precautions:

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

— Records needed: Net injected dose, dose remaining in syringe, time of injection. This will ensure proper calculation of tracer uptake (SUV).
4.2. DOSE OF OTHER NECESSARY MEDICATIONS

All medications being taken by the patients are recorded for legal purposes and to ensure proper patient preparation in follow-up studies.

4.2.1. Furosemide

— For renal/pelvis delayed imaging [4.3] (Fig. 4.1).
— Dose: 2 mg/kg up to 40 mg.
— Best given after initial whole-body images. Patient must hydrate for at least 30 minutes 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].

i) Brown fat uptake: Will occur mainly in children, adolescents, young women, cold weather (Fig. 4.2).

ii) Muscle uptake: Will occur mainly in anxious patients and patients undergoing head and neck surgery.
— P.O. diazepam dose 1 to 2 mg.*
— Intravenous dose: 5 mg (adult dose) or 0.06 mg/kg.
— Best if given 30 minutes prior to radiotracer injection. If diazepam has to be given after whole-body images have been performed:

i) Re-schedule patient for another day and administer diazepam prior to imaging.

ii) To perform imaging on the same day: Discontinue fasting, instruct patient to return in the afternoon after fasting for 4 hours. Administer diazepam prior to imaging.

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].

i) Oral propranolol dose: 10–40 mg (adult) or 1-5 mg/kg (paediatrics).

ii) Administer 30 to 60 minutes prior to radiotracer injection.

iii) Precautions should be taken when administering propranolol in the following situations:

* Per os (P.O.) is a phrase in Latin which means ‘by mouth’ or ‘by way of the mouth’.
— 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 procedures below are acceptable:

— Intravenous dose of 1-2 U of ‘regular’ insulin. Check blood glucose levels every 30 minutes. 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 re-scheduled.

— Intravenous dose of 0.03-0.05 U/kg of ‘regular’ insulin. Check blood glucose levels every 15 minutes. 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 re-scheduled [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 agent 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 artifacts that lead to a significant overestimation of the SUV [4.9]. Other dilute positive and negative oral contrast agents cause less overestimation and do not affect PET image quality [4.10-4.12]. Water is useful to visualize the stomach and proximal small bowel; however, it is absorbed at the distal ileum and does not allow good visualization of the colon. A low-attenuation 0.1% barium sulfate 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, careful assessment of a history of allergies due 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, 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 [4.13].
— If intravenous contrast is being planned to be used 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 the individual institutions. In the cases of these patients there may be a need 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

— Time to image post injection should be strictly followed for every patient to ensure proper patient follow-up. Please refer to chapter 5 – Response evaluation in FDG-PET/CT.

— The recommended time to image after radiotracer injection is 60 minutes to ensure a higher tumour/background ratio.

— The patient should void prior to image acquisition.

— Patients can be positioned with their arms raised above their heads, which is standard practice in CT. When leaving the arms next to the patient, beam artifact from the long bones of the arms and forearms degrade the quality of images in 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: 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 artifacts (Fig. 4.3).

— Do not move: Motion will cause mis-registration artifacts.

4.3.3. Brain acquisition

— For brain tumours or suspected metastases.

— Note that this does not substitute MRI images for detection and assessment of primary tumours or metastases.

— These images should have high resolution (longer acquisition times per bed position (e.g. 15 minutes).

— Brain FDG PET images can be acquired at 30-45 minutes after radiotracer injection.

— For primary brain tumours, getting a delayed set of FDG PET images at 4-6 hours after radiotracer injection, increases considerably the tumour to background contrast.
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 high probability of metastases to head, brain or lower limbs, such as lymphomas, melanomas, neuroblastomas, and osteosarcomas (Fig. 4.4). Arms should be positioned outside the field of view.

4.3.4.2. Head and neck lesions

These can be delayed to approximately 2 hours post-injection to ensure 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 intravenous 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 visualization of this region.

4.3.4.3. Dedicated lung acquisition

Additional delayed and dedicated high resolution images only of the lungs (after the routine images have been performed).

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

4.3.4.4. Pelvic lesions

Additional delayed high resolution images only of the pelvic region (after the routine images have been performed) after furosemide injection, hydration and voiding (Fig. 4.6) [4.16].

4.3.4.5. Abdominal lesions

Additional delayed high resolution images only of the abdomen (after the routine images have been performed) to detect peritoneal carcinomatosis. Furosemide injection, hydration and voiding may be needed to increase detection of nodes in the pelvic region (Fig. 4.7) [4.17].

4.3.5. Estimation of lesion uptake

Lesion uptake is measured by standardized uptake value (SUV) and is based on radioactivity in the lesion, injected activity and body weight. If quantifying the average of all pixels within the ROI, the result will be SUVavg, whereas with the maximum the result will be expressed as the SUVmax.

\[
SUV = \frac{\text{Mean ROI activity (mCi/ml)}}{\frac{\text{Injected activity (mCi)}}{\text{Body Weight (g)}} \text{ or lean body mass (LBM)} \text{ or body surface area (BSA)}}
\]
### 4.4. IMAGE ACQUISITION AND PROCESSING

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

#### TABLE 4.1.

<table>
<thead>
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<th>Reconstruction Method</th>
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<th>Brain</th>
<th>Head and Neck</th>
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<tr>
<td></td>
<td>Iterative (cranial/caudal)</td>
<td>Iterative (cranial/caudal)</td>
<td>Iterative (cranial/caudal)</td>
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#### TABLE 4.2. CT IMAGING OPTIONS IN PET/CT

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Indication</th>
<th>Breathing</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>CT ONLY for attenuation correction and anatomic mapping</td>
<td>Oral Initial staging</td>
<td>Breath holding in quiet end-expiration</td>
<td>Low radiation dose</td>
<td>Limited anatomic information</td>
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<tr>
<td>No IV Restaging</td>
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<td></td>
<td>Complete metabolic information</td>
<td></td>
</tr>
<tr>
<td>PET combined with CT of diagnostic quality with IV contrast</td>
<td>Oral Initial staging</td>
<td>Breath holding in quiet end-expiration</td>
<td>Complete metabolic information</td>
<td>Increased radiation dose</td>
</tr>
<tr>
<td>IV Restaging</td>
<td></td>
<td></td>
<td>Complete anatomic information</td>
<td>Requires IV contrast</td>
</tr>
<tr>
<td>PET combined with CT of diagnostic quality without IV contrast</td>
<td>Oral Initial Staging</td>
<td>Breath holding in quiet end-expiration</td>
<td>Complete metabolic information</td>
<td>Increased radiation dose</td>
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<tr>
<td>No IV Restaging</td>
<td></td>
<td></td>
<td>Complete anatomic information</td>
<td>Risk of missing small pulmonary nodules</td>
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<td>PET/CT with special interest in the chest</td>
<td>Oral Initial staging: Lung cancer</td>
<td>Breath holding in quiet end-expiration followed by Breath holding at end of full inspiration</td>
<td>Complete metabolic information</td>
<td>Limited evaluation of hilar regions.</td>
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<td>No IV Oesophageal cancer</td>
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<td>Complete anatomic information in the chest</td>
<td>Limited evaluation of the abdomen and pelvis.</td>
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### TABLE 4.3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameters for CT scan for attenuation correction and anatomic localization 3D PET/CT</th>
<th>Parameters for CT scan for attenuation correction and anatomic localization for patients with Head and Neck tumors, 3D PET/CT</th>
<th>Parameters for CT scan for attenuation correction and diagnostic parameters 3D PET/CT</th>
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#### 4.4.1. Protocol for CT imaging during the acquisition of PET/CT

CT uses an external source of radiation to provide three-dimensional images of the density of the 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 co-registered to the anatomic information from CT in a single examination [4.18, 4.19]. 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 patient needs, clinician request and 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 anatomic 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 anatomic correlation, the CT parameters should be set to minimize patient radiation dose, while still ensuring that the CT images are of sufficient quality to allow for accurate anatomic correlation of PET findings [4.20]. There are different 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. Table 4.1 displays the most frequently used options.
— PET/CT with CT for attenuation correction and anatomic 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 head and neck patients. No intravenous contrast is given. The radiation dose is low. The patient is instructed to breath holding 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 not formally reported. CT findings of potential significance are included in the PET report. The majority of these patients 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 breath holding 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 is interpreted 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 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 breath holding 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 contraindicated. The referring clinician is given a PET and CT reports.

— PET/CT with special interest in the lungs: This option can be used in patients with lung or oesophageal cancers. PET/CT with CT for attenuation correction and anatomic localization. The CT is used as a transmission scan for attenuation correction. All patients receive oral negative contrast with the exception of head and neck patients. No intravenous contrast is given. The radiation dose is low. The patient is instructed to breath holding 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 not formally reported. The CT scan for attenuation correction is followed by a CT scan of the chest with breath hold in full inspiration. The referring physician is given a PET report and a Chest CT report.

i) 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 anatomic area of interest. The scout scan is acquired during continuous table motion; with the x-ray tube/detector assembly typically locked in the frontal position, generating an anatomic overview image that is similar to a conventional x-ray at a given projection. The scout is used to define the axial examination range of the PET/CT study. The axial extent of the CT and PET portions 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. Remember that body parts not included in the CT field of view, will not be attenuation corrected in the PET scan, leading to streak artifact.

ii) Image registration between PET and CT: PET images are acquired over several minutes per bed position with the patient breathing quietly. To minimize motion artifacts, 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 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 on breath-holding in quiet end-expiration. Scanning proceeds only after the patient has successfully practiced 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 [4.21].

iii) Diagnostic CT with intravenous contrast: When indicated, the CT scan can be performed with intravenous contrast material using appropriate injection techniques. High intravascular concentrations of intravenous contrast agents may cause an attenuation-correction artifact 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 [4.22].
REFERENCES TO CHAPTER 4


LEGENDS FOR ILLUSTRATIONS

- **Fig. 4.1:** FDG images of the kidneys show 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. Biopsy revealed renal tuberculosis.

- **Fig. 4.2:** FDG images on the left side show brown fat uptake. FDG images on the right do not show brown fat uptake after administration of benzodiazepines.

- **Fig. 4.3:** Lung images of a hyperventilating patient. Notice the lung nodule (full arrow) and, immediately above (dotted arrow), a lung nodule artifact, caused by hyperventilation. Notice the artifact in the dome of the liver as well.

- **Fig. 4.4:** Lower extremity coronal image in a melanoma patient showing metastatic lesions in the right thigh and foot.

- **Fig. 4.5:** Images of the head and neck performed using 3 minutes per bed (left side) and delayed, 8 minutes per bed (right side). Notice 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.

- **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.
5. RESPONSE EVALUATION IN FDG-PET/CT

5.1. BACKGROUND

5.1.1. Why do we need response evaluation

Greater understanding of the 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. However, in disseminated solid tumours, this goal is rarely achieved. Instead, the aim is to prolong survival. Demonstrating improvements in survival often takes years to establish. 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 an individual patient, most cancer treatments are associated with significant side effects and costs. Thus, it becomes 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 progressive world of drug development, it thus becomes imperative to have surrogate end points to survival which provide earlier answers about 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 endpoint for efficacy. There is therefore a need for some surrogate metrics for survival after treatment.

5.1.2. Tumour shrinkage as a response criteria

Tumour shrinkage in response to therapy is one such parameter which has served as the standard of response evaluation in oncology. There are a large number of studies which demonstrate 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 the measurement of tumour size. The measurements may be bi-dimensional as recommended by the older World Health Organisation (WHO) criteria or uni-dimensional as recommended by the Response Evaluation Criteria in Solid Tumours (RECIST criteria). The detailed methodologies of these criteria and each of their relative merits and demerits is beyond the purview of this document. However, as PET/CT studies replace PET alone studies throughout the world, it becomes imperative for nuclear medicine physicians to be well 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. Inter-observer 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 and 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 characterizing 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 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 a profound change in tumour size despite their effectiveness [5.1, 5.2].

Many tumours like lymphomas, sarcomas, mesotheliomas and gastrointestinal stromal tumours (GIST) do not shrink even in response to effective therapy. Situations exist where no tumour shrinkage may be evident on radiological follow-up but a clear histological response can be seen. Often the size of a tumour may first increase in certain situations consequent to 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 indices into consideration possibly because these parameters are difficult to quantify objectively especially in follow up studies.

5.2. RESPONSE EVALUATION BY PET/CT

Response evaluation by anatomic methods alone was 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 which have been used to date in both the clinical trial setting as well as for individual patients. The basic premise of using F18 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. Consequently, it is reasonable to expect that declines 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. Abundant data now exists 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 volume of tumour cells would be expected in progressive tumour.

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 change in tumour metabolism, FDG-PET imaging can provide a method by which tumour response can be measured in the absence of marked anatomic change. A decrease 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 anatomic measurements. FDG-PET/CT has also been used to successfully 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 being recognized as an important tool for response monitoring in oncology it is important to remember that quantification in PET may be affected by a countless number of 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 radiotherapy, 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 responding 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 insight 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 nonlinear 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 quantitation with dynamic imaging and Patlak analysis, are technically challenging and 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 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. $SUV_{BW}$ vs. $SUV_{LBM}$

The standardized uptake value (SUV) is the semi-quantitative method 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 normalised to lean body mass also called SUL can be calculated by the following formula [5.10].

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

$LBM (Kg) = 45.5 + 0.91 \times [\text{height (cm)} - 152]$ for females

$LBM (Kg) = 48.0 + 1.06 \times [\text{height (cm)} - 152]$ 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 decision 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 ROI located in the most metabolically active part of the tumour is a more robust measure especially when used in comparison studies. The use of the SUV Peak value is recommended by the PERCIST criteria (See also section 5.4.10 on Assessing Response by PERCIST criteria). Even though the use of Standardized Uptake Values (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. In this situation, the dependence of SUVs on body composition and plasma FDG clearance is a known limitation for this technique compared with nonlinear 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 ROI

Determining accurate and reproducible regions of interest is critical to obtain 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 one is drawing the ROI. There are many prescribed methodologies for drawing the ROIs. Free hand held drawings are frequently used. On the other hand many commercially available softwares can create user generated threshold based ROI. Recently there has been a mounting interest in creating volumes of interest (VOI) as these have been shown to likely 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. With the newer PET/CT systems which are capable of accurately registering these PET volumes to CT derived anatomic volumes, many incorporate technically difficult algorithms that have been 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 to include necrotic areas or not) and used consistently in the 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 minutes after FDG injection, and FDG uptake is usually significantly higher at later time points. Stahl et al. [5.11] demonstrated a 50% higher tumour FDG uptake 90 minutes after FDG injection compared with 40 minutes 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 hours 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 at <5–10 minutes.

5.4.5. Correcting for the plasma glucose level

Since FDG and glucose compete with each other for intra-cellular 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 value may be corrected for plasma glucose by the following formula.

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

(Assuming a normal blood glucose level of 100mg/dL = 5.55mmol/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. \(^{18}\text{F}\) decays to roughly 49.93% of the initial activity over the period of 110 minutes.

— Poor calibration of counting equipment; in order for the counting rates of the scanner to be correctly converted to activity concentrations, precise calibration of the PET scanner needs to be performed. This is usually done using the PET scanner to measure the counts from a cylinder with a known dose of \(^{18}\text{F}\). Errors in the calibration process can lead to incorrectly high or low SUVs. The Quality Control of instruments is beyond the scope of this document, therefore we kindly refer you to the IAEA Publication of the Human Health Series No.1, ‘Quality Assurance for PET and PET/CT Systems’ for complete information on this subject.

— Partial volume effects: with 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 anatomic 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 better define 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 on the calculation of semi-quantitative metrics like SUV. Use of contrast CT images as the attenuation maps tends to overestimate SUV as compared to 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 same scanner model for serial scanning of the same patient. In those cases where different equipment/different techniques were employed the comparison between the estimated lesion SUV’s 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 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 radiotherapy is involved. It has been seen that persistent FDG uptake after therapy is a sign of therapy failure. In contrast a 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 chemotheraphy or radiotherapy, one has to consider that only small amounts of residual viable tumour may be present. In this case the differentiation between ‘responders’ and ‘non-responders’ by FDG-PET can be challenging. In order to achieve the highest sensitivity for detection of residual tumour tissue, FDG-PET should be performed as late as possible after 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 radiotherapy 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 radiotherapy and this should be kept in mind while reporting post radiotherapy response. Usually the absence of an obvious mass lesion on CT with just residual thickening and stranding on the corresponding CT images must alert the reading physician to the FDG uptake being consequent to 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 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 [5.12]. The presence of marked differences in liver FDG uptake may visually 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. With the wide variability of acquisition parameters and equipment types across the world there have been many attempts to standardize the use of PET in clinical trials such as those published in the guidelines of the European Organization for Research and Treatment of Cancer (EORTC) [5.13], the Netherlands Society of Nuclear Medicine [5.14], and the National Cancer Institute [5.15]. PERCIST [5.16] 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 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 of change in metabolic activity from baseline and the number of weeks from the initiation of therapy be recorded to provide a continuous plot of metabolic activity within the tumour (Table 5.1).

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 (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 [5.17]. PERCIST specifies that the SUL peak is to be obtained on the single most active lesion on each scan. 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 at 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 a sum of the activity of up to 5 target lesions (no more than 2 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, PERCIST criteria defines 4 response categories.

— *Complete metabolic response* is defined as the disappearance of metabolic tumour activity in both target and non-target lesions. Since there may be residual FDG uptake noted within the residual lesion due to inflammatory changes post treatment, a decline of uptake to a value equal to or less than that of surrounding tissue is considered adequate for definition of complete response.

— *Partial metabolic response* is defined by a decline of $> 30\%$ in SUL peak with at least a 0.8-unit decline in SUV.

— *Progressive metabolic disease* includes an increase of $> 30\%$ in SUL peak with at least a 0.8-unit increase, a 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.

— **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 (morphologic) size remains an important factor under PERCIST and is to be measured according to RECIST 1.1. If lesions increase or decrease 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 which can be used to measure global changes in tumour glycolysis is the Total Glycolytic Volume. The TGV is calculated by multiplying the mean SUV times the total tumour volume (mL) [5.18], the volume of the lesions determined from the PET-FDG images by an adaptive thresholding technique. Alternatively another index, the Total Lesion Glycolysis (TLG) may be derived from multiplying the tumour volume on CT with the FDG uptake on PET [5.19].

\[
TGV = \text{mean } SUV \times \text{total tumour volume (ml)}
\]

The percent response is computed by expressing the change in TLG in the post treatment PET as a percentage of the TLG in the pre-treatment PET-FDG images. TLG has been tested in several malignancies with mixed results in comparison to SUV metrics. TLG has been shown to have a weaker correlation with response in bone metastases in breast cancer patients [5.20] and in sarcomas [5.21], 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 further evaluate the efficacy of TLG. For further specifics regarding PET scanning, such as information regarding patient preparation and scan acquisition parameters, please see the PERCIST source article by Wahl et al.
TABLE 5.1. POSITRON EMISSION TOMOGRAPHY RESPONSE CRITERIA IN SOLID TUMOURS (PERCIST 1.0)

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete metabolic response</td>
<td>Normalization of all lesions (target and non-target) to SUL less than mean liver SUL and equal to normal surrounding tissue SUL</td>
</tr>
<tr>
<td></td>
<td>Verification with follow-up study in 1 month if anatomic criteria indicate disease progression</td>
</tr>
<tr>
<td>Partial metabolic response</td>
<td>&gt; 30% decrease in SUL peak; minimum 0.8 unit decrease</td>
</tr>
<tr>
<td></td>
<td>Verification with follow-up study if anatomic criteria indicate disease progression</td>
</tr>
<tr>
<td>Progressive metabolic disease</td>
<td>&gt; 30% increase in SUL peak; minimum 0.8 unit increase in SUL peak</td>
</tr>
<tr>
<td></td>
<td>&gt; 75% increase in TLG of the 5 most active lesions</td>
</tr>
<tr>
<td></td>
<td>Visible increase in extent of FDG uptake</td>
</tr>
<tr>
<td></td>
<td>New lesions</td>
</tr>
<tr>
<td></td>
<td>Verification with follow-up study if anatomic criteria indicate complete or partial response</td>
</tr>
<tr>
<td>Stable metabolic disease</td>
<td>Does not meet other criteria</td>
</tr>
</tbody>
</table>

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

Although there may be some variability in the optimal criteria for assessing tumour response and that predicting patient outcome 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. However, 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 in the use of FDG-PET in lymphoma based on the literature and the collective expertise of its members [5.22].

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 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. Use of attenuation-corrected PET was strongly encouraged.

5.5.2. Response evaluation in interim PET/CT

These 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/CTs in lymphoma are done both for assessing chemosensitivity and for individual response adapted treatment modifications. In 2009, an international workshop on interim FDG-PET took place in Deauville, France, to reach a consensus on simple and reproducible criteria for interim FDG-PET. The experts proposed for Classical Hodgkin Lymphoma (cHL) that 1) a baseline FDG-PET/CT should be performed prior to therapy initiation and 2) that a visual analysis using a five point-scale should be applied (Table 5.2).

<table>
<thead>
<tr>
<th>Five Point scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No uptake</td>
</tr>
<tr>
<td>2</td>
<td>Uptake ≤ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Uptake &gt; mediastinum but ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>Uptake moderately more than liver uptake, at any site</td>
</tr>
<tr>
<td>5</td>
<td>Markedly increased uptake at any site and new site of disease</td>
</tr>
</tbody>
</table>

Table adapted from André et al [5.23]

For the therapeutic decision, the cut-off should be determined according to the strategy. A cohort of ABVD-treated HL patients was collected with the aim to validate the proposed criteria. This International validation study is currently under progress.

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 chemo- and radiotherapy 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. Furthermore, very few patients with solid tumours have a pathological complete response to chemo- or radiotherapy. Even patients where FDG-PET scans done after completion of treatment show a near complete disappearance of FDG uptake, will frequently have microscopic residual disease, eventually leading to tumour recurrence. Neither PET/CT nor conventional imaging procedures can assess the extent of residual microscopic disease as accurately as histopathology. Therefore, studies on lung, colorectal, and breast cancer have focused on detecting non-responding tumours early rather than on identifying patients who are cured by chemo- or radiotherapy. In this context, the goal of FDG-PET is to guide decisions in order 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.
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 [5.24], 68% in prostate cancer, and 73% in breast cancer [5.25]. Bone metastases have however been considered 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 considered 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 which is seen in response to hormonal therapy in patients with breast cancer which may actually hallmark 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 gastro-intestinal stromal tumours. Other commonly used cytostatic agents include: the EGFR kinase inhibitors like gefitinib, erlotinib, cetuximab and more recently, the EGFR/HER2 dual kinase inhibitor lapatinib, the antiangiogenic agents like 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 remain similar in clinical trials using cytostatic agents as for cytoreductive therapies, the key difference is in selecting the optimal time of 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, whereas 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 of 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 week 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 change in uptake that can be considered significant. While the guidelines for assessing partial response in cytoreductive drugs have been reasonably standardised 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 optimise the timing for post-treatment scanning for cytostatic agents.

Few studies have demonstrated that 3′-deoxy-3′-[18F]-fluorothymidine (FLT) PET was 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 like perfusion, proliferation and protein metabolism at least in a subset of patients.

To conclude, FDG-PET/CT is a useful endpoint for assessing response to targeted therapies. The biologic 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.

REFERENCES TO CHAPTER 5


6. PET/CT REPORTING IN ONCOLOGY

The PET/CT report is an essential part of every imaging procedure. It is a permanent document in digital or written format that summarizes the communication of important components from 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. The report also serves as a means for communication to 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. Reports should employ clear and unambiguous language. It is important that the report be concise and to the point; a long assay is unlikely to be read with risk of key information being 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

This is a concise statement based on the information provided by the referring physician that includes the specific reason that 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)’. Specific reasons to perform the PET/CT should also be included, such as ‘Patient with history of colon cancer and recent elevation in CEA’.

The indications for PET/CT should be categorized as:

- 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 portion of the report, the report is unlikely to have any impact on patient management. The referring physician finds it 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.

i) 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 non-small cell lung cancer (NSCLC), are in general highly FDG avid while others, such as adenocarcinomas, show minimal to no FDG avidity.

ii) When there is a specific abnormality to be evaluated it 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).

iii) 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).

iv) 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 should contain information regarding the patient which could impact the interpretation of the examination. The most common information pertains to histopathologic results and previous treatments such as prior chemotherapy or radiation, completed within 3 months to the PET/CT. Other pertinent information includes concurrent and on-going therapy like granulocyte colony stimulating factors (G-CSF) and interleukins. Relevant surgeries, including dates, history of infection, and systemic processes may modify FDG uptake in different tissues and lesions. This can potentially interfere with interpretation as the case of sarcoidosis, AIDS, tuberculosis, and vasculitis.
Relevant history includes:

— *Biopsy* or surgical pathology results.

— *Chemotherapy* including date of completion.

— *Radiation therapy* including date of completion.

— *Treatments*.

— *Medical/Surgical history* that may have relevance for PET/CT interpretation.

When requested, provide information needed for billing in a clear statement explaining the reason the PET/CT is performed.

6.2. TECHNIQUE

6.2.1. PET procedure

Radiopharmaceutical type FDG must include administered activity and route of administration. Any significant dose infiltration should be reported. The areas of the body evaluated by the scan field should be described. Appropriate anatomic nomenclature should be used for this description. 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 thigh. 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 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 acquisitions for head and neck cancer, or delayed images of the abdomen and pelvis after furosemide administration.

Uptake time is the time between injection and scanning. It should be reported. In some cases, a range is appropriate, such as 60-90 minutes. 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 should be measured immediately prior to FDG administration on 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 not ideal blood glucose levels or when follow up studies are being performed at different blood glucose level.

Medications administered as part of procedure (i.e. anxiolytics, muscle relaxants, beta blockers). These medications are usually given to reduce FDG uptake in the muscles or in brown fat and may be required in future exams. 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 intravenous or oral contrast. If oral contrast is used, the type of contrast should be noted as positive or negative contrast. Positive contrast may cause artifactual elevations in FDG uptake and this should be explained in the report.

Because PET/CT involves merging two complementary but separate imaging techniques, there are added challenges associated with reporting and billing for the PET/CT examinations. For the CT portion of the examination to have reliable value as a source of anatomic 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 anatomic 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 anatomic localization, but anatomic diagnosis as well. A PET/CT report, therefore, must always combine both PET and CT findings and render an integrated interpretation that merges the anatomic 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 can 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

Comparison 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, previous PET, previous PET/CT, and previous MRI. All appropriate imaging studies and clinical data results are relevant. Dates of prior PET or PET/CT studies used for comparison should be given. If prior studies were done by a different scanner or different facility, or acquired by using a different technique (e.g., 2D or 3D), this should be included in the report. If no previous PET studies are available, this should be stated as well.

6.4. DESCRIPTION OF FINDINGS

6.4.1. Quality of the study

An example: limited quality because of motion or mis-registration, muscular uptake, or hyperglycemia.

6.4.2. Limitations

When appropriate, identify factors that can limit the sensitivity and specificity of the examination such as with small lesions or an inflammatory process.
6.4.3. Description

Describe the location, extent, and intensity of abnormal FDG uptake in relation to the uptake in normal comparable tissues, and describe the relevant morphologic 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 can refer to the diagnostic CT scan report for findings not related to the PET/CT examination.

6.4.4. Clinical issues

This addresses or answers 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 European Organization for Research and Treatment of Cancer has published criteria for these categories, although these criteria have not yet been validated in outcome studies. A change in the intensity of uptake with semi quantitative measurements, expressed in absolute values and percent change, may be appropriate in some clinical scenarios. However, the technical protocol and analysis of images need to be consistent in the 2 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 PET/CT studies. The two most common styles are ‘focused’ and ‘anatomic site’.

6.4.5. Focused

These findings are described in the order of importance to the clinical issues of the patient. This type of report follows the 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.

These 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 should be communicated immediately to the referring physician. Examples include pneumothorax and abdominal aortic aneurysms. Normal physiologic FDG uptake in muscle, bowel and other organs is also described.

6.4.6. Anatomic site

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

6.5. IMPRESSION (CONCLUSION OR DIAGNOSIS)

The impression is the conclusion of the report and it is the most important section because it answers the clinical question. Several 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. An 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.

Please refer to Appendix I for sample reports.
BIBLIOGRAPHY FOR CHAPTER 6


7. FUTURE DIRECTIONS OF PET

7.1. INTRODUCTION

FDG PET and PET/CT have revolutionized the care of the cancer patient over the last 20 years. Currently, it is widely recognized that FDG PET and PET/CT is a superior technique, may times performing better than conventional imaging. Its current indications compile a list that has been growing over the years due to the better understanding of this imaging modality; including the advantages and limitations it has in defining and characterizing malignant disease. From the initial use in staging, re-staging cancer and characterization of the indeterminate pulmonary nodule, FDG PET and later PET/CT, has also been applied with great success in assessing response to therapy, determining recurrence of disease and the evaluation of patients with elevated tumour markers. In addition, it is also being used, although is not considered yet a standard indication, in radiation therapy 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 has represented a significant advance over stand-alone PET in many ways. Not only the duration of the study has been cut in at least half of what it used to be, but probably more important, it provides superior anatomical detail from the multi-slice CT scanner incorporated into the system. This additional morphological information characterizes with great accuracy the abnormal signal detected on the PET scanner, and through the superb quality fused images, pinpoints the location of disease with high precision. As occasionally happens, the abnormal PET signal can come from an anatomical structure that on the basis of the image provided by the multi-slice CT appears to be completely normal or is non-diagnostic. Therefore, currently there is a clear understanding/agreement among the medical community, of the benefits of combining metabolic and morphological information in a single imaging modality such as PET/CT.

Despite being and outstanding radiotracer with many advantages, FDG has certain limitations. First, is of rather limited use in several tumours which low metabolic rate such as prostate cancer, are well differentiated as is the case with many hepatocellular carcinomas, or as is the case with very mucinous tumours like signed ring cell type of tumours. Moreover, -and it is a well-recognized cause of false positives, there can be prominent FDG uptake in inflammatory and infectious diseases, which could potentially provide an important source of new indications for FDG-PET/CT imaging in benign conditions. However, for oncology 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. One of them, are the technological advances in imaging technology and computer science, which together are going to enable future scanners 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 is becoming mature enough for the introduction of new, dedicated imaging devices, such as the PET/MRI or the PET mammography (PEM).
The second major development is 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 in cancer cell biology.

Over the last few years there has been a vertiginous advance in the understanding of cancer cell biology at the molecular level. This has brought the opportunity for the recognition of many different therapeutic targets. Molecular imaging has exploited this knowledge to develop a whole 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 biologic 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 last 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 in many occasions with $^{11}$C, its short half-life of only 20 minutes has limited its use to hospitals and imaging centres that have an on-site cyclotron. Therefore, other radionuclides with longer half-lives such as $^{18}$F, of almost two hours, or even $^{68}$Ga with 68 minutes have become more attractive options. The list of Non-FDG PET tracers is long (Table 7.1). However, this chapter describes the current status of the ones that could have a potential effect in medical oncology.

### Table 7.1. Non-FDG PET Tracers in Oncology

<table>
<thead>
<tr>
<th>PET radiopharmaceutical</th>
<th>Biochemical process</th>
<th>Application in Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F-Sodium Fluoride</td>
<td>Hydroxyapatita- Bone turnover and flow</td>
<td>Detection of bone metastasis</td>
</tr>
<tr>
<td>$^{18}$F-Choline or $^{11}$C-Choline</td>
<td>Membrane-lipid metabolism (Choline)</td>
<td>Prostate cancer, HCC</td>
</tr>
<tr>
<td>$^{18}$FLT</td>
<td>Tumor cell proliferation</td>
<td>Early assessment of response</td>
</tr>
<tr>
<td>$^{18}$F-DOPA</td>
<td>Aminoacid</td>
<td>Brain, NET, MTC, INSU, FCH</td>
</tr>
<tr>
<td>$^{68}$Ga-DOTA-SSA</td>
<td>Receptor Binding SSR</td>
<td>NET</td>
</tr>
<tr>
<td>F-MISO,F-AZA,F-EF5, Cu-ATZM</td>
<td>Hipoxia</td>
<td>HN, Lung</td>
</tr>
<tr>
<td>$^{11}$C-Methionine</td>
<td>Aminoacids</td>
<td>Brain</td>
</tr>
<tr>
<td>$^{18}$FES</td>
<td>Receptor-Binding</td>
<td>Breast</td>
</tr>
<tr>
<td>$^{18}$F-FDHT</td>
<td>Receptor Binding</td>
<td>Prostate</td>
</tr>
<tr>
<td>F-Galacto-RGD</td>
<td>Angiogenesis</td>
<td>Oncology (Preclinical stages)</td>
</tr>
<tr>
<td>I-124-Annexin V, $^{64}$Cu Annexin V</td>
<td>Apoptosis</td>
<td>Oncology (Preclinical stages)</td>
</tr>
<tr>
<td>I-124-cG250</td>
<td>Tumour antigen binding</td>
<td>Renal Cancer</td>
</tr>
</tbody>
</table>

*HCC Hepatocellular Carcinoma, NET Neuroendocrine Tumours, MTC Medullary Thyroid Cancer, INSU Insulinoma, 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 lower radiation 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 last 15 years, avalanche photodiodes (APDs) have been intensely researched; as a result, the reliability and robustness of APDs 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 volume increases. Moreover, APDs are not only compact but also insensitive to magnetic fields and therefore ideal as PET light detectors in combined PET/MRI scanners. A new alternative to current APDs is the new generation of Geiger-mode APDs, or silicon PMs (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 has been made commercially available through 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. 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 3D 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: 1) a PET/CT-like combination in which images are obtained serially, using the same couch for PET and MRI scanners, and 2) 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 physiologic 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 specially 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 sub-optimally 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 pre-transplant 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 pre-treatment planning, patient selection for certain therapeutic agents, and treatment response prediction and assessment.

7.5. DEVELOPMENT OF NON-FDG PET TRACERS

As important as the technological advances in PET devices, is the development of new PET radiotracers for oncology (Table 1). Their clinical use varies greatly from country to country, in part due to the different regulatory agencies involved in the control of these tracers.

7.5.1. ¹⁸F-Sodium Fluoride

¹⁸F Sodium Fluoride is the oldest of all the Non-FDG PET tracers. In fact, its use started in Nuclear Medicine in the 1960’s with the rectilinear scanners for bone imaging. However, in the 1970’s it was completely replaced by conventional bone scanning with ⁹⁹mTc diphosphonate imaging. Nevertheless, both of them are metabolized in a similar way – although with some important differences—. Sodium Fluoride behaves in the body in a similar way to calcium ion, and gets deposited in the hydroxyapatite crystal of the bone matrix in a proportion directly related to bone turnover and blood flow. The advantage over the diphosphonates is that is less bound to the proteins in the blood, and a higher fraction is taken/retain in the skeleton (80% vs. 60%). Therefore, with Sodium Fluoride, imaging can be initiated before one hour after injection, whereas with ⁹⁹mTc-diphosphonates there is a minimum waiting time of 2 hours.

Sodium Fluoride PET or PET/CT imaging is clearly a superior imaging technique in comparison with standard bone scintigraphy (Figure 7.1), even when SPECT is used. Not only is faster than a conventional bone scan, provides sharper images of the skeleton with similar radiation dosages to patients, but, 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 improves though precise localization and characterization of skeletal lesions.

### 7.5.2. 11C-Choline or 18F-Choline

11C-Choline and 18F-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 system or high affinity sodium-dependent systems. There is also a choline-specific transporter protein. Once inside the tumour cell, it rapidly accumulates, and eventually gets fosforilated by choline kinase to phosphocholine. Phosphocholine constitutes a substrate for the formation of phosphatidylcholine, which is a major constituent of cells membranes.

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 on the use of 11C-Choline by Hata in 1997, and later in 2001 by DeGrado using 18F-Choline, there are many publications demonstrating the clinical benefits of this PET probe in prostate cancer.

By far, the main indication for 11C-Choline is in the evaluation of patients with biochemical recurrence of disease. In this regard, outperforms conventional imaging, with sensitivities that increase as the PSA gets higher (Figure 7.2).

**FIG. 7.1:** Axial images of the pelvis and chest (right lower images) of a 18F-Sodium Fluoride PET/CT scan, in a breast cancer patient. Arrows point to osseous metastases not detected on a conventional bone scan done a few days before.
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 radiation therapy. Currently, the patient has evidence of biochemical recurrence of disease with a PSA of 3.15 ng/ml. The arrows point to the left lower paraaortic, 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 x 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, first used as an anti-HIV agent without a radioactive label.

FLT imaging takes advantage of the pyrimidine salvage pathway of DNA synthesis. As such 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), thereby trapping it in the cell. Subsequently, following the salvage pathway it gets phosphorylated twice, to from FLT-thrphosphate. However, it differs from the natural pyrimidines in that it does not get incorporated into the growing DNA strand as thymidine does. Nevertheless, FLT is accumulated in the tumour cells in proportion to TK1 activity. The activity of TK1 is greatly over-expressed in tumour cells and up-regulated just before and during S-phase, with greatly reduced concentrations in the G0/G1 phases of the cell cycle. Therefore, in practice TK1 active 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 radiolabeled 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 application in the assessment of different 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 last decade, F-DOPA has been more widely used in tumours derived from the neural crest tissue, which in 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 of infancy F-DOPA PET has quickly become an invaluable diagnostic aid, with sensitivities in the 90% to 100% range, accurately guiding curative surgical resection. For the detection of insulinomas, F-DOPA is a promising molecular probe, potentially very useful, 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 68.3 minutes half-life, 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 analogs, has proven in several comparative studies to be a superior imaging modality. Not only it has increased spatial resolution but, the ability to do whole-body imaging with a short uptake time of 60 minutes (by contrast with SRS is 24 hours), 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 in malignant tissue. The resulting adaptive changes in the proteome and genome of the tumour cells are believed to lead to more aggressive clones which 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 radiotherapy and chemotherapy, increased risk of invasion and metastasis, and worse prognosis 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-Fluoromimidazole (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 have 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, when oxygen is abundant in normally oxygenated cells, the parent compound is quickly regenerated by re-oxidation and metabolites do not accumulate. However, in hypoxic cells, the low oxygen partial pressure prevents re-oxidation of F-MISO metabolites, resulting in tracer accumulation in hypoxic cells. Because F-MISO only accumulates in hypoxic cells with functional nitroreductase enzymes, F-MISO only accumulates in viable cells but not dead necrotic cells.

7.5.7. Aminoacid and protein imaging

The most widely used amino acid for PET tumour imaging has been $^{11}$C-Methionine. The mechanism of uptake in tumour cells is poorly understood, although it is probably dependant
on amino acid transport. Unlike FDG, \(^{11}\text{C}\)-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 \(^{11}\text{C}\)-Methionine, and conditions such as oedema, fibrosis and necrosis do not exhibit any uptake. However, although 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, and area were 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, FHET)

\(^{18}\text{F}\)-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 patients with positive uptake can -up to a third of them-, respond to hormonal therapy, compared to a less than a quarter if there is no uptake.

Dihydrotestosterone (DHT) is the primary ligand of the androgen receptor (AR). Fairly recently, \(16\beta\)^\(^{18}\text{F}\)-fluoro-\(5\alpha\)-dihydrotestosterone (\(^{18}\text{F}\)-FDHT), an androgen analog, has been synthesized. Therefore, only a few studies have been published to date in prostate cancer patients. However, it has already been demonstrated that metastatic and recurrent prostate cancer lesions can be detected with this PET tracer. \(^{18}\text{F}\)-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 proof 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 done in animals. A few radiolabeled anti-VEGF antibodies have been reported. HuMV833 a humanized anti-VEGF monoclonal antibody, has been labelled with \(^{124}\text{I}\) and investigated in a phase 1 clinical trial. Recently, bevacizumab has been labelled with \(^{89}\text{Zr}\) for PET imaging in mice. \(^{64}\text{Cu}\) 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 a prominent level of VEGFR-2 expression.

Among all the integrins discovered to date the most widely studied is \(\alpha5\beta3\), 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 agonist to this receptor now exists, including \(^{64}\text{Cu}\)-DOTA-PEG6cRGDyK2 and \(^{18}\text{F}\)-Galacto-RGD. Promising humans studies with \(^{18}\text{F}\)-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 AnnexinV labeled with PET tracers such as \(^{124}\text{I}\) or \(^{18}\text{F}\) AnnexinV or \(^{64}\text{Cu}\) labelled streptavidin, after pretargeting with AnnexinV.
Immuno-PET is based on the labelling of monoclonal antibodies (MoAb) or its fragments with PET tracers, to allow imaging on a PET or PET/CT scanner. Chimeric G250 which is a MoAb 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, to eventually allow its commercialization for the pre-surgical diagnosis of clear cell renal cell cancer.

7.6. CONCLUSION

The technological advances in computer science coupled with the vertiginous developments in detector technology and scanner electronics, with more sophisticated reconstruction algorithms, is allowing considerable improvement in the quality of PET imaging, with studies acquired faster. Added benefit of these developments is delivering less radiation dose to the patient, and cost savings in PET radiopharmaceuticals. At the same time, the continuous advance in CT technology, and the merging of MRI and PET is opening new possibilities in molecular imaging.

Although FDG PET and PET/CT imaging has proven to be very useful for a large number of tumours and indications that keep expanding, the large clinical experience accumulated with FDG has at the same time allowed us to understand its limitations. In addition, with the now routine use of targeted therapy, there is a pressing clinical need to prognosticate, predict and assess early response to therapy in cancer patients. The deeper knowledge of tumour biology and the advances in radio-chemistry, are bringing the opportunity to non-invasively characterize malignant tumours and obtain a deeper insight into many of its functions with PET imaging. Therefore, Non-FDG PET and PET/CT is contributing to make a reality the goal of personalized cancer therapy. There is a long list of Non-FDG PET tracers at different stages of development, with some of them probably becoming commercially available in the near future.
BIBLIOGRAPHY FOR CHAPTER 7


8. TAKE HOME MESSAGES

8.1. THE MOLECULAR BASIS BEHIND THE FDG IMAGE

— Cancer cells used glucose anaerobically to produce lactic acid in non-hypoxic tissues, rather than relying on the supposedly more efficient TCA (tricarboxylic acid 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 uptake glucose under aerobic conditions constitutes the basis for the detection and staging of human cancers with 18F-fluorodeoxyglucose (FDG) and Positron Emission Tomography (PET).

— FDG-PET imaging has evolved into a technique of proven clinical value and substantial clinical potential addressing important aspects in the daily management of cancer patients. Its inherent ability to interrogate the biologic 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, and therefore, allowing for better characterization of the physiologic or pathologic nature of a particular imaging finding.

This is the reason for which 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 analog of 2-deoxyglucose, and is used as a tracer of glucose metabolism

— FDG’s distribution is not only limited to malignant tissue. Inflammatory and infective 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 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 intra-cellularly 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 properly interpret FDG tumour images 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 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 (SNM) has published a generic form that is easy to adapt to each PET/CT facility individual 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 effect 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 radiation therapy planning.

8.4. CLINICAL FACTORS THAT COMMONLY AFFECT FDG BIODISTRIBUTION AND THEREFORE 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.
— Radiation therapy, 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 study. 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 fetus, the studied should be carried out following the ALARA principle of ‘as low as reasonably achievable’.

— The most effective ways to decrease the absorbed dose to the fetus are 1) to encourage the mother to drink water, 2) to void frequently after the injection of the FDG activity, 3) to use a ‘low-dose CT’ and 4) to limit the scan area to cover only the region of interest.

— A thorough medical history should be obtained, including history of claustrophobia, movement disorders, as well as other diseases and 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, radiotherapy and chemotherapy.

— Allergies: If intravenous 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. 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.

— Patients should arrive to the Nuclear Medicine laboratory at least 30 min prior to their scheduled appointment.

— Patients should fast for at least 4 hours prior to injection. In children below 6 years of age fasting should not exceed 3 hours, due to the fact that by the time the PET/CT study is finished, the child will have fasted for more than 4 ½ hours.

— Patients should be well hydrated to guarantee proper voiding.

— All patients are to refrain from any strenuous activity or exercise for 24 hours 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 minutes 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 in whom 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 (2D versus 3D).

- **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 minutes to ensure a higher tumour/background ratio.

Estimation of lesion uptake: lesion uptake is measured by standardized uptake value (SUV) and is based on radioactivity in the lesion, injected activity and body weight. If quantifying the average of all pixels within the ROI, the result will be SUVavg, whereas with the maximum the result will be expressed as the SUVmax.

\[
SUV = \frac{\text{Mean ROI activity (mCi/ml)}}{\frac{\text{Injected activity (mCi)}}{\text{Body Weight (g)}}}\\
\text{or lean body mass (LBM)}}\\
\text{or body surface area (BSA)}}
\]

8.7. TREATMENT RESPONSE EVALUATION WITH PET/CT

- Most cancer treatments are associated with significant side effects and costs. Thus it becomes 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 end, in the rapidly progressive world of drug development it thus becomes imperative to have surrogate end points to survival which provide earlier answers about efficacy of therapy.

- Tumour shrinkage in response to therapy is one such parameter which has served as the standard of response evaluation in oncology. There are a large number of studies which demonstrate 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 the measurement of tumour size. The measurements may be bi-dimensional as recommended by the older WHO criteria or uni-dimensional 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. Therefore, there is a growing need to incorporate biologically relevant functional and prognostic information in the response evaluation criteria.
— The basic premise of 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 declines 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.

— Abundant data now exists 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 volume of tumour cells would be expected in progressive tumour.

— FDG PET scanning can provide a method by which tumour response can be measured in the absence of marked anatomic change. A decrease 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 anatomic measurements. FDG-PET/CT has also been used to successfully 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 being 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 thus 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 radiotherapy, 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 chemo- and radiotherapy 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 in order 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. PET/CT REPORT

— 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. The report also serves as a means for communication to the patient.

— Reports should employ clear and unambiguous language. It is important that the report be concise and to the point; a long assay is unlikely to be read with risk of key information being missed.

— The PET/CT report is divided in 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 patient over the last 20 years.

— PET/CT has represented a significant advancement over stand-alone PET in many ways (e.g. reduced study duration; superior anatomical detail from the multi-slice CT images).

— Despite being an outstanding radiotracer with many advantages, FDG has known limitations (rather limited use in several tumours which low metabolic rate; false positives, due to inflammatory and infectious diseases etc.).

— The future of PET/CT imaging resides in two main developments. One of them, are the technological advances in imaging technology and scanner electronics (new detectors, Time of Flight, PET/MRI etc.) and computer science (new reconstructions algorithms etc.). Added benefit of these developments is delivering less radiation dose to the patient, and cost savings in PET radiopharmaceuticals.

— The other is 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 in cancer cell biology.

— The deeper understanding of the specific biologic features for each different type of cancer, and the nowadays widespread use 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.
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, $^{18}$Fluorocholine or $^{11}$C-Choline and 3-Deoxy-3-fluorothymidine (FLT), amongst others).

All these developments can help considerably in achieving the goal of personalized cancer therapy.
APPENDIX I. SAMPLE REPORTS

I.1. Sample Report 1 – Suspicious 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 years 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 minutes after the intravenous administration of 10 mCi of 18 F-FDG. PET images were obtained from the orbits to mid thighs using 3D acquisition. The patient’s fasting blood glucose level was 120 mg/dL. The patient was positioned in the PET/CT scanner approximately 60 minutes after injection of the radiopharmaceutical. A CT scan from the orbits to upper thighs was obtained for attenuation correction and anatomic localization. Images were displayed in the axial, coronal and sagittal planes. Injection site was in the right antecubital fossa.

FINDINGS:

1 cm spiculated nodule is seen unchanged at the anterior aspect of the right middle lobe with intense FDG uptake (SUVm 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 physiologic 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 for metastatic disease.
I.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 minutes after the intravenous administration of 10 mCi of 18 F-FDG. PET images were obtained from the sternal notch to mid thighs using 3D acquisition. A CT scan from the sternal notch to upper thighs was obtained from the sternal notch to upper thighs for attenuation correction and anatomic 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 intravenous 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 (SUVm 7.5 on image 19). There is a 1.5 cm left level 2 highly FDG avid lymphadenopathy (SUVm 4.5 on image 23). No other FDG avid lymphadenopathy was seen in the rest of the neck. Physiologic 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. Physiologic 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. Physiologic FDG uptake is seen in the kidneys and urinary bladder. There is an infrarenal abdominal aortic aneurysm measuring 5.1 cm X 4.8cm X 6.2 cms 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 for other metastatic lesions.

2) Unexpected finding: 5.1 cm infrarenal abdominal aortic aneurysm.

The findings were called to the referring physician.
CONTRIBUTORS TO DRAFTING AND REVIEW

Drafting

Etchebehere, E.           Hospital Sirio-Libanes, Sao Paulo, Brazil
Gerbaudo V.H.            Brigham and Women's Hospital, Harvard Medical School, Boston, USA
Núñez, R.                Instituto Tecnológico de Servicios Sanitarios, Centro Oncológico MD Anderson, Madrid, Spain
Obando, J.A.             Yale University School of Medicine, VA Connecticut Health Care System, New Haven, USA
Paez, D.                 International Atomic Energy Agency
Sen, I.                  Fortis Hospital, Gurgaon, India

Review

El-Haj, N.               International Atomic Energy Agency
Fanti, S.                University of Bologna, Italy
Paez, D.                 International Atomic Energy Agency
Rehani, M.               International Atomic Energy Agency

Consultants meeting

Vienna, Austria: 25–27 July 2011