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GUIDELINES

Guidelines for ^{18}F-FDG PET and PET-CT imaging in paediatric oncology

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Abstract
Objective The purpose of these guidelines is to offer to the nuclear medicine team a framework that could prove helpful in daily practice. These guidelines contain information related to the indications, acquisition, processing and interpretation of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in paediatric oncology. The Oncology Committee of the European Association of Nuclear Medicine (EANM) has published excellent procedure guidelines on tumour imaging with ^{18}F-FDG PET (Bombardieri et al., Eur J Nucl Med Mol Imaging 30:BP115–24, 2003 [2]. These guidelines, published by the EANM Paediatric Committee, do not intend to compete with the existing guidelines, but rather aim at providing additional information on issues particularly relevant to PET imaging of children with cancer.
Conclusion The guidelines summarize the views of the Paediatric Committee of the European Association of Nuclear Medicine. They should be taken in the context of "good practice" of nuclear medicine and of any national rules, which may apply to nuclear medicine examinations. The recommendations of these guidelines cannot be applied to all patients in all practice settings. The guidelines should not be deemed

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inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results.

Keywords ^{18}F-FDG PET · Pediatric PET

Introduction

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is now a well-established modality in adult oncology imaging. It is widely used for staging, assessment of response to therapy, and follow-up in a variety of cancers. Despite the relatively small number of PET units in paediatric medical centres, there is an increasing number of published studies indicating that lymphoma, common and uncommon solid tumours in children accumulate FDG and thus are amenable to investigation with FDG PET. It is strongly suggested that PET scanning has the potential of significantly influencing patient management in paediatric oncology.

Currently, in adult oncology imaging, there is a transition phase from stand-alone PET to PET-computed tomography (CT), with PET-CT most likely becoming the accepted international standard in paediatric cancer imaging as well. Nevertheless, many stand-alone PET scanners will continue to be used within the next few years. These guidelines try to reflect this transition phase by providing some recommendations specific for stand-alone PET, but also addressing relevant issues specific to PET-CT imaging. It is envisaged that, if—as it seems—PET/CT scanners become more and more established and gradually replaces stand-alone PET scanners, these guidelines will need appropriate revision and update.

Children are not just small adults and differ in their psychology, normal physiology, and pathophysiology. Furthermore, different tumour entities or tumour subtypes with different tumour biology may be seen in children in comparison to adults, which should be taken into account when performing PET in paediatrics.

Indications

More frequently requested indications for PET-imaging with ^{18}F-FDG in paediatric oncology are:

- Lymphoma (HD und NHL): staging, response to therapy, restaging, assessment of residual masses after therapy, planning of radiation therapy.
- Sarcoma (osteosarcoma, Ewing's sarcoma and soft tissue sarcoma, in particular rhabdomyosarcoma): staging, response to therapy, restaging/detection of relapse.
- Neuroblastoma (in MIBG-negative cases or PET with specific tracers for tumours of the sympathetic nervous system).
- CNS tumours (grading, prognostic stratification, response to therapy, detection of recurrence, radiation therapy planning—other PET tracers may be used, e.g., labelled amino acids). Please refer to the existing European Association of Nuclear Medicine (EANM) brain imaging guideline for details [1].

Less frequent indications for PET imaging in paediatric oncology include evaluation of germ cell tumours, hepatoblastoma, Wilms tumour, malignancy of unknown primary, and neurofibromatosis type 1 for suspected malignant transformation of neurofibroma.

Contraindications

Although uncommon in paediatrics, the possibility of pregnancy for female patients of child-bearing age should be ruled out. As in any diagnostic procedure in a patient who is known or suspected to be pregnant, a clinical decision is necessary to consider the benefits against the possible harm of carrying out the scan.

Pre-examination procedures

Patient preparation A thorough explanation of the scan should be given to the patient and his/her parents or carers by the technologist or physician (including hydration, time/duration of scanning, and details of the procedure itself). Information should be given both verbally and in writing to ensure compliance and keep the anxiety of the child and parents/carers to a minimum. Ideally, parents or carers obtain written information together with the appointment letter and, in addition, are contacted in advance by phone to provide information, answer questions and to identify possible problems such as need for sedation or anaesthesia. The patient should be advised to refrain from strenuous exercise the day before the exam to avoid high tracer uptake in skeletal muscle. The child should fast for at least 4–6 h before the study (to maintain low glucose and low insulin levels), but should drink water to maintain good hydration. The prohibition of soft drinks and sweets during this preparation phase should be addressed explicitly. In infants, tracer injection should be timed as close to the next breast/milk feeding as possible. A feed may be given from 30 min after tracer injection.

Pre-injection The nuclear medicine physician or technologist should obtain and document all information that is available for optimal interpretation of PET studies, especially:

- Relevant patient's history including type of suspected or known primary tumour
- Current symptoms

- Results of previous imaging studies
- History of therapy with exact dates (surgery, chemotherapy, radiotherapy)
- History of recent infections/inflammations
- Presence of urinary tract abnormalities
- Possible interference from medications the patient is on
- Presence of Hickman/central lines, Port-a-Caths, drainage sites

Ideally, i.v. access should be obtained outside the nuclear medicine department to reduce stress for the child immediately before tracer injection and thus to maximise the child's cooperation when she/he is in the nuclear medicine department. If available and permitted by national regulations, a local anaesthetic cream can be used to reduce discomfort due to the injection. The fasting blood glucose level needs to be determined. The preferred fasting blood glucose is below 120 mg/dl (6.66 mmol/l). If the blood glucose level is ≥120 mg/dl (6.66 mmol/l), the referring physician should be notified that the study may have a decreased sensitivity and be given the option of re-scheduling the patient. The report should reflect the diagnostic uncertainties imposed by not ideal blood glucose levels.

Uptake of FDG in brown adipose tissue is noted in 15–20% of PET scans in children and adolescents limiting the ability of the study to detect or rule out disease in these regions. It has been observed that brown fat uptake is encountered less frequently by ensuring that the room, where the child stays during the tracer uptake phase, is warm. A warm blanket may also help reduce tracer uptake in brown fat. It has been suggested that a moderate dose of oral diazepam can partly or completely block FDG uptake in brown adipose tissue. Other groups advise to use premedication with propranolol for this purpose [14, 15]. In the Department of Nuclear Medicine of the University of Leipzig, Germany, oral propanolol (1 mg/kg, max. 40 mg) 60–90 min before administration of FDG is a standard premedication for all patients between age 15 and 30 years without contraindications for propranolol. Propranolol is also given routinely to children of 10 years of age and older with lymphoma. The frequency of interfering FDG uptake in brown adipose tissue may also be reduced by premedication with intravenous fentanyl (0.75–1.0 mcg/kg), which, according to Gelfand at al., appears to be an effective alternative to moderate dose oral diazepam (0.10 mg/kg) [8]. The patient should avoid exercising, talking, or chewing immediately before and after FDG administration to minimise muscle uptake.

A maximum dose of 20 mg furosemide (0.5–1 mg/kg body weight) can be given before or after the injection of FDG to enhance diuresis and to reduce FDG activity in the genito-urinary tract, which is a well-known pitfall. Bladder catheters are not generally recommended because catheterisation increases the risk of infection and causes additional stress for the child. Catheterisation may be justified in rare cases, in which accumulation of tracer in the urinary tract is highly likely to impair evaluation of known lesions close to the genito-urinary tract. Administration of benzodiazepines or furosemide might be more valuable in imaging with stand-alone PET. Many centres using PET-CT avoid the use of these medications because the additional anatomic information is often sufficient to accurately localise the focal area of increased tracer uptake.

Radiopharmaceutical injection, injected activity and administration

If possible, injection of radiotracer into central lines should be avoided because retention of tracer in the line or at its tip can mimic FDG-avid disease and therefore may result in a false positive finding. This is important in the evaluation of patients with possible involvement of the mediastinum, especially when stand-alone PET is used. If a central line has to be used for tracer injection due to difficult i.v. access, the line should be flushed with a sufficient amount of 0.9% normal saline solution by someone experienced in "no touch" technique (at least 20 ml, caution: paediatric infusion solutions may contain glucose).

The amount of activity that needs to be administered to obtain sufficient image quality depends largely on the crystal of the PET camera and the acquisition parameters (especially 2D or 3D mode). If available, acquisition in 3D mode (image acquisition without septa) appears preferable over 2D mode because of its higher sensitivity (in combination with detectors using fast scintillator materials). This may not apply to very large patients (body mass index >34), in which the fraction of scattered events may increase to a level that will degrade image quality. Use of 2D mode appears favourable for those patients to reduce scatter, particularly on scanners that utilize BGO detectors [4].

Different methods are in use in different European countries to calculate the injected activity of FDG in children. In general, the injected activity should be adjusted to the patient's weight and to the type of acquisition (2D or 3D). The broad variety of injected activities across Europe (with the resulting great discrepancy in the quality of the studies) prompted the EANM to suggest a minimum injected activity of FDG, in the hope to reduce the great variety in scan quality in the continent. The latest version of the EANM paediatric dosage card and the corresponding addendum for ^{18}F and ^{18}F-FDG (Table 1, [13]) suggest a minimum injected activity of FDG of 26 MBq for 2D mode scan acquisitions and 14 MBq for 3D mode scan acquisitions. The EANM dosimetry and paediatrics committees decided to reduce the values of the minimum recommended

Table 1 Recommended activity based upon the revised EANM Dosage Card for 2D and 3D whole-body 18F-FDG PET [13]

Weight (kg)	Activity (MBq) 2D	Activity (MBq) 3D	Weight (kg)	Activity (MBq) 2D	Activity (MBq) 3D
3	26	14	32	189	102
4	30	16	34	200	108
6	44	24	36	207	112
8	55	30	38	218	118
10	70	38	40	229	124
12	81	44	42	237	128
14	92	50	44	248	134
16	104	56	46	259	140
18	115	62	48	267	144
20	126	68	50	277	150
22	137	74	52–54	292	158
24	148	80	56–58	311	168
26	159	86	60–62	329	178
28	167	90	64–66	348	188
30	178	96	68	363	196

The dosage recommendations should be taken in context of "good practice" of nuclear medicine and do not substitute for national and international legal or regulatory provisions. The national diagnostic reference levels should not be exceeded. For calculated activities of less than 70 MBq in very young and lightweight children, careful consideration should be given in administering the lowest possible activity that will not lead to loss of diagnostic value, taking into account the state of the art acquisition techniques and the available PET scanners.

activity for ^{18}F-FDG (which was initially set to 70 MBq [12]) after considering new reports from two groups, who describe their clinically satisfactory experience using low ^{18}F-FDG activities in very young and lightweight children [10, 16].

However, it is recognised that other ways of calculating the injected activity of FDG in children are possible (for example, 6 MBq/kg body weight FDG in 2D mode scanning acquisition and 3 MBq/kg body weight in 3D mode scanning acquisition [10]).

In general, careful consideration should be given in administering the lowest possible activity that will not lead to a loss of the diagnostic potential, taking into account the current state of the art acquisition techniques and the sensitivity of the PET scanner available. The maximum activity may be limited by national regulations.

Postinjection

The patient should rest until the start of PET scanning. Standard imaging time commences at approximately 1 h postinjection. Some centres may prefer to wait up to 2 h after injection before imaging to increase tracer uptake within the tumour. Whatever time interval is used, it is important to be consistent and use the same time period between tracer injection and scanning at the initial and the subsequent scans. Infants not having anaesthesia or sedation may be fed from 30 min after tracer injection. Before the start of image acquisition the child should be encouraged to void. The nappy should be changed in infants before the scan.

Radiation dosimetry

The estimated absorbed radiation dose to various organs in healthy subjects after administration of ^{18}F-FDG according to the ICRP Publication 80 is set out in Table 2 [11].

Stand-alone PET versus combined PET-CT

Please note that Table 2 only provides the radiation dose related to the administration of radiotracer for the emission scan. Additional radiation exposure originates from the transmission scan that needs to be acquired for attenuation correction. In stand-alone PET, attenuation correction has traditionally been performed by using transmission data from a rotating external positron-emitting rod source. Alternatively in combined PET-CT scanners, attenuation values obtained from the CT portion transformed to values appropriate for 511 keV photons are used for attenuation correction of PET images. With the increasing number of PET-CT systems, the additional radiation exposure for the child related to the CT portion of the examination has become an issue of concern. In general, there is a trade off between CT image quality and radiation dose, and therefore, the amount of additional radiation depends primarily on the desired quality of CT images. As a consequence, it needs to be determined at each institution, individually for each patient, if the CT should be used only for attenuation correction, for attenuation correction and anatomic localization (so called "low-dose CT"), or if diagnostic quality is needed (so-called "diagnostic CT"). Currently, the diagnostic impact of low-dose CT scans as part

Table 2 Radiation dose to various organs in healthy subjects after administration of 18F-FDG according to the ICRP Publication 80 [11]

Organ	Absorbed dose per unit administered activity (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	0.012	0.015	0.024	0.038	0.072
Bladder	0.16	0.21	0.28	0.32	0.59
Bone surfaces	0.011	0.014	0.022	0.035	0.066
Brain	0.028	0.028	0.030	0.034	0.048
Breast	0.0086	0.011	0.018	0.029	0.056
Gallbladder	0.012	0.015	0.023	0.035	0.066
Stomach	0.011	0.014	0.022	0.036	0.068
Small Intestine	0.013	0.017	0.027	0.041	0.077
Colon	0.013	0.017	0.027	0.040	0.074
Heart	0.062	0.081	0.12	0.20	0.35
Kidneys	0.021	0.025	0.036	0.054	0.096
Liver	0.011	0.014	0.022	0.037	0.070
Lungs	0.010	0.014	0.021	0.034	0.065
Muscles	0.011	0.014	0.021	0.034	0.065
Oesophagus	0.011	0.015	0.022	0.035	0.068
Ovaries	0.015	0.020	0.030	0.044	0.082
Pancreas	0.012	0.016	0.025	0.040	0.076
Red marrow	0.011	0.014	0.022	0.032	0.061
Skin	0.0083	0.010	0.016	0.027	0.052
Spleen	0.011	0.014	0.022	0.036	0.069
Testes	0.012	0.016	0.026	0.038	0.073
Thymus	0.011	0.015	0.022	0.035	0.068
Thyroid	0.010	0.013	0.021	0.035	0.068
Uterus	0.021	0.026	0.039	0.055	0.10
Remaining organs	0.011	0.014	0.022	0.034	0.063
Effective dose (mSv/MBq)	0.019	0.025	0.036	0.050	0.095

of a PET-CT examination is under scientific evaluation. A diagnostic CT should not generally be performed as a standard investigation, unless it is indicated. For children with sarcoma, for example, it might be considered useful to obtain a low-dose whole-body CT for attenuation correction and anatomic localization with an additional diagnostic chest CT acquired in the same scanner to obtain a possibly higher sensitivity for detection of pulmonary metastases. Optimized CT protocols in children should include weight- and axial diameter-adapted CT parameters as well as age-adapted amounts of contrast agents. In principle, a decrease of a patient's radiation dose is achieved by lowering the tube voltage or tube current, increasing the rotation speed, and/or applying higher pitch factor. In addition, online dose modulation systems are used to lower radiation burden.

The question whether PET-CT is preferable compared to stand-alone PET in combination with separate anatomic imaging modalities has been recently addressed by a controversy published in the European Journal of Nuclear Medicine and Molecular Imaging, reflecting also the different opinions within the Paediatric Committee [5–7, 9]. In this controversy, Hahn and Pfluger hold the view that a PET/CT scanner is not preferable to a stand-alone PET scanner because of the additional radiation exposure from the CT scan; they refer to the results from Fahey et al., who compared radiation exposure associated with low-dose CT versus an external radioactive source for attenuation correction in paediatric PET examinations. For paediatric patients, they found that adequate CT-based attenuation correction could be obtained with ultralow-dose CT (80 kVp, 5 mAs, and a pitch of 1.5:1) with a radiation dose (0.30 mGy) that is approximately 100 times lower compared to the dose from a diagnostic CT scans. However, even this low-dose CT-based attenuation correction is associated with radiation exposure for the child that is nearly ten times higher than that of radioactive source-based attenuation correction (0.035 mGy). Hahn and Pfluger also argue that, in most body regions (brain, head and neck, spine, abdomen, pelvis, and skeleton), MRI is the modality of choice for morphological tumour imaging in children without any radiation exposure in contrast to CT. The only exception is evaluation of pulmonary lesions, for which diagnostic CT is more sensitive than MRI and/or PET. Various software solutions are available to perform fusion and co-registration of separate MRI and PET datasets for interpretation.

Franzius et al. on the other hand, having evaluated more than 350 paediatric PET-CT examinations, emphasise the benefits of combined PET-CT with low-dose CT such as improved lesion localisation and the possibly superior sensitivity and specificity, which might outweigh associated radiation risks in young cancer patients. However, they also show that the radiation exposure of low-dose CT has to be minimized; they make the point that specific lower limits of CT acquisition parameters (mAs, kV), as allowed by the manufacturers, are currently not as low as desirable for small children. Franzius et al. report an increasing demand of a diagnostic CT scan as part of the PET-CT examination by the referring paediatricians, obviating the inconvenience of performing two single examinations, when there is an indication for both. They also point out that attenuation correction with CT has the advantage of a much shorter acquisition time, which improves compliance and leads to a more limited use of sedation and anaesthesia.

A minor potential problem in applying a CT-based attenuation correction algorithm may arise from metallic objects such as port systems. They may lead to over-correction of the emission data and therefore to an area of falsely high FDG uptake. Visual comparison with the non-attenuation-corrected PET data sets can help to avoid mistakes related to this issue. There is increasing evidence that use of oral or intravenous contrast in PET-CT imaging does not cause significant artefacts related to attenuation overcorrection as previously suspected. In addition, reconstruction artefacts using PET-CT may result in differences in the PET and the CT chest images. The CT scan is normally acquired during mild expiration to obtain the best alignment of the diaphragm. However, it may be difficult to obtain cooperation of a child younger than 4 years of age. Therefore, data acquisition on shallow breathing may be preferable in very young children [5–7].

Positioning of the child and sedation

To ensure an optimal position in the scanner and to avoid movement artefacts, all patients should be comfortably immobilised during study acquisition with Velcro straps, tapes, or cushions. For smaller children, cushions filled with small plastic balls, which fit the body contour, are commercially available. The need for sedation has to be assessed individually and an experienced physician, ideally a paediatric anaesthetist, should be involved. An appropriate environment, an adequate attitude toward the child, a well-trained child-friendly technologist, and involved parents during the procedure, all help in making a child cooperative and may obviate the need for sedation in the majority of cases. For children younger than 2 years of age, sedation can be avoided in many cases, if scanning is performed during the child's normal sleeping period.

Image acquisition

The extent of the acquisition depends on the indication. For example, in follow-up FDG PET scans in patients with lymphoma and no bone or bone marrow involvement, it may suffice to image from the base of the skull to the upper thighs. In neuroblastoma and sarcoma patients and in lymphoma patients with suspected bone or bone marrow disease, the entire legs and arms should be included. Acquisition parameters depend largely on the detector and the type of scanner used, as discussed in depth in the FDG-PET Procedure Guideline for Tumour Imaging by the EANM Oncology Committee. Compared to PET imaging in adults, data acquisition with high sensitivity is even more important in children to reduce the injected activity. This will lower the radiation burden and reduce the acquisition time. A shorter acquisition will be associated with likely reduced child's motion during the scan; hence, the need for sedation will decrease.

Interpretation

It is important to keep in mind the physiologic FDG distribution to avoid image misinterpretation. FDG uptake in the thymus is a common finding in children and young adults, which can be normally identified because of its characteristic appearance of an inverted "V". Thymus hyperplasia after chemotherapy is a common finding, and it can be difficult to differentiate it from residual/recurrent disease in the anterior mediastinum. FDG uptake in naso-/oropharyngeal lymphoid tissue such as the Waldeyer's ring is often more prominent in children compared to the adult population. Uptake in mastication muscles may become visible in babies who suck pacifiers or are fed within the first 30 min of the tracer injection. High FDG uptake is often seen symmetrically in skeletal growth plates. Diffusely elevated FDG uptake in the bone marrow has been observed in patients after the end of chemotherapy as evidence of physiologic regeneration. Increased uptake in bone marrow and spleen can be secondary to treatment with granulocyte colony-stimulating factor (G-CSF). Different half-lives of G-CSF pharmaceuticals need to be taken into account for interpretation of these findings. Increased bone marrow uptake can also be seen after treatment with erythropoietin. Prominent symmetrical laryngeal uptake is often observed in smaller children if they cry after tracer injection. Tracer uptake in adipose brown tissue is frequent in children. It is most often symmetric and can involve the neck, supraclavicular, mediastinal, axillary, paraspinal, and perirenal regions. Fused images using hybrid PET-CT or software-based fusion images of PET data and diagnostic anatomic cross-sectional images are most helpful in con-

firming the location of the area of tracer uptake within the adipose brown tissue. Chugani reported that there are significant changes in the distribution of tracer uptake in the brain depending on the age of the child [7]. In the newborn, the highest degree of glucose metabolism is in the primary sensory and motor cortices, cingulate cortex, thalamus, brain stem, cerebellar vermis, and hippocampal region. At 2 to 3 months of age, glucose utilization increases in the parietal, temporal, and primary visual cortices, basal ganglia, and cerebellar hemispheres. Between 6 and 12 months, there is increased glucose consumption in the frontal cortex. Initially, there is a rise in the rate of glucose utilization from birth until about age 4 years, at which time the child's cerebral cortex consumes twice as much glucose as an adult. From age 4 to 10 years, a very high rate of glucose consumption is maintained. Subsequently, a gradual decline of glucose metabolic rate takes place, to reach adult values by age of 16–18 years.

Given the potential causes for misinterpretation of PET studies in children, scans should be reported by nuclear medicine physicians/radiologists with specific expertise on paediatric PET.

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