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GUIDELINES

EANM procedure guidelines for PET brain imaging using [^{18}F]FDG, version 2

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Abstract These guidelines summarize the current views of the European Association of Nuclear Medicine Neuroimaging Committee (ENC). The purpose of the guidelines is to assist nuclear medicine practitioners in making recommendations, performing, interpreting, and reporting the results of fluorine-18 fluoro-2-deoxyglucose ([^{18}F]FDG) PET imaging of the brain. The aim is to help achieve a high standard of FDG imaging, which will increase the diagnostic impact of this technique in neurological and psychiatric practice. The present document replaces a former version of the guidelines that were published in 2002 [1] and includes an update in the light of advances in PET technology, the introduction of hybrid PET/CT systems and the broadening clinical indications for FDG brain imaging. These guidelines are intended to present information specifically adapted for European practice. The information provided should be taken in the context of local conditions and regulations.

Keywords Glucose · Metabolism · PET · Dementia · Oncology · Epilepsy · Movement disorders

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Background and definitions

In the brain, glucose metabolism provides approximately 95% of the ATP required for brain function. Under physiological conditions, as well as in several diseases affecting the brain, glucose metabolism is tightly connected to neuronal activity. Therefore, changes in neuronal activity induced by disease are reflected in an alteration in glucose metabolism. [^{18}F]FDG is suitable for imaging regional cerebral glucose consumption with PET since it accumulates in brain tissue depending on facilitated transport of glucose and hexokinase-mediated phosphorylation. [^{18}F]FDG PET is currently the most accurate in-vivo method for the investigation of regional human brain metabolism and is widely available in Europe. It is increasingly being used to study the brain for diagnostic purposes. Its clinical use can be regarded as established for a number of diagnostic questions in neurology, neurosurgery and psychiatry [2–6].

Depending on the clinical question and type of equipment FDG imaging may include:

A. *Static limited field tomographic images*: A single tomographic image has been obtained after the tracer has been taken up in the brain.
B. *Dynamic tomographic images*: multiple sequential images in a field of view, covering the whole brain. This type of acquisition may be used when absolute quantification of regional metabolic rates of glucose is needed.
C. *2-D and 3-D acquisition mode*: The majority of the state-of-art PET systems and new PET/CT systems acquire images in 3-D mode. Some PET systems have the capability to acquire images in both 2-D and 3-D mode. In 2-D mode coincidences are detected only within a single detector ring and between adjacent detector rings (through the positioning of septa between the rings), while in 3-D mode all coincidence detections in the field of view are acquired (i.e. including oblique planes). New PET/CT scanners, particularly those with LSO or GSO crystals, only acquire images in 3-D mode. The sensitivity in 3-D mode is greatly enhanced and can be recommended, particularly if a short acquisition time is needed.
D. *Attenuation correction*: Attenuation correction is mandatory for [^{18}F]FDG PET brain imaging.
   D.1. Transmission imaging: A set of images at a position corresponding to the emission image is acquired with an external source of radiation. Usually these images are acquired with the PET camera itself. The standard procedure for full-ring PET systems is currently the measurement of attenuation prior to FDG injection using a ^{68}Ge/^{68}Ga source. Alternatively, some PET systems have transmission sources with ^{137}Cs.
   D.2. Hybrid attenuation correction: These methods calculate an attenuation image based on a short transmission measurement followed by image segmentation.
   D.3. CT scan: PET/CT systems have the ability to use the CT scan for attenuation correction. The advantage of the CT scan is that the detection of X-rays from the CT scan is not affected by the emission photons. Therefore, a CT scan can be performed after the injection of the radiopharmaceutical, without affecting the accuracy of the attenuation correction. A CT scan can be done for diagnostic purposes using a regular tube current, or only for the purpose of attenuation correction with a low tube current (typically 10–30 mAs), i.e. a low-dose CT scan. The latter has the advantage of reducing significantly the radiation exposure almost to the level of germanium-based transmission measurements (see below) while retaining an appropriate transmission map.
   The choice of the type of CT scan depends on the purpose of the imaging and the clinical indications. If anatomical information is already available, a low-dose CT scan for the purpose of attenuation correction can be considered, while if recent anatomical information is not available a diagnostic CT scan (with contiguous slices) may be preferred.
   The advantage of CT vs. transmission imaging is the time needed to perform the acquisition, which is much reduced (<10 s vs. 5 to 10 min), particularly with new multislice CT scanners. A reduced scanning time can be helpful, particularly in less-compliant patients (i.e. patients with dementia).
   D.4. Mathematical attenuation correction: Correction procedures estimating the attenuation based on an estimation of organ extent from emission data (i.e. according to Chang). Skull attenuation may be included to improve accuracy.
   It is important to note in this respect that the different correction procedures lead to systematic differences in the resulting images, with the consequence that images obtained with different correction procedures are not directly comparable (e.g. with statistical subtraction analyses on a voxel-wise basis). Differences may appear especially in the occipital and cerebellar regions [7].
   In full-ring PET systems mathematical attenuation correction can lead to results that are sufficient for clinical purposes. Although this is the least time-consuming approach, it has to be used with caution and in a consistent way.

Indications

There may be other indications as well as those listed below.

A. Common indications

A.1. Dementing disorders. Indications include early diagnosis and differential diagnosis of dementing disorders, such as Alzheimer's disease and frontotemporal dementia [8–10]. Typical topographic patterns of hypometabolism may help diagnose the main neurodegenerative diseases at a predementia stage, i.e. mild cognitive impairment [11].

A.2. Neurooncology. FDG PET can be used in differential diagnosis of cerebral space-occupying lesions, detection of viable tumour tissue (i.e. recurrence) and for noninvasive grading [12].

A.3. Epilepsy. A common indication (interictal injection) is the preoperative evaluation of partial epilepsy in adults and in children to identify the functional deficit zone [13, 14].

A.4. Movement disorders. FDG PET can be used for the differentiation between Parkinson's disease and atypical parkinsonian syndromes [15, 16].

B. Contraindications (relative)

B.1. Pregnancy.

B.2. Breast feeding. Mothers should interrupt breast feeding for 24 h if PET is indicated.

B.3. Lack of cooperation, or inability to cooperate, with the procedure.

Procedure

A. Patient preparation

A.1. Prearrival

Patients should fast for at least 4 h to allow optimal cerebral FDG uptake not influenced by increased serum glucose levels.

A.2. Preinjection

A.2.1. Blood glucose levels should be checked prior to FDG administration. When hyperglycaemia is present (>160 mg/dl), there is increased competition between elevated plasma glucose and FDG at the carrier enzyme and, because it is usually associated with high intracellular glucose levels, also at hexokinase. Therefore FDG uptake is reduced in whole brain and stochastic noise is increased. In addition, decreased contrast between white and grey matter uptake can be expected, which might further decrease diagnostic accuracy.
Acute correction of hyperglycaemia with insulin usually does not improve brain image quality substantially, probably because the correction of increased intracellular glucose level lags behind the correction of the plasma glucose level. Quantitation of regional cerebral glucose metabolism with FDG PET also requires steady-state conditions which are not maintained during falling plasma glucose levels after administration of insulin.
Best results in the clinical FDG imaging of the brain in diabetics can be achieved in a euglycaemic situation during adequate therapeutic management [17, 18].
In brain tumours, hyperglycaemia does not need to be corrected and can even enhance detectability.

A.2.2. Before the scanning procedure is started, patients should void the bladder for maximum comfort during the study. The patient should be advised to void again after the scanning session to minimize radiation exposure.

A.2.3. Patients should be positioned comfortably in a quiet, dimly lit room several minutes before FDG administration and during the uptake phase of FDG (at least 20 min). They should be instructed not to speak, read or be otherwise active. It is desirable to have the cannula for intravenous administration in place 10 min before FDG administration.

A.2.4. For preoperative evaluation of epilepsy, continuous EEG recording is required. Monitoring should start before injection (ideally 2 h before) in order to ensure that FDG is not administered in a postictal situation, and should be maintained at least until 20 min after injection. For adequate image interpretation it is of critical importance to be aware of the precise history of seizures occurring prior to imaging.

B. Information pertinent to performance of the procedure

- History of diseases, especially neurological and psychiatric disorders, and current neurological and psychiatric status, and history of surgery, radiation, trauma to the brain.
- History of diabetes, fasting state, use of corticosteroids (with an effect similar to that of hyperglycaemia).
- Patient's ability to lie still for 30 min to 1 h. If sedation is necessary it should be performed as late as possible. The intention should be to administer FDG prior to sedation.

– Information about (recent) morphological imaging studies (CT, MRI), as well as about functional brain examinations (EEG, neuropsychology) in peculiar conditions.
– Current medication and when last taken, especially psychotropic pharmaceuticals. These may influence regional metabolic rate of glucose [19]. In parkinsonian patients it is important to know whether the measurements are conducted in a clinically defined "off" state, since the administration of levodopa has been found to reduce glucose metabolism regionally [20, 21]. If possible, centrally acting pharmaceuticals should be discontinued on the day of the PET examination, according to the clinical status of the patient.

C. Precautions and conscious sedation

Continuous supervision of the patient during the whole scanning procedure is necessary. This is especially important for patients with epilepsy and dementing disorders.

In uncooperative patients (e.g. due to their cognitive/behavioural state such as in dementia), it may be worthwhile to apply conscious sedation (e.g. using a short-acting benzodiazepine, such as intravenous midazolam). The sedative medication should be given at least 20 min after tracer injection, preferably starting only a few minutes before data acquisition.

Appropriate monitoring (pulse oximetry) should be performed to recognize the possibility of cardiopulmonary depression and appropriate antidote/emergency back-up should be available. Doses of sedation should be reduced in elderly patients.

D. Radiopharmaceutical

D.1. Radionuclide

Fluorine-18.

D.2. Radiopharmaceutical

18-Fluoro-2-deoxyglucose.

D.3. Recommended activity

Adults:

- 300–600 MBq (typically 370 MBq) in 2-D mode
- 125–250 MBq (typically 150 MBq) in 3-D mode

Children (EANM dosage card v.1.5.2008, 3-D is recommended especially in children):

- 25.9 MBq baseline activity (minimum 26 MBq) in 2-D mode
- 14.0 MBq baseline activity (minimum 14 MBq) in 3-D mode
- Activity administered = baseline activity × multiple (dosage card)

D.4. Radiation dosimetry

In infants and small children, acquisition should be performed in 3-D mode in order to decrease the radiation burden. Infants have a greater relative brain mass (10%) than adults (2–3%), so the percentage of uptake of the injected FDG activity is higher. Although in newborn infants, sufficient image quality may be achieved with an injected activity of as low as 10 MBq [22] (which is also a result of reduced attenuation losses), the advocated minimal dose stated from the paediatric dose card of the EANM is followed in these guidelines.

The doses of radiation in adults and children are shown in Table 1.

The activity recommendations mentioned here are valid for full-ring PET cameras. The administered activity may vary for other systems according to differences in sensitivity.

D.5. Radiation dosimetry of brain transmission scans

– The effective dose rate is typically 3.5×10^{-6} mSv/MBq per minute using ^{68}Ge.
– For CT, the effective dose depends on collimation and scan type (axial, helical) [23].
– Based on transmission scans of 10 min and CT-based scans of 5–10 s (values for GE Advance NXi systems), the effective doses per scan are:
  - 20–30 μSv for germanium-based transmission
  - between 220 and 450 μSv for high-quality CT
  - approximately 20 μSv for low-dose high-speed CT

E. Data acquisition

Acquisition parameters for FDG imaging of the brain with dedicated PET scanners.

Table 1 Radiation dosimetry

	Organ receiving the largest dose		Effective dose mSv/MBq
	Organ	Dose (mGy/MBq)	
Adults	Bladder wall	0.13	0.019
Children (≥5 years)	Bladder wall	0.34	0.056

Calculations based on: ICRP 106, page 87.

E.1. Positioning of the patient

Especially if tomographic cameras with a field of view similar to or smaller than the length of brain are used, careful positioning of the patient's head is critical. The orbitomeatal line is often used for standardization of positioning. To prevent movement artefacts, the patient should be informed of the need to avoid (voluntary) movements of the head, and the patient's head can be fixed in place.

E.2. Transmission scan

If attenuation correction is based on transmission images, better results are generally achieved when the images are acquired before FDG injection if clinically feasible. If additional postprocessing such as segmentation is performed, the images may be obtained after injection of radiotracer. Acquisition counts collected may vary between PET systems and the postprocessing procedures used. Institutions using standard full-ring dedicated PET cameras with an axial field of view over 16 cm typically acquire transmission images of more than 100 million detected events over 10 to 20 min.

For PET/CT systems, the CT scan can be used for attenuation correction. The scanning parameters may vary according to the type of CT scanner. Usually the tube voltage is set at around 140 kV. The CT scan can be performed after injection of FDG and has the advantage of significantly reducing the total scan time (usually <10 s). However, the absorbed dose delivered by the CT scan to the patient can be reduced by lowering the tube current (see Radiation Dosimetry above) if anatomical information is not needed. When performing PET/CT of the brain it is recommended to check for movements between the CT and the PET sessions, which might produce artefacts in the attenuation correction.

E.3. Static emission scan

The acquisition should not start earlier than 30 min after injection. Better contrast between grey and white matter as well between tumour and normal brain tissue can be achieved with a longer time interval between FDG administration and data acquisition (e.g. 60 min up to several hours for tumours). It is recommended that a standardized acquisition protocol with a fixed time for starting the acquisition (e.g. 30 min or 60 min after injection) is used in order to render the data from different patients or repeated scans comparable. If data are acquired in 3-D mode, appropriate scatter correction is mandatory. The duration of emission image acquisition should be related to the minimum required number of detected events. Typically data are acquired over 15–30 min aiming to collect 50–200 million detected events. Even though shorter acquisition times down to 5 min can still be used for diagnostic pattern evaluation [24], which can be useful for moderately agitated patients, a minimum of 10–15 min in 3-D mode is recommended.

If movement artefacts are expected (especially in children or demented patients), it can be helpful to perform dynamic acquisition over the intended period of time (e.g. six 5-min frames), check the sinograms, and add only the sinograms of the properly acquired time period prior to reconstruction. List-mode acquisitions can be used for the same purpose.

E.4. Quantification procedures

- The quantitative assessment of cerebral FDG/glucose metabolism may require, besides a dynamic emission scan, an arterial input function, determination of plasma FDG and glucose concentrations, the total activity of administered FDG, and the patient's height and weight for estimation of body surface area (in the clinical setting, arterialized venous blood samples, for example obtained by heating the limbs, may provide reasonable results as well). In addition there is a need for a calibration factor between scanner events in terms of detected events per voxel per second and in vitro measurement of activity concentrations in counts per millilitre per second [4].
- Although dynamic image acquisition from the start of injection up to 60–90 min after injection is considered the most accurate procedure, in the clinical setting most centres use simplified protocols based on static images [25–27].
- For tumour imaging typically semiquantitative estimates of glucose metabolism such as the SUV (standardized uptake value) are used. For this kind of quantification, standardized acquisition times are mandatory. A static image is sufficient, typically acquired at 30 or 60 min after injection (after FDG has reached a plateau concentration in the lesion). In addition, the exact total activity of FDG administered and the patient's weight and height for measurement of body surface area are required. A calibration factor is needed as well. These semiquantitative estimates can be corrected for blood glucose concentration.

F. Interventions

Usually interventions are not necessary to answer routine clinical questions. In the localization of eloquent cortical areas before surgery, stimulation paradigms like language or motor tasks can be used. These paradigms usually start at

the time of injection and have to be maintained for a time period of at least 15–20 min [28, 29].

G. Image processing

Processing of images acquired with dedicated PET scanners.

G.1. Reconstruction

- Images are reconstructed in the form of transaxial images of at least 128×128 pixels; a usual pixel size is 2–4 mm. Depending on the resolution of the PET system, a final image resolution of 4–6 mm FWHM typically yields images of adequate resolution and noise. Commonly used filters are Hanning or Shepp-Logan which should be finely tuned depending on application, injected activity, camera and acquisition type. and even physician's preference. Iterative reconstruction methods, including ordered-subset expectation maximization (OSEM) are also available. Such methods may improve target-to-background ratio and are used in many recent PET and PET/CT systems.

G.2. Data display for analysis

- A standardized image display is advocated to ensure an appropriate, symmetrical and most readily interpretable representation of the reconstructed dataset.
- Internal landmarks can be used for reorientation to achieve a standardized image display. Reorientation procedures based on the intercommisural line are commonly used [30].
- The display of additional coronal and sagittal images is mandatory.
- Three-dimensional display of the dataset can be helpful for more accurate topographic orientation in some clinical questions.
- Depending on the indication, other than standard reorientation may be helpful, e.g. parallel to the temporal lobe in the evaluation of epilepsy.
- Three-dimensional display of the dataset (e.g. by volume rendering or surface projections such as 3D-SSP) can be helpful for more accurate topographic orientation in some clinical questions and to appreciate overall patterns of disease. However, volume and surface renderings may be subject to artefacts and should be used with caution and in combination with the standard slice displays.

G.3. Quantification

- The regional metabolic rate of glucose can be estimated by compartmental modelling or by using graphical analytical approaches. A correction factor, the so-called "lumped constant" [31], can be used to convert the FDG values to values reflecting glucose metabolism [25]. However, little is known about the dependency of the lumped constant on (patho)physiological conditions.
- If data from age-matched normal controls are available, it is possible to apply stereotactic normalization and voxel-based analytical approaches such as 3D-SSP or statistical parametric mapping in order to determine abnormalities of FDG uptake in an observer-independent way and to improve diagnostic accuracy in various settings [14, 32–34].

H. Interpretation criteria

H.1. Visual interpretation

- The images should be critically examined during interpretation for the presence of movement or attenuation artefacts.
- It is desirable to have a normal database available, preferably obtained on the same type of camera, under the same acquisition circumstances (e.g. eyes open/closed) and using the same type of reconstruction and attenuation correction. Matching spatial resolution is the most important parameter needed for optimal database use. This allows assessment of normal variability of regional FDG uptake and improves diagnostic accuracy.
- It is helpful to interpret the data on the computer screen because this allows variation in colour scale, background subtraction and contrast. Data interpretation should take into consideration global changes, such as relative cortical hypometabolism and regional decreases or increases in FDG uptake. Increased uptake can be observed in active epileptogenic foci, tumours and inflammation.
- Even without a normal database, evaluation of surface projections (e.g. 3D-SSP) may enhance the accuracy and consistency of the individual patient data. Several commercially available tools are available that allow this feature.
- Known morphological changes such as atrophy should be considered in the interpretation. It is at least helpful to fuse FDG images with the MRI (or CT) scan of the individual. In PET/CT systems, fused PET/CT images can be immediately visualized after image reconstruction without the need for specific software for image registration. Examples where image fusion is mandatory are:
- The accurate evaluation of brain tumours and identification of the metabolically most active part of a brain tumour prior to biopsy.

- Localisation of eloquent cortical areas (e.g. Broca's area) prior to tumour resection.
- Matching of cortical hypometabolism with morphological abnormalities on MRI or with the EEG focus for planning of epilepsy surgery.

H.2. Quantification

Quantification in terms of deviations of normal values or semiquantitatively assessing changes in follow-up studies, is helpful in assisting visual interpretation.

Quantification can be performed with anatomically adjusted regions of interest or on a voxel-wise basis (see above).

For comparison with normal datasets, results should be interpreted in combination with the visual inspection and should only be considered as abnormal if they are outside the mean ± two standard deviations of normal data, preferably obtained from healthy age-matched controls.

I. Reporting

I.1. General

The report should include all pertinent information, including the name of the patient and other identifiers, such as birth date, name of the referring physician(s), potentially interfering medications or abnormal glycaemia, type of examination, date of examination, radiopharmaceutical, including administered activity, and patient history, including reasons for requesting the study.

I.2. Body of the report

I.2.1. Procedures and materials: Include in the report a description of image acquisition, i.e. type of transmission imaging (germanium-based, other transmission sources, e.g. ^{137}Cs, or CT) and emission imaging, whether acquired in 2-D or 3-D mode, and procedure performed, such as arterial blood sampling. If the camera type had a restricted field of view, report on areas that are included in the image. If the patient was sedated, briefly describe the procedure, including type of medication and time of sedation in relation to the radiotracer injection. In epileptic patients, briefly describe the procedure of EEG recording, when performed.

I.2.2. Findings: Describe whether the FDG-PET finding is normal or abnormal. If findings are abnormal, describe the location and intensity of abnormal FDG uptake. Functional topography can be used as well as anatomical descriptions. State quantitative or semiquantitative measures if performed.

I.2.3. Limitations: Where appropriate, identify factors that can limit the sensitivity and specificity of the examination (i.e. movement, small lesions).

I.2.4. Clinical issues: The report should address or answer any pertinent clinical issues raised in the request for the imaging examination.

I.2.5. Comparative data: Comparisons with previous examinations and reports, if available have to be part of the report. Furthermore, results of morphological imaging modalities (CT, MRI) should also be taken into account in interpretation. Nondiagnostic CT scans used only for attenuation in PET/CT should be used with caution for structural interpretation.

I.3. Interpretation and conclusion

I.3.1. If the PET examination reveals a generally accepted disease pattern, this should be said in the conclusion, using a statement that indicates the most probable diagnosis. Any (subjective) interpretation not based on such criteria has to be explicitly stated and considered as hypothetical.

I.3.2. A differential diagnosis should be given when appropriate.

I.3.3. When appropriate, follow-up or additional studies should be recommended to clarify or confirm the suspected diagnosis.

J. Quality control

See procedure guidelines of the EANM.

K. Sources of error

- Unintended cerebral activation (i.e. visual or motor activation)
- Artefacts (patient movement, camera-related, induced by inappropriate processing)
- Psychotropic drugs or corticosteroid use
- Sedation
- No or insufficient attenuation correction
- Soft tissue or skull uptake following surgery in the area of the skull or brain
- Recent radio- or chemotherapy

See also Cook et al. [35].

Issues requiring further clarification

- The exact role of partial volume effect correction methods in clinical diagnostic settings needs to be further evaluated.

– The exact role of attenuation correction with MRI in clinical diagnostic settings needs to be further evaluated.

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Disclaimer These guidelines summarize the views of the ENC of the EANM and reflect recommendations for which the EANM cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions. The guidelines have been brought to the attention of the National Societies of Nuclear Medicine.

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