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Brain Tumor Imaging: European Association of Nuclear Medicine Procedure Guidelines

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BACKGROUND INFORMATION AND DEFINITIONS

The most widely used tracer in oncology is FDG, a glucose analogue. It is actively transported across the blood-brain-barrier (BBB) into the cells where it phosphorylated by hexokinase, then effectively ‘trapped’ intracellularly because dephosphorylation is slow. FDG uptake is enhanced in tumors due to both increased transport and phosphorylation. In the brain, however, high glucose utilisation by normal grey matter hampers the detection of tumor tissue by FDG-PET, depending on the metabolic grade of the tumor. Coregistration with structural data is then required for more sensitive analysis.

In comparison with FDG, better tumor delineation is reported for radiolabeled amino acid. Among them, [methyl- ^{11}C]-L-methionine (MET) used in conjunction with PET is the most frequently used (Chen 2005). In an effort to overcome the disadvantages of its short half-life and complex metabolism and despite a changed amino acid structure, several fluoro- and iodo-amino acid analogs have been developed. These agents include 3-[^{123}I]iodo- α -methyl-L-tyrosine (IMT) for SPECT and O-(2-[^{18}F]fluoroethyl)-L-tyro-

sine (FET) for PET, which are transported by the same specific amino acid transport system L as MET, but are not incorporated into proteins (Langen et al. 2002). Their rapid accumulation into brain tumors is independent of BBB disruption. Among the ^{18}F -labeled amino-acids, FET has been selected as a representative of this category due to ease of synthesis, high in vivo stability, and fast brain and tumor uptake kinetics. Other natural or artificial amino acids have been labeled to measure tumor metabolism, but they are beyond the scope of these guidelines. Despite differences in blood clearance, uptake kinetics, and relation to protein synthesis, MET, IMT, and FET show similar results in the diagnostic evaluation of cerebral tumors, supporting their parallel review in these guidelines.

COMMON INDICATIONS

Indications

In the brain, glucose metabolism provides ~95% of adenosine triphosphate (ATP) required for brain function. Under physiological conditions glucose metabolism is tightly connected to neuronal activity. Besides neurooncology, FDG is indicated

for a number of diagnostic questions in dementing disorders, epilepsy, and movement disorders, which are beyond the scope of this chapter (Bartenstein et al. 2002).

Detection of Viable Tumor Tissue

Conventional CT and MRI techniques cannot reliably differentiate viable tumor tissue from treatment-induced nonneoplastic changes, such as oedema, postoperative changes or radiation necrosis. FDG-PET can be used in differential diagnosis of cerebral space occupying lesions and detection of viable tumor tissue (i.e., recurrence). Radiolabeled amino acid imaging is, however, superior to FDG-PET in confirming low-grade recurrence (Mehrkens et al. 2008; Van Laere et al. 2005).

Tumor Delineation

Radiolabeled amino acid tracers are superior to CT and MRI for estimation of true tumor extension in low as well as in high-grade gliomas (Kracht et al. 2004). In low grade tumors, oedema surrounding the tumor cannot be differentiated from tumor cell infiltration with MRI or CT. In anaplastic astrocytomas and glioblastomas, too, the area of contrast enhancement does not reflect tumor extent correctly. Radiolabeled amino acid tracers are also superior to FDG for tumor delineation in low-grade tumors, for which FDG uptake is found to be decreased compared with normal cortex or basal ganglia. The higher ratio for labeled amino acid tracers is due to the lower uptake of radioactivity in normal brain tissue. This is in sharp contrast with FDG with its high uptake in normal brain tissue, which can obscure delineation depending on the tumor glucose rate. With FET, however, large brain vessels might be visualised as blood pool radioactivity exceeds radioactivity in the normal brain tissue (Pauleit et al. 2003).

Selecting the Best Biopsy Site

Stereotactic biopsy remains the gold standard in the classification and grading of glioma. However, histopathological grading may be limited by sampling error due to well-known heterogeneity of gliomas or may not in all instances predict the biological behavior of brain tumors and thus the patient's prognosis. FDG as well as labeled amino acids imaging is recommended to guide the stereotactic biopsy (Pirotte et al. 2004).

Non-invasive Tumor Grading

The role of labeled amino acids in the grading of cerebral gliomas is controversial and FDG-PET appears better suited to differentiate between tumor grades (Kaschten et al. 1998). MET and IMT uptake tends to correlate with cell proliferative activity and MET uptake with microvessel density (Kracht et al. 2003). Radiolabeled amino acid imaging may aid in differentiating high-grade gliomas from histologically benign brain tumors or nonneoplastic lesions (Floeth et al. 2008). The intensity of MET uptake may represent a prognostic factor for WHO Grade II and III tumors considered separately. Oligodendroglioma and oligo-astrocytoma could have greater uptake than high-grade gliomas. In contrast to MET (Moulin-Romsee et al. 2007), dynamic FET PET imaging has recently shown to allow differentiation of low versus high grade brain tumors on an individual patient basis. Time activity curves show slight increase in low grade gliomas, whereas high grade gliomas present with an early peak (10–20 min) followed by a decrease (Popperl et al. 2007).

Therapy Planning

In conjunction with anatomical imaging, radiolabeled amino acid imaging may be

used to better define the tumor volume to resect or irradiate (Levivier et al. 2004; Veas et al. 2009; Weber et al. 2008).

Tumor Response

FDG as well as labeled amino acid uptake changes may predict the response to loco-regional chemo- and radiotherapy as it may allow early detection of residual tumor after surgery (Brock et al. 2000; Galldiks et al. 2006).

Contraindications (Relative)

- Pregnancy (mothers should interrupt breast feeding for 24 h if PET is indicated; no data are available for IMT).
- Evident lack of cooperation or inability to cooperate.

PROCEDURE

Patient Preparation

Prearrival

Patients should be informed of the procedure to fully cooperate.

Preinjection

Patient should be fasting for at least 4 h for FDG as well as for radiolabeled amino acids: the former to allow for optimal cerebral FDG uptake not influenced by increased serum glucose levels and the latter to ensure stable metabolic conditions.

Prior to the *FDG administration*, blood glucose levels should be checked. When hyperglycemia is present (>160 mg/dL), there is increased competition of elevated plasma glucose with 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 of white and grey matter uptake can be expected, which might further decrease diagnostic accuracy. Acute correction of hyperglycemia 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 application of insulin. Best results for clinical FDG-imaging in the brain of diabetics can be achieved in an euglycaemic situation during adequate therapeutic management.

To avoid variation of FDG uptake in normal brain tissue, several minutes before FDG administration and during the uptake phase of FDG (at least 20 min), patients should be positioned comfortably in a quiet, dimly lit room. They should be instructed not to speak, read or otherwise be active. It is desirable to have the cannula for i.v., administration in place 10 min before FDG administration.

Because the *L-type amino acid* transporter is an exchanging transporter the influence of plasma amino acid concentrations on the uptake of MET, FET, and IMT is complex. On the one hand, there is competitive inhibition of the transport system by natural L-amino acids, reducing radiolabeled amino acid uptake in tumor tissue. On the other hand, preloading with amino acids has been shown to increase tumor uptake of radiolabeled amino acids; the unlabeled intracellular amino acids being transported outside by the L-transporter in exchange for radiolabeled amino acids in the plasma (Lahoutte et al. 2002). For IMT, block the

thyroid gland by an adequate regimen (e.g., perchlorate 1,000 mg given at least 30 min prior to injection) to prevent possible thyroid uptake of free radioactive iodine.

Information Pertinent to Performance of the Procedure

- Patient history with particular focus on previous surgery and/or radiation therapy as well as current and past neurological or psychiatric status.
- History of diabetes, fasting state.
- Information regarding recent morphological imaging studies (CT, MRI).
- Current medication and when last taken, especially psychotropic pharmaceuticals. These may influence regional metabolic rate of glucose (rCMRGl).
- Patient's ability to lie still for 20–40 min for PET to ~1 h for SPECT.

Precautions and Conscious Sedation

- Continuous supervision of the patients during the whole scanning procedure is necessary. This is especially important for patients with tumor associated seizures.
- In uncooperative patients, it may be worthwhile to apply conscious sedation (e.g., by a short acting benzodiazepine such as i.v., midazolam). For FDG, administration should take place at least 20 min after tracer injection, preferably starting only a few minutes before data acquisition.
- Appropriate monitoring (pulse-oxymetry) should be performed to recognize the possibility of cardiopulmonary depression and appropriate antidote/emergency backup should be foreseen. Doses of sedation should be reduced in elderly patients.

Radiopharmaceutical

Radiopharmaceutical

- [^{18}F]Fluoro-2-deoxyglucose (FDG).
- 3-[^{123}I]Iodo- α -methyl-L-tyrosine (IMT).
- [Methyl- ^{11}C]-L-methionine (MET).
- O-(2-[^{18}F]Fluoroethyl)-L-tyrosine (FET).

Recommended Dosage

The dose recommendations for FDG, MET, and FET mentioned here are valid for full ring dedicated PET-cameras with BGO-crystals in 3D-mode.

- FDG: in adults, 125–250 MBq (typically 150 MBq) in 3D-mode. In children, 2–4 MBq/kg in 3D-mode with a minimum of 10 MBq in newborn infants.
- IMT: 100–400 MBq (typically 185 MBq).
- MET: 200–250 MBq.
- FET: 200–250 MBq.

The administered dose may increase using 2D-mode and vary for other systems according to differences in sensitivity. For the radiolabeled amino acids, the activity to be administered to children should be a fraction of the adult activity calculated from body weight according to the factors given by the EANM Pediatric Task Group.

Radiation Dosimetry (Table 2.1)

Radiation Dosimetry of Brain Transmission Scans

Based on transmission scans of 10 min and CT-based scans of 5–10 s, the effective doses per scan are: 20–30 μSv for Germanium-based transmission, ~20 μSv for low-dose high-speed CT, and between 220 and 450 μSv for high-quality CT.

TABLE 2.1. Radiation dosimetry of FDG, IMT, MET, and FET

	Organ receiving the largest radiation dose (mGy/MBq)	Effective dose (mSv/MBq)
FDG adults	0.17 Bladder wall	0.019
FDG children (5 years)	0.48 Bladder wall	0.050
IMT	0.047 Bladder wall	0.0073
MET	0.091 Bladder wall	0.0074
FET	0.072 Bladder wall	0.023

Calculations based on (Schmidt et al. 1997), ICRP 53 (addenda 4 and 5) and ICRP 80.

Data Acquisition

Time Delay from Injection to Beginning of Data Acquisition

- Whatever the tracer, it is recommended to use a fixed acquisition period to ensure that data are comparable between subjects and in intraindividual follow-up studies.
- FDG: the acquisition should not start earlier than 30 min p.i. Better contrast between grey and white matter as well as between tumor and normal brain tissue can be achieved with a longer time interval between FDG administration and data acquisition (e.g., 3–8 h for tumors) (Spence et al. 2004).
- IMT: 15 min p.i.
- For MET or FET, many centers start a dynamic 40 min acquisition just after tracer injection. Image from 20 to 40 p.i. is used for the clinical reading.

Set Up for Data Acquisition

Patients should void prior to acquisition for maximum comfort during the study and should be advised to void after the scan session to minimize radiation exposure. They should also be informed regarding the total acquisition time and positioned for maximum comfort. Because postprocessing routines allow correcting for minor obliquities of head orientation, patients' comfort (which reduces the probability of motion during acquisition) is more important than perfect alignment of the head. Careful

positioning of the patient's head may, however, become critical if tomographic cameras with a field of view similar to or smaller than the length of brain are used. The patient has to be informed regarding the necessity to avoid (voluntary) movements of the head and has to be asked for her/his active cooperation. If cooperation is poor sedation may be used. The patient's head should be only lightly restrained. If movement artefacts can be expected, it can be helpful to perform dynamic acquisition over the intended period of time, check the sinograms and add only the sinograms of the properly acquired time period prior to reconstruction.

FDG, MET or FET Positron Emission Tomography

- *Transmission scan.* If attenuation correction is based on transmission images, better results are generally achieved when the images are acquired before tracer injection. If additional postprocessing like segmentation is performed, the images may be obtained after injection of radiotracer. Acquisition counts collected may vary between the 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 counts over 10–20 min. In the case of PET-CT system, the CT scan can be used for the

purpose of attenuation correction. The scanning parameters may vary according to the type of CT scanner. Usually the tube voltage is set at 140 kV, which permits the conversion of the Hounsfield units into attenuation coefficients at 511 keV. The CT scan can be performed after the injection of FDG and has the advantage to significantly reduce the total scan time (usual duration is <10 s). However, the dose of 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.

- *Emission scan.* As semiquantitative estimates of tumor-to-background uptake ratios are typically used, it is recommended to use a standardized acquisition protocol with a fixed time for start of acquisition to make the data of 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 counts. For FDG, typically data are acquired over 15–30 min aiming to collect 50–200 million counts. Even though shorter acquisition times can still be used for diagnostic pattern evaluation (Chen et al. 2005), a minimum of 15 min in 3D mode is advocated. For MET and FET typically data are acquired for 20 min (20–40 min p.i.), often supplemented by dynamic data starting directly with tracer injection.

IMT Single Photon Emission Tomography

- Multiple detectors (triple or dual head) or other dedicated SPECT cameras for brain imaging should be used for acquisition. Single detector units cannot generally be recommended. They may only be used if scan time is prolonged appropriately, a dose in the upper suggested range is applied, and meticulous care is taken to produce high-quality images.
- LEHR or LEUHR parallel-hole collimators are the mostly available collimator sets for brain imaging. All purpose collimators are not suitable. The use of medium energy collimators could be advantageous; however, usually they are hampered by a low sensitivity. They may only be used if acceptable count rates are obtained. If available, collimator sets specifically adapted to the characteristics of ^{123}I may be used. Fan-beam collimators may be generally preferred over parallel-hole collimators due to the advantageous trade-off between resolution and count rate capability. The acquisition parameters are summarized in Table 2.2.

TABLE 2.2. Acquisition parameters for IMT-SPECT

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- Rotational radius: smallest possible with appropriate patient safeguard
 - Matrix: 128×128
 - Angular sampling: $\leq 3^\circ$ (360° rotation)
 - Zoom: acquisition pixel size should be 1/3–1/2 of the expected resolution; therefore it may be necessary to use a hardware zoom to achieve an appropriate pixel size
 - Acquisition mode: Step and shoot mode is predominantly used. Continuous mode acquisition may provide shorter total scan time, reduce mechanical wear to the system and improve patient comfort
 - Total scan time: depending on the imaging device, typical scan time for a triple head camera is about 30–50 min (e.g., 120 projections; 40 projections per head; 60 s/projection)
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Image Processing

PET Reconstruction

Images are reconstructed in the form of transaxial images of at least 128×128 pixels, a usual pixel size is 2–4 mm. Commonly used filters are Hanning or Shepp-Logan but they should be fine-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, may improve target-to-background ratio and are used on many recent PET and PET-CT systems.

SPECT Reconstruction

- Review of projection data: unprocessed projection data should be reviewed in cinematic display prior to filtering to assess presence and degree of motion artifacts, target-to-background ratios and other potential artifacts. Inspection of projection data in sinogram form may also be useful.
- *Reconstruction* of the entire brain volume at highest pixel resolution (i.e., one pixel thick) using filtered backprojection or iterative reconstruction.
- *Filtering*: data should be filtered in all three dimension (x,y,z). This can be achieved either by two-dimensional prefiltering the projection data or by applying a 3-dimensional postfilter to the reconstructed data. Low-Pass (e.g., Butterworth) filters should generally be used. Resolution recovery or spatially varying filters have to be used with caution, as they may produce artifacts. Therefore, the latter cannot be recommended for general use.
- *Attenuation correction*: Attenuation correction has to be performed. It could be performed either using a measured cor-

rection matrix or a calculated homogeneous correction matrix according to Chang (linear attenuation coefficient for ^{123}I : $\mu = 0.10\text{--}0.12 \text{ cm}^{-1}$). Shape contouring should be used if available. Contours should include scalp and not just grey matter. Contours should be defined for each individual transaxial slice. Correct shape and position of the contours should be reviewed prior to calculation of the corrected slices. In the case of SPECT-CT systems, the CT component of the scan can be used to perform the attenuation correction (Delbeke et al. 2006).

Reformatting of PET and SPECT Images

Transaxial slices have to be reformatted into three orthogonal planes. Generate transverse sections parallel to a given anatomic orientation (e.g., AC-PC line), assuring a high degree of standardization in plane orientation. In addition, coronal sections orthogonal to the transverse sections and correct for obliquities should be created.

Comparative Evaluation

ROI techniques need to be used to assess tumor uptake. ROI definition depends on the question to be answered (e.g., based on the area of maximal uptake or on the morphological information obtained by CT or MRI). When using quantitative criteria for image interpretation the same methods for ROI definition as described in the corresponding study in the literature should be applied.

Interpretation Criteria

Visual Interpretation

The images should be critically examined during interpretation for the presence of

movement, attenuation or camera related artefacts. Data evaluation must consider relevant morphologic information (CT, MRI). Morphologic changes should be known for the interpretation. In many cases it is recommended to fuse FDG or amino-acid images with the CT or MRI scan of the individual, especially to better delineate tumor extent or to identify accurately the metabolically most active part of a brain tumor prior to biopsy. In PET-CT or SPECT-CT systems, fused images can be immediately visualised after image reconstruction without the need of specific software for image registration. Images should be read on the computer screen rather than from hard copies, because this allows variation in color table and adjustments of background subtraction or contrast. However, inappropriate thresholding may result in artefacts and use of non-continuous color tables may overestimate findings due to abrupt color changes.

Quantification

Quantification is helpful in assisting visual interpretation and to objectify tumor uptake of FDG or labeled amino acids. Usually transverse/oblique slices are picked for ROI definition. For evaluation either only the slices with the highest lesion uptake are picked or the entire tumor volume is taken into account. Interpretation of quantitative results is based on the comparison of tumor-to-background uptake ratio. The exact threshold value depends on the tracer, the techniques used for acquisition and ROI definition, and the question to be answered. It should be compared with the corresponding studies in the literature. For example, the best cutoff level of FDG uptake ratios in the differentiation of high-grade from low-grade tumors is 1.5

for tumor-to-white matter ratios and 0.6 for tumor-to-cortex ratios (Delbeke et al. 1995). 1.8 is the best cutoff value of the IMT uptake ratio between mean uptake in a 90% isocontour tumor ROI and that in the contralateral reference region, to differentiate between gliomas from nonneoplastic lesions (Kuwert et al. 1996) as well as between recurrent tumors and benign post-therapeutic lesions (Kuwert et al. 1998). Peak tumor activity-to-contralateral reference region >1.7 after tumor resection with IMT (Weber et al. 2001) or >2.0 in patients suspicious for recurrence with MET (Van Laere et al. 2005) is of poor prognosis. When using the ratio between the mean activity in a 25 mm² tumor ROI and that in the mirror reference region, 1.6 is the best threshold value to characterize neoplastic tissue with FET (Pauleit et al. 2005).

Estimation of the rCMRglc can be performed by compartmental modelling or using graphical analytic approaches. A correction factor, the so called “lumped constant”, can be used to convert the FDG values to values reflecting glucose metabolism. Such factor is however, lower in normal brain compared to that of glioma (Spence et al. 1998), so that semiquantitative estimates of glucose metabolism such as the SUV (standardised uptake value) are typically preferred for tumor imaging. For this kind of quantification, standardised acquisition times are mandatory. A static image is sufficient, typically acquired at 30 or 60 min p.i. (after FDG has reached a plateau concentration in the lesion). In addition, the exact total dose of FDG administered and the patient’s weight and height for measurement of body surface area are required. A calibration factor is also needed. These semiquantitative estimates can be corrected for blood glucose concentration.

Reporting

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, type of examination, date of examination, radiopharmaceutical, including administered dose, glycemia for FDG, and patient history, including reasons for requesting the study.

Body of the Report

- Procedures and materials. Include in the report a brief description of the imaging procedure (i.e., type of transmission and emission imaging) and assessment of scan quality (if compromised give the reason, e.g., motion artifacts etc.). If sedation is performed, briefly describe the procedure, including type and time of medication given in relation to the radiotracer injection.
- Findings. Describe whether the FDG or amino acid imaging finding is normal or abnormal. If findings are abnormal, describe the location and intensity of abnormal radiotracer uptake. State what criteria were used for interpretation (visual assessment or semiquantitative measures).
- Limitations. Where appropriate, identify factors that can limit the sensitivity and specificity of the examination (i.e., movement, small lesions).
- Clinical issues. The report should address or answer any pertinent clinical issues raised in the request for the imaging examination.
- Comparative data. Results of morphological imaging modalities (CT, MRI) are essential for interpretation. Every

attempt should be made to obtain the images of these studies and not only the written interpretation for comparison with the PET or SPECT studies. Comparisons with these imaging modalities, previous examinations with radiolabeled amino acids or FDG-PET (if available), should be part of the report.

Interpretation and Conclusion

A precise diagnosis should be given whenever possible. Interpretation should be based on the results of the visual and more important quantitative evaluation and conclude on whether an abnormal FDG or radiolabeled amino acid brain uptake is visualized (e.g., its extent and characteristics such as inhomogeneity) keeping in mind the potential sources of error (see Table 2.3). When appropriate, follow-up or additional studies should be recommended to clarify or confirm the suspected diagnosis.

TABLE 2.3. Sources of error (see also Cook et al. 1999)

- Artifacts (patient movement, camera related, induced by inappropriate processing)
- No or insufficient attenuation correction
- Physiologic MET uptake in the pituitary gland, contrasting with that of IMT, and sometimes in choroids plexus
- Small regional differences of normal brain uptake in normal brain emphasizing the careful choice of an appropriate reference region
- False-negative results for radiolabeled amino acids in ~20% of untreated low-grade gliomas, especially those poorly vascularized. False-negative results are, however, very rare in pretreated recurrent low-grade gliomas
- High tumor uptake does not always indicate high-grade glioma (oligodendroglioma, low-grade desmoplastic infantile ganglioglioma, pilocytic astrocytoma)
- Mild uptake of radiolabeled amino acids can be observed in brain hematoma or close to surgery and/or radiation therapy, brain abscess, acute or subacute ischemic lesions, apparently in postischemic hyperperfusion areas, or focal cortical dysplasia
- Soft tissue or skull uptake following surgery in the area of the skull or brain
- Recent radio- or chemotherapy

ISSUES REQUIRING FURTHER CLARIFICATION

In clinical diagnostic settings, the exact role of partial volume correction methods or of attenuation correction with MRI need to be further evaluated. The clinical impact of image fusion for planning stereotaxic surgery or radiotherapy (e.g., gamma-knife), especially for the treatment of patient with suspected recurrences, also requires further clarification. Other ^{18}F -labeled amino acid analogues for brain tumor imaging are currently under development. Among them FDOPA is the most studied. When proofs of its clinical utility accumulate, FDOPA could be another tracer to include in an amended version of the guidelines.

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