EANM Procedure Guidelines for Brain Tumour Imaging using Labelled Amino Acid Analogues

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I. Purpose

These guidelines summarize the views of the European Association of Nuclear Medicine Neuroimaging Committee (ENC). The purpose of the guidelines is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of radiolabelled amino acid analogues PET or SPET imaging of brain tumours. Aim is to help in achieving a high quality standard of tumour imaging using radiolabelled amino acids, which allows increasing the diagnostic impact of this technique in neuro-oncological practice.

The present document has been inspired by a review of the literature and the individual experience of experts in European countries. The guideline intends to present information specifically adapted to the European practice. The information provided should be taken in the context of local conditions and regulations.

II. Background information and definitions

Increased amino acid transport in brain tumour cells results from overexpression of the transporter systems and is related to alterations in the tumour vasculature and tumour cell proliferation. Radiolabelled amino acids offer significant improvement in the diagnostic evaluation of cerebral tumours in comparison with conventional anatomical imaging. They also display contrast by far superior to that obtained with FDG because of the low uptake of amino acids in normal brain tissue and they might be more tumour specific, as their uptake is less influenced by inflammation (1).
The most frequently used radiolabelled amino acid is [methyl-^{11}C]-L-methionine (MET) used in conjunction with PET. 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 acids have been developed. These agents include 3-[^{123}I]iodo-α-methyl-L-tyrosine (IMT) for SPET and *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) for PET, which are transported by the same specific amino acid transport system L as MET, but are not incorporated into proteins (2). Their rapid accumulation into brain tumours is independend of blood-brain barrier disruption. Among the ^{18}F-labelled amino-acids, FET has been selected as representative of this category due to ease of synthesis, high *in vivo* stability, and fast brain and tumour uptake kinetics (3). Other natural or artificial amino acids have been labelled to measure tumour

metabolism; 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 tumours supporting their parallel review in these guidelines.

III. Common indications

Indications

A. Detection of viable tumour tissue. CT and MRI cannot reliably differentiate viable tumour tissue from treatment-induced non-neoplastic changes, such as oedema, postoperative changes or radiation necrosis. Radiolabelled amino acid imaging is superior to FDG-PET in confirming low-grade recurrence.

B. Tumour delineation. Radiolabelled amino acid tracers are superior to computed tomography and magnetic resonance imaging for estimation of true tumour extension in low as well as in high-grade gliomas (4). In low grade tumours, oedema surrounding the tumour cannot be differentiated from tumour cell infiltration by MRI or CT. In anaplastic astrocytomas and glioblastomas, too, the area of contrast enhancement does not reflect tumour extent correctly. Radiolabelled amino acid tracers are also superior to FDG for tumour delination in low-grade tumours, for which FDG uptake is found to be decreased compared with normal cortex or basal ganglia. The higher ratio for labelled 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 tumour glucose rate. With FET however, large brain vessels might be visualised as blood pool radioactivity which exceeds radioactivity in the normal brain tissue (5).

C. 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 behaviour of brain tumours and thus the patient's prognosis. Labelled amino acids imaging is recommended to guide the stereotactic biopsy (6).

D. Non-invasive tumour grading. The role of labelled amino acids in the grading of cerebral gliomas is controversial and FDG-PET appears better suited to differentiate between tumour grades (7). MET and IMT uptake tends to correlate with cell proliferative activity and MET uptake with microvessel density (8). Radiolabelled amino acid imaging may aid in differentiating high-grade gliomas from histologically benign brain tumours or non-neoplastic lesions. The intensity of MET uptake may represent a prognostic factor for WHO Grade II and III tumours considered separately. Oligodendroglioma and oligo-astrocytoma could have greater uptake than high-grade gliomas (9).

E. Therapy planning. In conjunction with anatomical imaging, radiolabelled amino acid imaging may be used to better define the tumour volume to resect or irradiate (10).

F. Tumour response. Labelled amino acid uptake changes may predict the response to locoregional chemo- and radiotherapy as it may allow early detection of residual tumour after surgery.

Contraindications

A. Pregnancy (mothers should interrupt breast feeding for 24 hrs if PET is indicated; no data are available for IMT)

B. Evident lack/unability of cooperation

IV. Procedure

A. Patient preparation

A.1. Pre-arrival
Patients should be informed of the procedure to fully cooperate.

A.2. Pre-injection

A.2.1. Patient should be fasting for more than 4 hours to ensure stable metabolic conditions. Since 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 one hand, there is competitive inhibition of the transport system by natural L-amino acids, reducing radiolabelled amino acid uptake in tumour tissue. On the other hand, pre-loading with amino acids has been shown to increase tumour uptake of radiolabelled amino acids; the unlabelled intracellular amino acids being transported outside by the L-transporter in exchange for radiolabelled amino acids in the plasma (11).

A.2.2. For IMT, block the thyroid gland by an adequate regimen (e.g. perchlorate 1000 mg given at least 30 min prior to injection) to prevent possible thyroid uptake of free radioactive iodine.

A.2.3. Before starting the scanning procedure patients should void the bladder for maximum comfort during the study. Advise the patient to void again after the scanning session to minimize radiation exposure.

B. Information pertinent to performing the procedure

- Patient history with particular focus on previous surgery and/or radiation therapy as well as current and past neurological or psychiatric status.

- Patient's ability to lie still for 20 min for PET to 1 hr for SPET. If sedation is necessary, it should be given earliest one hour prior to the acquisition.

- Information about morphologic imaging studies (CT, MRI).

C. Precautions

Continous supervision of the patients during the whole scanning procedure is necessary. This is especially important for patients with tumour associated seizures.

D. Radiopharmaceutical

D.1. Radiopharmaceuticals
- 3-[^{123}I]Iodo-α-methyl-L-tyrosine (IMT)
- [Methyl-^{11}C]-L-methionine (MET)
- *O*-(2-[^{18}F]Fluoroethyl)-L-tyrosine (FET)

D.2. Preparation of the radiopharmaceuticals
Radiopharmaceuticals will be delivered ready to use.

D.3. Quality control check
Check for radiochemical purity and other parameters of quality assessment as recommended.

D.4. Dose in adults
- IMT: 100-400 MBq (typically 185 MBq)
- MET: 200-250 MBq
- FET: 200-250 MBq

The dose recommendations for MET and FET mentioned here are valid for full ring dedicated PET-cameras with BGO-crystals in 3D-mode. The administered dose may increase using 2D-mode and vary for other systems according to differences in sensitivity. 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 Paediatric Task Group.

D.5. Radiation dosimetry in adults

	Organ receiving the largest radiation dose mGy/MBq	**Effective dose equivalent mSv/MBq**
IMT	0.047 bladder wall	0.0073
MET	0.027 bladder wall	0.0052
FET	0.060 bladder wall	0.0165

Data are taken from the literature (5,12,13).

E. Data acquisition

E.1. Time delay from injection to begin of data acquisition

- IMT: 15 min p.i.
- Many centers start a (dynamic) 40 min acquisition just after MET or FET injection. Image from 20 to 40 p.i. is used for the clinical reading.
- It is recommended to use a fixed acquisition period to ensure that data are comparable between subjects and in intraindividual follow-up studies.

E.2. Set up for data acquisition

E.2.1. Positioning of the patient

- Patients should void prior to acquisition for maximum comfort during the study. Advice patients to void after the scan session to minimize radiation exposure.

- Patients should be informed about the total acquisition time and positioned for maximum comfort. Since 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. The patient has to be informed about 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. It is not recommended to rigidly fix the head in place.

- If movement artefacts can be expected, segmentation of data acquisition into multiple sequential acquisitions may permit to exclude bad data, e.g. remove segments of projection data with patient motion.

E.2.2. MET or FET positron emission tomography

- Acquisition parameters for MET and FET imaging of the brain with dedicated PET scanners

- *Transmission scan.* If attenuation correction is based on transmission images, better results are generally achieved when the images are acquired before MET of FET 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 to 20 min.

- *Emission scan.* As semiquantitative estimates of amino acid uptake tumour-to-background 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.

E.2.3. IMT single photon emission tomography

- Multiple detectors (triple or dual head) or other dedicated SPET 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.

- Acquisition parameters
  - Rotational radius: smallest possible with appropriate patient safeguard
  - Matrix: 128 x 128
  - Angular sampling: $\leq$ 3° (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 to 50 min (e.g. 120 projections; 40 projections per head; 60 sec/projection)

F. Interventions

Usually no interventions are performed.

G. Image processing

G.1. PET reconstruction

- Processing images acquired with dedicated PET scanners

- Images are reconstructed in the form of transaxial 128 x 128 pixel images, a usual pixel size is 2-4 mm. Depending on the resolution of the PET system a final image resolution of 5-8 mm FWHM typically yields images of adequate resolution and noise. Commonly used filters are Hanning or Shepp-Logan.

G.2. SPET reconstruction

G.2.1. 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.

G.2.2 Reconstruction

- methods: filtered backprojection and iterative reconstruction
- make sure to reconstruct the entire brain volume
- reconstruct data at highest pixel resolution, i.e. one pixel thick

G.2.3. Filtering

- Data should be filtered in all 3 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.

G.2.4. Attenuation correction

- Attenuation correction has to be performed mandatory.
- Methods
  - Use of a calculated homogeneous correction matrix according to Chang (linear attenuation coefficient for ^{123}I: $\mu = 0.10 - 0.12$ 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.

  - Use of a measured correction matrix e.g. from a simultaneously assessed transmission scan or from a CT scan

G.3. Reformatting of PET and SPET images

- Transaxial slices have to be reformatted into 3 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 create coronal sections orthogonal to the transverse sections and correct for obliquities.

G.4. Comparative evaluation

- ROI techniques have to be used to assess tumour 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.

H. Interpretation criteria

H.1. Visual interpretation

- The images should be critically examined during interpretation for 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 amino-acid images with the CT or MRI scan of the individual, especially to better delineate tumour extent or to identify accurately the metabolically most active part of a brain tumour prior to biopsy.

- Images should be read on the computer screen rather than from hard copies, because this allows variation in colour 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.

H.2. Quantification

- Quantification is helpful in assisting visual interpretation and to objectivize tumour uptake of labelled 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 tumour volume is taken into account.

- Interpretation of quantitative results is based on the comparison of tumour-to-background uptake ratio. The exact threshold value depends on the tracer, the techniques used for ROI definition and the question to be answered. It should be compared with the corresponding studies in the literature. For example, 1.8 is the best cutoff value of the IMT uptake ratio between mean uptake in a 90% isocontour tumour ROI and that in the contralateral reference region, to differentiate between gliomas from non-neoplastic lesions (14) as well as between recurrent tumours and benign postherapeutic lesions (15). Peak tumour activity-to-contralateral reference region greater than 1.7 after tumour resection with IMT (16) or greater than 2.0 in patients suspicious for recurrence with MET (17) is of poor prognosis. When using the ratio between the mean activity in a 25 mm^2 tumour ROI and that in the mirror reference region, 1.6 is the best threshold value to characterize neoplastic tissue with FET (18).

I. Reporting

I.1. General

Reports should include all pertinent information, including name of patient and other identifiers, such as birthdate; name of the referring physician(s); type and date of examination; radiopharmaceutical including the administered activity; patient history, including the reason for requesting the study.

I.2. Body of the report

I.2.1. Procedures and materials

- Include in the report a brief description of the imaging procedure 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.

I.2.2. Findings

Describe whether the 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).

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

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 radiolabelled amino acids or other functional imaging techniques such as FDG-PET (if available), have to be part of the report.

I.3. Interpretation and conclusion

I.3.1. Precise diagnosis should be given whenever possible.

I.3.2. Interpretation should be based on the results of the visual and more important quantitative evaluation and conclude on

- whether an abnormal radiolabelled amino acid brain uptake is visualised.
- its extent and characteristics (e.g. inhomogeneity)

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 TGQA&C of the EANM

K. Sources of error

- 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 (19)
- Small regional differences of normal brain uptake in normal brain emphasizing the careful choice of an appropriate reference region
- False negative results in approximately 20% of untreated low-grade gliomas, especially those poorly vascularized. False negative results are however very rare in pretreated recurrent low-grade gliomas
- High tumour uptake does not always indicate high-grade glioma (oligodendroglioma, low-grade desmoplastic infantile ganglioglioma, pilocytic astrocytoma)
- Mild uptake of radiolabelled amino acids can be observed in brain hematoma or close to surgery and/or radiation therapy
- Brain abcess
- Acute or subacute ischemic lesions, apparently in postichemic hyperperfusion areas
- Focal cortical dysplasia

V. Issues requiring further clarification

Measured versus calculated transmission for attenuation correction (e.g. role of PET-CT)

Image fusion for planning stereotaxic surgery or radiotherapy (e.g. gamma-knife), especially for the treatment of patient with suspected recurrences

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VII. Disclaimer

The European Association has written and approved guidelines to promote the use of nuclear medicine procedures with high quality. These general recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures and exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be different than a spectrum usually seen in a more general setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition resources available to care for patients may vary greatly from one European country or one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

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Version III

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