

EANM procedure guideline for brain perfusion SPECT using ^{99m}Tc -labelled radiopharmaceuticals, 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 when making recommendations, performing, interpreting, and reporting the results of brain perfusion single photon emission computed tomography (SPECT) studies using ^{99m}Tc -labelled radiopharmaceuticals. The aim is to achieve a high quality standard for brain perfusion SPECT imaging, which will increase the diagnostic impact of this technique in clinical practice. The present document replaces a former version of the guideline published in 2001 which was

inspired by the Society of Nuclear Medicine Procedure Guideline for Brain Perfusion SPECT [1], the views of the Society of Nuclear Medicine Brain Imaging Council [2], and the individual experience of experts in European countries. The guidelines are intended to present information specifically adapted to European practice. The information provided should be taken in the context of local conditions and regulations.

Keywords Brain · Perfusion · SPECT · HMPAO · ECD · Epilepsy · Dementia

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Background and definitions

SPECT is a technique that produces tomographic images of the three-dimensional distribution of a radiopharmaceutical. Applied to the brain, this technique can be used to measure regional cerebral perfusion.

There are three physiological properties that radiopharmaceuticals must have to be useful for the measurement of brain perfusion by SPECT: they must cross the blood–brain barrier; their extraction must approximate unity and be independent of blood flow so that their initial distribution will be proportional to regional cerebral blood flow (rCBF); and they must be retained within the brain in their initial distribution long enough for diagnostic tomographic images to be obtained [3]. Ideally, tracer uptake should show no redistribution, so that the initial tracer uptake, reflecting rCBF at a fast time window after injection, remains almost unchanged for several hours. This frozen image is then independent of rCBF variations occurring after the fixation time.

Several radiopharmaceuticals are commercially available for brain perfusion SPECT. In Europe, the most widely used radiopharmaceuticals for rCBF SPECT are ^{99m}Tc-labelled compounds, ethyl cysteine dimer (ECD, Neurolite) and hexamethyl propylene amine oxime (HMPAO, Ceretec). Differences between the two commercially available radiopharmaceuticals, ECD and HMPAO include in vitro stability, uptake mechanism, cerebral distribution [4] and dosimetry. In normal brain tissue, the kinetic properties of the two agents are very similar. They enter the brain cells due to their lipophilic nature and remain there due to conversion into hydrophilic compounds. For ECD retention, de-esterification is the crucial reaction leading to hydrophilic conversion, while for HMPAO, instability of the lipophilic form and glutathione interaction have been proposed. Differences in the retention mechanisms may account for some different behaviour of the tracers in specific disorders such as subacute stroke, where ECD distribution seems to reflect metabolic activity more closely, whereas HMPAO is better correlated with cerebral perfusion [5]. As a consequence, both tracers can be used, but they are not interchangeable.

It has to be kept in mind that with the techniques used in clinical practice, ECD and HMPAO SPECT do not provide absolute quantitative flow values but rather estimate relative regional flow differences based on the comparison of count density ratios between various regions (e.g. right/left asymmetries, ratio in relation to reference regions, etc.).

This guideline deals with the indications, assessment, processing, interpretation and reporting of brain perfusion

SPECT using the commercially available ^{99m}Tc-labelled radiopharmaceuticals ECD and HMPAO.

Indications

A. Common indications

A.1. Evaluation of cerebrovascular disease [6]:

- Acute stroke: Perfusion SPECT provides valuable information in acute stroke with respect to complications, outcome or choice of treatment strategy [7, 8].
- Chronic ischaemia: In chronic cerebrovascular disease rCBF SPECT with assessment of functional reserve capacity (using cerebrovascular dilator challenge) may guide decisions regarding vascular surgery [9–11].
- Preoperative evaluation (e.g. during temporary balloon occlusion) for potential ischaemia following carotid artery sacrifice [12].

A.2. Presurgical lateralization and localization of epileptogenic foci. Ictal SPECT studies (preferably complemented by interictal investigations) are indicated in temporal and extratemporal focal epilepsies for localisation of foci prior to epileptic surgery [13–17].

A.3. Evaluation of suspected dementia. Indications include the early detection and differential diagnosis of various forms of dementia [18], such as Alzheimer's disease [19], Lewy body dementia [20], Parkinson's disease with dementia [21], vascular dementia [22], and frontotemporal dementia [23]. In the pre-dementia phase of these diseases, known as mild cognitive impairment, SPECT can detect a functional deficit and thus guide prognosis [24].

A.4. Evaluation of traumatic brain injury. SPECT has shown perfusion abnormalities in traumatic brain injury despite normal morphology, and results are considered to have a prognostic value for persistence of neuropsychological sequelae [25].

A.5. Evaluation of suspected inflammation. Perfusion SPECT may be indicated and provide helpful information in progressive inflammatory disorders (e.g. Rasmussen's syndrome) [26], viral encephalitis (e.g. herpes simplex encephalitis) [27], vasculitis (e.g. systemic lupus erythematosus, Behçet's disease) [28,29], and HIV-encephalopathy [30].

A.6. Assessment of brain death. Scintigraphic assessment of arrest of cerebral perfusion (even in

planar technique; specific acquisition modes may apply) is an accurate technique to confirm brain death [31]. Besides the common indications mentioned here, brain perfusion SPECT can be useful in other indications such as movement disorders (differential diagnosis of parkinsonism) and psychiatric diseases (e.g. for follow-up of depression) [32].

B. Contraindications

- Pregnancy.
- Breast feeding: mothers should interrupt breast feeding for 24 h if SPECT is indicated.
- Lack of cooperation, or inability to cooperate, with procedure.

Procedure

A. Patient preparation

A.1. Prearrival

Prior to the investigation patients should preferably avoid excessive stimulants (such as caffeine, cola, and energy drinks), alcohol, smoking, and any drugs known to affect cerebral blood flow. It may be necessary to discuss drug withdrawal with the clinician caring for the patient.

A.2. Preinjection

Check and ensure that the patient is able to cooperate during the investigation.

Achieve a stable environment at the time of injection and the uptake period.

- Place the patient in a quiet, dimly-lit room.
- Place an intravenous cannula 10 to 15 min prior to injection.
- Position the patient in a comfortable (preferably supine) position.
- Instruct the patient to keep the eyes open (or use an eye-mask) and keep the ears unplugged.
- Instruct the patient not to speak, read, or move from at least 5 min before to 5 min after injection.
- Do not interact with the patient from at least 5 min before to 5 min after injection.
- Record carefully any event that might influence rCBF during drug delivery (e.g. patient motion, talking, etc.).

It is advised to maintain the same environment for all perfusion studies in the same centre.

Assess the ability of the patient to lie still for approximately 30 to 60 min:

- 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. by a short-acting benzodiazepine, such as intravenous midazolam). The sedative medication should be administered at least 5 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 backup should be available. The doses of sedative medication should be reduced in elderly patients.

B. Information pertinent to performing rCBF SPECT studies

- Patient history with particular focus on neurological and psychiatric disorders, current neurological and psychiatric status, previous surgery, radiation, or trauma to the brain.
- Information about (recent) morphological imaging studies (CT, MRI).
- Information about (recent) brain functional studies (EEG, functional/perfusion MRI, SPECT/PET).
- Current medication, and when last taken.

C. Precautions

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

D. Radiopharmaceutical

D.1. Radionuclide

Technetium-99m.

D.2. Pharmaceutical

- ECD.
- HMPAO stabilized, or if not available, in unstabilized form.

D.3. Preparation of the radiopharmaceutical

- Use pertechnetate from generators which have been eluted within the last 24 h.

- Use fresh generator eluates not older than 2 h, particularly for HMPAO.
- For HMPAO: inject the tracer no sooner than 10 min after radioligand reconstitution.

D.4. Quality control

Radiochemical purity should be determined on each vial prior to injection using the methods outlined in the package inserts. It should be >90% for ECD and >80% for HMPAO.

D.5. Time interval for injection

Inject the radiopharmaceuticals after quality control check, but not later than 30 min after reconstitution for unstabilized ^{99m}Tc -HMPAO, 4 h for stabilized ^{99m}Tc -HMPAO, and 6 h for ^{99m}Tc -ECD.

D.6. Administered activity

- *Adults*: 555–1110 MBq (typically 740 MBq) of either radiopharmaceutical.
- *Children*: see EANM paediatric dosage card table (v. 1.5.2008):
 - For ECD: “baseline activity”=32 MBq (minimum recommended activity=110 MBq).
 - For HMPAO: “baseline activity”=51.8 MBq (minimum recommended activity=110 MBq)
 - Administered activity=“baseline activity” × multiple (from dosage card).

D.7. Radiation dosimetry

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

Table 1 Radiation dosimetry

	Organ receiving the largest radiation dose		Effective dose (mSv/MBq)
	Organ	Dose (mGy/MBq)	
Adults			
^{99m}Tc -ECD ^a	Bladder	0.05	0.0077
^{99m}Tc -HMPAO ^b	Kidney	0.034	0.0093
Children (≥5 years)			
^{99m}Tc -ECD ^a	Bladder	0.11	0.022
^{99m}Tc -HMPAO ^b	Thyroid	0.14	0.027

^a ICRP 106, page 107

^b ICRP 80, page 100

E. Data acquisition

E.1. Time from injection to start of data acquisition

- Try always to keep the same time delay from injection to the start of data acquisition.
- ^{99m}Tc -ECD: For best image quality allow a delay of 30–60 min since wash-out from non-specific uptake improves the signal to noise ratio in this period.
- ^{99m}Tc -HMPAO: For best image quality allow a delay of 30–90 min [33].
- Imaging should be completed within 4 h after injection. Excessive delay should be avoided because of radioactive decay.

E.2. Set-up for data acquisition

E.2.1. Positioning of the patient:

- The patient should void prior to acquisition for maximum comfort during the study. The patient should be advised to void again after the acquisition to help reduce radiation exposure.
- The patient should be informed about the total acquisition time and positioned for maximum comfort. Since postprocessing routines allow correction of minor obliquities of head orientation, the patient's comfort (which reduces the probability of motion during acquisition) is more important than perfect alignment of the head. The patient should be told of the necessity to avoid (voluntary) movements of the head and 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.

E.2.2. Imaging devices:

- Multiple detector (triple or dual head) or other dedicated small to medium field of view SPECT cameras for brain imaging should be used for acquisition since these devices generally produce results superior to those obtained with single-head cameras.
- Single-detector units may only be used if the scan time is prolonged appropriately (so as to reach at least 5 million total detected events) and meticulous care is taken to produce high-quality images.

- LEHR or LEUHR parallel-hole collimators are the most readily available collimator sets for brain imaging. They may be used if acceptable count rates are obtained. All-purpose collimators are not suitable. As a general rule of thumb, use the highest resolution collimation available. Fan-beam collimators are generally preferred over parallel-hole collimators due to the advantageous trade-off between resolution and sensitivity. In case of fanbeam collimators, ascertain that the whole head is in the field-of-view, especially the cerebellum.
- Acquisition parameters:
 - *Rotational radius*: smallest possible for parallel-beam collimators, with appropriate patient safeguards. A radius less than 15 cm ensures best image quality. Avoid circulating around the shoulders.
 - *Matrix*: 128×128 (or higher).
 - *Angular sampling*: 3° (360° rotation).
 - *Zoom*: acquisition pixel size should be one-third to one-half 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 times, improve patient comfort and reduce mechanical wear of the system.
 - *Total detected events*: >5 million (without scatter correction).
 - *Total scan time*: depending on the imaging device, typical scan time for triple head cameras is around 20–25 min (e.g. 120 projections, 40 projections per head, 20–25 s/projection); for dual head cameras it is closer to 30 min (e.g. 120 projections, 60 projections per head, 30 s/projection).
 - Segmentation of data acquisition into multiple sequential acquisitions (e.g. 6×5 min) may permit exclusion of bad data, e.g. remove segments of projection data with patient motion.

F. Interventions

F.1. Vasodilatory challenge

The following recommendations are focused on acetazolamide (Diamox™). Acetazolamide is a carboanhydrase-

inhibitor and leads to an increase in rCBF in normal cerebral vessels via dilatation.

F.1.1. Indications: Evaluation of cerebrovascular reserve in TIA, completed stroke, carotid artery stenosis or occlusion, vascular anomalies, and evaluation of the results of carotid surgery, preoperative evaluation of need for selective carotid shunting during carotid endarterectomy [5, 9], evaluation of cerebrovascular reserve before and after cerebrovascular surgery or stent placement [10, 11]. Furthermore, it may be used to aid in distinguishing vascular from neuronal causes of dementia.

F.1.2. Contraindications:

- Known sulfa allergy.
- Use of acetazolamide is not recommended within 3 days of an acute stroke and recent intracranial haemorrhage.
- Use of acetazolamide may provoke migraine in patients with a history of migraine (relative contraindication).
- Caution should be applied in renal and hepatic insufficiency.

F.1.3. Acetazolamide dosage and properties:

- Dosage:
 - *Adults*: 1000 mg by slow intravenous push.
 - *Children*: 14 mg/kg body weight.
- Acetazolamide is a diuretic (patients should void prior to acquisition).
- Adverse effects: mild vertigo, tinnitus, (perioral) paraesthesia and, rarely, nausea. In general these effects are self-limited and do not require specific treatment. Postural hypotension may also occur.
- Since the diagnostic use for vasodilatory challenge in SPECT is not reported in the information sheet of acetazolamide, according to local laws it may be necessary to obtain specific consent to perform the acetazolamide test.

F.1.4. Study protocols:

- Since the vasodilatory effect is most pronounced around 15 to 20 min after injection of acetazolamide, the radiopharmaceutical should be injected within this narrow time frame.
- Various protocols have been used to study rCBF under baseline condition and acetazolamide provocation. The 2-day repeat study technique is simplest and therefore preferable (allow sufficient time between the investigations for residual activity to clear, e.g. 24–48 h). Either test,

baseline or challenge, may be performed first. A “challenge first” approach may be favoured since, if it is normal, the baseline study can be omitted. On the other hand, performing the baseline study prior to the challenge study can be advantageous if large perfusion defects are present, suggesting caution during the challenge procedure.

- One-day protocols using split-dose techniques (second dose at least twice the first dose) require more sophisticated evaluation and data processing, and are therefore less favoured in general practice.

F.2. Focal epilepsy

- Ictal SPECT studies

The tracer should be injected as soon as possible after seizure onset (via an intravenous line placed previously). It is recommended that prepared syringes be stored in the epilepsy monitoring unit to ensure the quickest possible injection time. Patients should have continuous video-EEG monitoring in order to relate the injection time exactly to the time point of behavioural and electrical seizure onset and end.

- Interictal SPECT studies

The conditions for tracer injection are as outlined above, but additionally continuous EEG monitoring should be performed from at least 2 h before until 15 min after injection to exclude the possibility that seizures occurred shortly before and during the uptake period of the radiopharmaceuticals. Interictal studies may add useful information to ictal studies. However, these cannot be recommended as a sole diagnostic procedure for focus detection.

G. Image processing

G.1. Review of projection data

Unprocessed projection data should be reviewed in cinematic display prior to filtering to assess the presence and degree of motion artefacts, target-to-background ratios and other potential artefacts. Inspection of projection data in sinogram form may also be useful.

G.2. Reconstruction

- Methods:
 - Filtered back-projection.
 - Iterative reconstruction. Iterative reconstruction methods, including ordered-subset expectation maximization (OSEM) are currently available, and may improve lesion detection accuracy.

- Ensure that the entire brain volume is reconstructed.
- Reconstruct data at the highest pixel resolution, i.e. one-pixel slice thickness.

G.3. Postreconstruction filtering

- Data should be filtered in all three dimension (x,y,z).
- Low-pass (e.g. Butterworth) filters should generally be used. The cut-off and order depend on application, injected activity, camera and acquisition type, and even physician preference (diagnostic reporting sensitivity). Resolution recovery or spatially varying filters have to be used with caution, as they may produce artefacts. Therefore the latter cannot be recommended for general use.

G.4. Attenuation correction

- Attenuation correction is recommended and should be performed in all cases.
- Methods:
 - Use of a calculated homogeneous correction matrix according to Chang (attenuation coefficient for ^{99m}Tc : $\mu=0.12\text{--}0.14\text{ cm}^{-1}$, depending on the application of scatter correction where higher coefficients should be used). Phantom experiments with a realistic head phantom (e.g. Alderson phantom) including cranial bone are recommended to find the optimal value. 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 or sequentially assessed transmission scan or from a CT scan (e.g. in SPECT/CT scanners).

G.5. Scatter correction

Scatter correction results in better signal to noise ratios and more accurate lesion detection, and is advocated. Various methods for scatter correction are available commercially. The most popular (triple energy window correction) requires data acquisition with a lower and upper scatter window on either side of the ^{99m}Tc photopeak.

G.6. Reformatting

- Transaxial slices should be reformatted into at least three orthogonal planes. Transverse sections are

generated parallel to a given anatomic orientation (e.g. AC-PC line) ensuring a high degree of standardization in plane orientation. Coronal and sagittal sections are created orthogonal to the transverse sections.

- Depending on the indication, views other than standard reorientation may be helpful, e.g. sections parallel to the long axis of the temporal lobe in the evaluation of epilepsy and Alzheimer's disease.
- Three-dimensional display of the dataset (e.g. by volume rendering or surface projections such as 3D-SSP) may 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.7. Semiquantitative evaluation

- Region of interest techniques may be used to compare regional blood flow abnormalities with the rCBF of corresponding structures in the contralateral hemisphere or other reference regions (e.g. cerebellum, hemisphere, total brain).
- If intraindividual comparison is performed (i.e. ictal vs. interictal, baseline vs. acetazolamide, baseline vs. follow-up for therapy control or assessment of disease progression) standardized evaluation is most useful.
- If data from age-matched normal controls are available for comparison, the use of analytical approaches based on stereotactic normalization and statistical subtraction is recommended in order to determine abnormalities of rCBF in an observer-independent way [34] (see section H.2.).

H. Interpretation criteria

H.1. Visual interpretation

- 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. The same colour table should be used for all patients.
- Data interpretation must consider relevant structural information (CT, MRI). Specific attention should be paid to the extent of perfusion abnormalities relative to the observed morphological defects and take into account possible effects of atrophy and partial volume. When available, image fusion may be helpful to further

substantiate rCBF changes in relation to structural observations. The exact role of partial volume effect correction methods in clinical diagnostic settings needs to be further evaluated.

H.2. Postprocessing objective analysis

Quantification in terms of deviations of normal values or semiquantitatively assessing changes in follow-up studies, is helpful in assisting visual interpretation. Three general forms of image analysis are [5]:

- Region of interest analysis: ROI techniques may be used to compare regional blood flow abnormalities with the rCBF of corresponding structures in the contralateral hemisphere or other reference regions (e.g. cerebellum, hemisphere, total brain).
- Spatial normalization, comparison to normal databases and voxel-based analysis.
 - For assessment of normality, it is desirable to have a normal (age-matched) database available with the same radiopharmaceutical (ECD or HMPAO), processed in the same way as patient studies (reconstruction, filtering, attenuation and scatter correction), and preferably studied with the same type of camera. Such comparison allows assessment of normal variability of rCBF and may help to avoid overinterpretation of the patient data.
 - Possible analysis methods include 3-D surface projection algorithms, which are useful in cortical disease (several commercially available packages exist), or voxel-base statistical mapping such as SPM (statistical parametric mapping) [35, 36].
 - These methods allow an objective analysis of individual patient data compared to a normal database. Added sensitivity and specificity should be considered in choosing the appropriate method, depending on the clinical setting.
- Subtraction analysis (after image count normalization to an appropriate reference region or the whole brain) provides a tool for subtracting an activation study from a baseline study. SISCOM (subtraction ictal SPECT coregistered to MRI) is frequently used in ictal/interictal analysis of epilepsy patients [37, 38].

I. Reporting

I.1. General

Reports should include all pertinent information, including the name of the patient and other identifiers, such as birth

date, name of the referring physician(s), type and date of examination, type of equipment, radiopharmaceutical including the administered activity, and patient history, including the reason for requesting the study and potentially interfering medications.

I.2. Body of the report

I.2.1. Procedures and materials:

- Include in the report a brief description of the imaging procedure (including the type of attenuation/scatter correction used), and assessment of scan quality (if compromised give the reason, e.g. motion artefacts, etc.)
- If sedation is performed, briefly describe the procedure including type and time of medication given in relation to the radiotracer injection.
- If interventions are performed briefly describe the protocol applied.

I.2.2. Findings: Describe whether the SPECT pattern is normal or not. If findings are abnormal, describe the location and intensity of abnormal tracer uptake. Functional topography (i.e. based on Brodmann areas) as well as anatomic descriptions can be used to precisely describe the location. Vascular topography (e.g. use of vascular atlases) may be appropriate in assessment of vascular disease. State what criteria were used for interpretation (visual assessment, quantitative or semiquantitative measures, comparison with normal database, etc.).

I.2.3. Limitations: Where appropriate, identify factors that could have limited the sensitivity and specificity of the result 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. Results of morphological imaging modalities (CT, MRI), and if available, image fusion should also be taken into account for interpretation.

I.3. Interpretation and conclusions

To the extent possible, provide a (differential) diagnosis based on generally accepted disease-specific patterns. Any interpretation not based on such criteria has to be explicitly stated as subjective and considered as hypothetical. 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.
- Artefacts (patient movement, camera-related, induced by inappropriate processing).
- Interference with drugs acting on cerebral blood flow.
- Normal variability.
- Level of contrast and background subtraction.
- Inappropriate thresholding may result in artefacts. Thresholding, if used, must be based upon knowledge of a normal database for specific radiopharmaceuticals and set-up.
- Colour table: Use of noncontinuous colour tables may overestimate findings due to abrupt colour changes.

Technological developments

New SPECT technologies are being developed that significantly improve the detection efficiency and spatial resolution of radionuclide imaging for small organs including the brain, and therefore may provide new capabilities for SPECT/CT imaging. MRI/SPECT image registration and fusion methods are extremely useful for overcoming the problems of the imprecise anatomical landmarks and low spatial resolution of SPECT images [39, 40].

Issues requiring further clarification

- Normal database issues.
- Quantification techniques.

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Disclaimer This guideline summarizes the views of the Neuroimaging Committee of the EANM and reflects 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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