

Updated Procedure Guideline of the German Society of Nuclear Medicine for Amyloid Brain PET Imaging 3.0

Aktualisierte Handlungsempfehlung der Deutschen Gesellschaft für Nuklearmedizin (S1-Leitlinie)
Beta-Amyloid-PET-Bildgebung des Gehirns 3.0



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Bibliography

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PREAMBLE

This represents a substantial development of the guideline on the topic first published in 2016. The following notable points have been updated: the sections on background information; the clinical benefit of the method; the resulting differential diagnostic considerations; the outlook for possible future extensions of the indication spectrum; the quantitative analysis of the PET images; the embedding of the method in diagnostic pathways; and the relation to alternative biomarker methods such as amyloid measurement in CSF/blood.

PRÄAMBEL

Hierbei handelt es sich um eine substanzielle Fortentwicklung der 2016 erstmals veröffentlichten Leitlinie zum Thema. Insbesondere wurden die Abschnitte zu Hintergrundinformationen, zum klinischen Nutzen der Methode, zu resultierenden differenzialdiagnostischen Erwägungen, zum Ausblick auf eventuelle zukünftige Erweiterungen des Indikationsspektrums, zur quantitativen Analyse der PET-Aufnahmen, zur Einbettung der Methode in diagnostische Handlungspfade und zum Kontext zu alternativen Biomarker-Methoden wie der Amyloid-im-Liquor/Blut-Messung aktualisiert.

I. Objective

This guideline is designed to provide guidance and support for brain PET examinations using radiopharmaceuticals that bind to beta-amyloid (A β)-plaques, with regard to indication, performance, evaluation, and interpretation. The aim is to achieve a high quality standard in the performance of this examination, thereby increasing the diagnostic relevance of A β PET imaging in clinical practice.

II. Background information

A. This guideline was prepared by the Working Group on Neuronuclear Medicine of the German Society for Nuclear Medicine. It takes into account the updated joint recommendations of the U.S. Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the U.S. Alzheimer's Association on the appropriate use of A β -PET imaging [1], as well as the joint procedural guidelines for A β -PET imaging of the SNMMI and the European Association of Nuclear Medicine (EANM) [2]. Appropriate procedure guidelines are also useful in a national context, since several A β PET radiopharmaceuticals are authorised for routine clinical use in Germany (► **Table 1**). Thus, amyloid imaging is one of the few PET methods licenced for diagnostic use in Germany. Currently, three A β PET radiopharmaceuticals are approved in Germany. These can therefore, in principle, be used at any nuclear medicine centre. Systematic training on interpreting PET images is necessary and well-established.

B. A β plaques, together with neurofibrillary tangles composed of hyperphosphorylated tau, are the histopathological hallmarks of Alzheimer's disease (AD). For several years, PET radiopharmaceuticals have enabled their non-invasive and in vivo visualisation and quantification. Methodologically, A β PET is the only non-invasive technique that allows direct in vivo detection of amyloid pa-

thology and assessment of its extent and distribution in the brain. A β PET therefore has applications both in routine clinical practice and in medical research. With the approval of anti-A β antibodies for the treatment of Alzheimer's disease, an increased use of A β PET imaging in routine clinical practice is particularly to be expected. It has been demonstrated that A β PET increases the confidence of the clinical diagnosis of Alzheimer's dementia and can help exclude Alzheimer's disease (AD) as the cause of dementia. In addition, A β PET may help estimate the likelihood of progression of MCI to manifest Alzheimer's type dementia. Based on current knowledge, the majority of amyloid-positive patients with MCI will progress to Alzheimer's-type dementia, whereas amyloid-negative patients are not expected to develop Alzheimer's dementia in the near future. It is not possible to reliably predict the timescale, and the occurrence of a non-Alzheimer's form of dementia in amyloid-negative MCI patients cannot be excluded. A β PET can also provide useful information for the differential diagnosis of AD compared with other forms of dementia. A β PET acts as an important biomarker for the detection of A β -Status (A), in addition to biomarkers for tau (T) and neuronal damage (N) of what is known as the ATN classification scheme [3, 4]. This paradigm shift has now also entered clinical diagnosis. In clinical research, A β PET is also used as a biomarker in testing potential drugs for AD, both to enrich study populations with actual cases of AD and to assess the pharmacological effects over time, for example of antibodies targeting A β plaques.

C. In AD, A β plaques accumulate at different times in various brain regions many years before the first symptoms. Cerebral A β pathology in AD usually develops according to Thal phases: In phase 1, A β pathology is found exclusively in the neocortex; in phase 2, it is also present in the allocortex; in phase 3, it additionally involves the diencephalon, striatum, and basal forebrain; in phase 4,

► **Table 1** Beta-amyloid PET radiopharmaceuticals available for clinical use, *For static imaging, **May be shortened in case of impaired patient cooperation [18], AMG = Medicinal Products Act, AMRadV = Ordinance on Radiated or Ionising Medicinal Products.

Radiopharmaceutical	Clinical routine applicability in Germany	Typical applied activity	"Critical" organ, its absorbed dose	Effective dose per typical applied activity	Typical PET acquisition start*	Typical PET acquisition duration**
[¹¹ C]PIB	Via § 13 AMG/AMRadV	370 MBq	Gallbladder, 42 µGy/MBq	2 mSv	40–50 min p. i.	20 minutes
[¹⁸ F]Florbetapir (Amyvid, Eli Lilly)	Approved	370 MBq	Gallbladder, 143 µGy/MBq	7 mSv	30–50 min p. i.	10 minutes
[¹⁸ F]Florbetaben (Neuraceq, Life Molecular Imaging/Lantheus)	Approved	300 MBq	Gallbladder, 137 µGy/MBq	6 mSv	90 min p. i.	20 minutes
[¹⁸ F]Flutemetamol (Vizamyl, GE)	Approved	185 MBq	Gallbladder, 287 µGy/MBq	6 mSv	90 min p. i.	20 minutes

it further extends to additional brainstem regions; and in phase 5, it also involves the cerebellum [5]. In AD, Thal phase 1 is generally already present in the prodromal stage of MCI. This implies, firstly that A β PET has a great potential for early diagnosis of AD or for the prediction of AD dementia. Secondly, in cases with manifest Alzheimer's dementia, A β PET should be clearly pathological.

D. According to criteria published by the U.S. National Institute on Aging together with the US Alzheimer's Association, the course of AD is divided into a preclinical, prodromal and dementia phase [6–8].

E. Regardless of stage, cerebral A β plaques are considered a *sine qua non* for the diagnosis of AD (“no Alzheimer's without plaques”). This implies that a negative A β PET scan makes AD highly unlikely. However, other neurodegenerative dementias are possible. Among other findings from amyloid imaging, it has become established that a relevant proportion of patients with clinical symptoms resembling AD do not have A β -plaques, meaning that other pathologies underlie the clinical presentation. A prospective study in a large patient cohort ($n > 11,000$) demonstrated that performing an A β PET examination led to changes in clinical management in approximately 60% of cases. Often this was due to the fact that no Alzheimer's pathology could be found in patients with clinical suspicion of AD [9]. A benefit of amyloid imaging is thus also particularly evident through the exclusion of AD [10]. Conversely, AD does not always have to be associated with the typical clinical presentation of the disease. A positive A β PET scan also supports the diagnosis of the less common atypical presentations of AD, including the frontal-executive variant, posterior cortical atrophy (PCA) [11], and rarer subtypes within the spectrum of frontotemporal lobar degeneration, particularly the logopenic variant of primary progressive aphasia (lvPPA) [12]. Pathological A β PET findings are also observed in dementia with Lewy bodies (approximately two-thirds of cases are A β -positive) and Parkinson's disease dementia (up to one-third of cases are A β -positive [13]). Therefore, these conditions cannot be differentiated from AD on the basis of A β PET alone, and A-positivity without corresponding clinical features cannot be used to diagnose AD. With increasing age, the prevalence of cortical A β plaques also rises in cognitively normal individuals (up to 25–35% [14]), although the significance of this finding – i. e., when and in which cases cerebral A β -plaques become symptomatic – remains unclear. The frequency with which cortical A β plaques are found in the brains of cognitively healthy individuals roughly corresponds to the prevalence of Alzheimer's dementia in people ten years older.

F. According to the updated joint recommendations of the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association [1], the clinically appropriate uses of A β PET are:

1. Patients presenting with MCI or dementia syndrome who are younger than 65 years and in whom AD pathology is suspected
2. Patients presenting with MCI or dementia syndrome that is often consistent with AD pathology (amnestic presentation) with onset at ≥ 65 years
3. Patients presenting with MCI or dementia syndrome that could be consistent with AD pathology but has atypical features
4. Patients with MCI or dementia with equivocal or inconclusive results on recent CSF biomarkers
5. To inform the prognosis of patients presenting with MCI due to clinically suspected AD pathology
6. To determine eligibility for treatment with an approved anti-A β antibody therapy
7. To monitor response among patients who have received an approved anti-A β antibody therapy

A β PET is contraindicated in principle in cases of known hypersensitivity to the radiopharmaceutical used, as well as in patients who are clearly unable to cooperate with the PET imaging procedure.

G. Overall, the recently revised S3 guideline “Dementia” issued by the German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology and the German Society of Neurology is the key reference for determining the indication for A β PET in Germany. The guideline now recommends A β PET imaging: (1) when the cause of dementia or MCI remains unclear after exclusion of reversible causes and after clinical and neuropsychological assessment and, if applicable, CSF biomarkers, and when differential diagnosis is expected to have an impact on clinical management (recommendation grade A, 86% consensus), and (2) when there is a reason to estimate the individual risk of dementia in people with a confirmed diagnosis of MCI. For this purpose, patients should be advised about the advantages and disadvantages and possible consequences before an A- β PET study is considered. It is proposed that after clarification, an A- β PET be offered (recommendation grade B, 82% consensus).

H. As part of a meeting under the auspices of the EANM, a multidisciplinary expert consensus on amyloid and FDG PET imaging was developed, which can provide a practical guide for clinical application [15].

I. Within the existing portfolio of biomarker methods supporting the clinical diagnosis of AD, A β PET, together with amyloid measurement in CSF/blood, is classified as a pathology-A- biomarker in the ATN framework and falls under the so-called Core-1 (diagnostic) category of the recently revised diagnostic and staging criteria for AD [4]. Current results in this context suggest that A β PET imaging and A β determination in CSF/blood are more complementing than competing methods [16]. While PET imaging detects aggregated amyloid, soluble A β is quantified in fluids. There are also biomarkers for tau pathology (phospho-tau measurement in CSF/blood or tau-PET) and biomarkers for neurodegeneration (measurement of total-tau in CSF/blood, [18 F]FDG-PET, atrophy detection by CT/MRI) [7, 17]. According to current knowledge, biomarker-supported diagnosis of AD is strongly recommended overall, and in this context A β PET imaging is explicitly endorsed [6–8]. Its value in improving diagnostic certainty appears to be particularly relevant in the prodromal stage of AD, as at this time the diagnosis cannot be made – or cannot be made with certainty – on the basis of clinical symptoms alone.

J. In Europe, two anti-A β antibodies, lecanemab and donanemab, are now approved for the treatment of AD. The evidence of A β pathology is an obligatory requirement for initiating these therapies. In this context, A β PET imaging can play a valuable role in identifying suitable patients, and in monitoring the responses to the biological therapy. The latter is particularly important for treatment with donanemab. In the pivotal approval study, treatment with donanemab was discontinued after 6 or 12 months if centiloids fell below a specific level – considered equivalent to amyloid negativity – once or twice. At 12 months, nearly 70% of patients achieved this target. Shortening the treatment duration from 18 to 6 or 12 months could result in significant savings in terms of drugs and resources, while also minimising potential risks.

K. The product information for the approved A β PET radiopharmaceuticals now includes not only visual analysis (see Section H.2) but also quantitative analysis of the PET data (see section H.3).

III. Procedure

A. Patient preparation

1. In accordance with the above mentioned U.S. recommendations, patients should be referred for A β PET by dementia experts, who have performed prior expert neurocognitive testing [1].
2. The following information is desirable to establish the justified clinical indication for an A β PET scan:

- a) Duration, type, and severity (MMSE score, CDR score, or similar test results) of the cognitive deficit
 - b) Family history of dementia
 - c) Any additional behavioural disorders, motor and especially language disorders, depressive symptoms and other neuropsychiatric disorders
 - d) If present, results of prior brain imaging studies (CT, MRI, perfusion SPECT, SPECT or PET of the dopaminergic neurotransmitter system, [18 F]FDG-PET, tau-PET)
 - e) If available, result of previous CSF tests for amyloid and tau
3. No special preparation is required before the patient arrives.
 4. Placement of an intravenous line: Short plastic tubing should be used for the lines to minimise absorption of the lipophilic radiopharmaceuticals by the tubing system. The syringe should likewise be prepared only shortly before injection.
 5. Urinary bladder
 - a) Before starting PET acquisition, the patient should void.
 - b) After the scan, the patient should void again to minimise radiation exposure.
 6. Sedation: If sedation is required, it should be administered as close as possible to the PET acquisition, in order to avoid potential effects of the sedative on cerebral blood flow and thus on the uptake and washout of the radiopharmaceutical in and from brain tissue.
 7. Motion artefacts: It is recommended that the patient be reminded immediately prior to PET acquisition of the importance of avoiding head movement during the examination. When using low dose CT for attenuation correction, the patient should also be explicitly advised that the CT is part of the PET scan, and so head movement should also be avoided during the CT and while they are being advanced into the PET ring.
 8. Psychotropic drugs: Based on current knowledge, psychotropic drugs do not interact with A β PET radiopharmaceuticals, and so these medications do not have to be discontinued for the PET test.

B. Medical history

1. Clinical history of cognitive disorders, their duration, associated clinical test results, other neurological or psychiatric disorders
2. Recent brain morphologic imaging (CT, MRI) or previous PET or SPECT of the brain
3. Current drug history and time of last intake.
4. Recent CSF puncture, particularly CSF amyloid and tau levels
5. Ability of the patient to lie still for the duration of the acquisition (approximately 20 minutes)

C. Monitoring

1. Because these patients are cognitively impaired, continuous monitoring of the patient throughout the examination is necessary.
2. Head movements during image acquisition should be documented and taken into account during evaluation.

D. Radiopharmaceuticals

► **Table 1** provides an overview of the current status of use, activity amounts, radiation exposure, and image acquisition times of the Aβ PET radiopharmaceuticals currently approved in Germany.

1. The ¹⁸F-labelled radiopharmaceuticals are delivered ready for use. Quality control is carried out by the manufacturer before delivery of the finished product.
2. The volume to be administered, the rate of administration and the shelf life are specified in the manufacturer's information.
3. The radiopharmaceuticals are administered intravenously according to the speed specified by the respective manufacturer, followed by flushing of the intravenous line with, for example, 10 ml of physiological NaCl solution.
4. Risks: Aβ PET radiopharmaceuticals are generally well tolerated (for the type and frequency of side effects, see package leaflet for each radiopharmaceutical). For radiation exposure, ► **Table 1**. As already noted, their use is in principle contraindicated in the case of hypersensitivity/incompatibility to the radiopharmaceutical used and in the case of apparent inability to cooperate.

E. Image acquisition

1. Depending on the clinical question and the available technical equipment, brain Aβ PET imaging includes:
 - a) Static PET acquisition (sufficient for most clinical questions), with radiopharmaceutical-specific start times and scan durations (► **Table 1**). Alternatively, in the case of list-mode acquisition, selection of partial frames adjusted to the total acquisition duration may be considered. In the case of severe motion, this allows individual frames to be either discarded or evaluated.
 - b) Dynamic PET acquisition (multiple sequential imaging, usually involving the entire brain, suitable for absolute quantification of regional Aβ-plaque level and other parameters as a measure of relative blood flow).
2. To minimise motion artefacts, the use of standard head restraint or head motion detection systems is recommended.
3. Care should be taken to ensure that the entire brain, including the cerebellum (reference region), is positioned in the field of view of the camera.

4. PET scanners to be used

- a) Modern PET/CT systems
- b) Dedicated full-ring PET systems
- c) Combined PET/MRI systems
- d) Possibly dedicated brain PET systems in future
- e) Please refer to the EANM guidelines on the quality standards of PET scanners to be used.

5. Emission measurement

- a) Depending on the radiopharmaceutical, the emission measurement begins at different times p.i. with varying durations (► **Table 1**).
- b) Other factors that may influence the acquisition time are the ability of the patient to cooperate, the amount of injected activity, the type of device and the recording protocol (2D or 3D).
- c) If implemented in the systems, the use of automated motion detection and correction methods is recommended.

6. Transmission measurement

- a) In the case of PET/CT systems, a low dose or ultra low dose CT scan is performed.
- b) In the case of dedicated full-ring PET systems, transmission is generally measured with ⁶⁸Ge/⁶⁸Ga sources.
- c) In the case of combined PET/MRI systems, measurements are MRI-based and take the bone compartment into account.
- d) In principle, transmission can be measured in all cases either before or after the administration of the radiopharmaceutical ("cold" or "hot" transmission measurement).
- e) In any case, to avoid attenuation correction artefacts, it is important to ensure that the head position does not vary between transmission and emission measurement.
- f) In particular, the use of standardised, database-based transmission matrices may also be envisaged in the future for anticipated dedicated brain PET systems. In this case, the need for an individual transmission measurement could possibly be eliminated.

F. Data processing

1. The pixel size in the reconstructed image should not exceed 4 mm. Depending on the transaxial field of view, a matrix size of 128 × 128 or 256 × 256 is required. The layer thickness should be one-third to one-half of the physical resolution of the PET system.
2. The other reconstruction parameters (e.g. filter parameters) should be selected so that the resolution in the reconstructed image is at least 8 mm (FWHM). At lower spatial resolution, differentiation of specific radiopharmaceutical binding to Aβ plaques in the cortex (thickness ≤ 5 mm) and nonspecific uptake in white matter is hampered. Lower resolutions also har-

bour the particular risk of false-positive findings as a result of “spill in”.

3. Iterative reconstruction methods should be used, as they generally provide better statistical image quality at the same spatial resolution than filtered back projection and avoid its typical artefacts.
4. Attenuation correction
 - a) For attenuation correction of the emission data in PET/CT or dedicated PET, the attenuation coefficient matrices determined from the transmission measurement (referred to as “μmaps”) are incorporated into the reconstruction of the emission data.
 - b) MRI sequences are typically employed in combined PET/MRI systems to correct attenuation of the emission data obtained from combined PET/MRI systems. These permit segmentation in the head region into soft tissue (water), fat, air and possibly bone and the empirical assignment of attenuation coefficients or the calculation of continuous attenuation coefficients. These in turn are used to calculate the emission data.
 - c) As mentioned above, standardised, database-based transmission matrices could be used in the future to correct attenuation of the emission data obtained in future dedicated brain PET systems.
5. Further standard PET corrections for dead time and scattered radiation should be applied.

G. Image representation

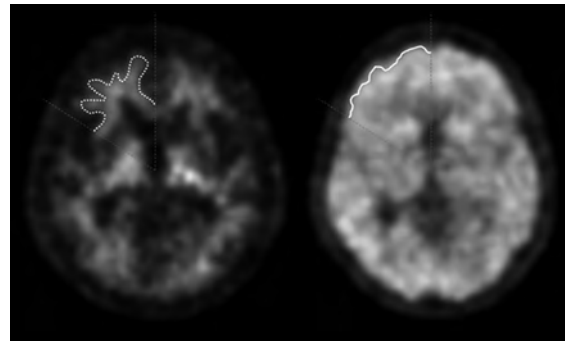
1. Reconstructed and corrected transaxial images should be displayed for quality control (exclusion of motion artefacts) and visual evaluation.
2. In addition, coronal and sagittal slice images should be routinely displayed, as these allow better delineation of areas of increased uptake in certain brain regions.
3. When multiplanar reconstruction software is used, the transaxial slices are usually oriented along the bicommissural plane (the line passing through the anterior and posterior commissures, which can be approximated by the line from the frontal to the occipital pole of the brain).
4. Correct axis-aligned orientation of the slice images is important to enable standardised analysis of the evaluable imaging data.
5. A 3D visualisation of the Aβ PET data may be beneficial in clinical use. However, such representations can also be influenced by artefacts and should therefore be compared with the sectional images.
6. Co-registration with structural MRI data may facilitate evaluation and interpretation. The final interpretation of PET data for the presence of Aβ PET plaques should be performed side-by-side rather than with PET/MRI fusion images.

H. Image analysis

1. General
 - a) The strengths of Aβ PET imaging lie in the short acquisition time, which is sufficient for reliable image interpretation, and in the fact that visual assessment usually yields a clear result. The objective of the image analysis is a binary result (“Aβ-positive” or “Aβ-negative”).
 - b) The extent of physiological inter- and intra-individual variability in cortical and subcortical uptake of radiopharmaceuticals should be taken into account.
 - c) The assessment of the course with the aim of showing a deterioration or improvement of the findings requires adequate normalisation techniques to avoid artificially generated differences. For this purpose, visual analysis should be carried out with an identical colour scale and intensity scaling. Especially in this case, a supplementary (semi-)quantitative image data analysis is helpful (e.g. calculation of parametric SUVR images or determination of centiloid values [19]). Centiloid-based analysis is currently the standard procedure, especially in the context of measuring the therapeutic success of the new amyloid-directed therapies (see below, Chapter 3 d (3)).
 - d) Visualisation of voxel-based deviations from the norm in radiopharmaceutical uptake (“Z-score maps”) can be advantageous for the visual identification of typical Aβ involvement patterns.
 - e) PET images should be evaluated by reference to recent anatomic imaging (CT or MRI). Particular attention should be paid to the influence of brain atrophy and morphological defects and the resulting partial volume effects on the PET signal.
2. Visual analysis
 - a) Images should be viewed on a computer monitor to allow interactive adjustment of contrast, background subtraction, and colour chart.
 - b) With regard to the presentation of PET data, Aβ PET radiopharmaceutical providers recommended grey scales or continuous or discontinuous colour gradations as well as different strategies for intensity scaling.
 - c) The Aβ PET radiopharmaceuticals currently available show differing degrees of uptake ([¹¹C]PIB less than the currently approved ¹⁸F-labelled radiopharmaceuticals), but they accumulate non-specifically within the cerebral white matter (reflecting non-specific binding to myelin). The key criterion for determining whether a brain region is Aβ-positive is whether – beyond this non-specific uptake in the white matter – relevant uptake is observed in the cerebral cortex (at least comparable in intensity to the white matter), i.e. whether the physiological contrast between higher uptake in the white matter and lower uptake in the cortex is eliminated

► **Fig. 1**). In cases where it is difficult to anatomically define the grey matter precisely on PET images (e.g. in advanced cerebral atrophy), co-registration of the PET data with individual anatomical MRI scans (T1-weighted, e.g. MPRAGE) is recommended.

- d) In accordance with the above mentioned Thal phases of cerebral amyloidopathy in AD, in particular the frontal cortex, posterior singular cortex/precuneus, lateral temporal, parietal and occipital cortex are interpreted with respect to their radiopharmaceutical uptake. Genetic forms of AD may also have, in particular, striatal accumulations. Typically, if one or two of the aforementioned brain regions are classified as pathological, the brain as a whole is rated as positive for A β plaques (see the manufacturer's information for the specific radiopharmaceutical used).
 - e) Typically, in AD the sensorimotor and primary visual cortices are largely spared from increased uptake. Other diseases associated with cerebral amyloidopathy, or late stages of AD, may deviate from this uptake pattern.
 - f) Radiopharmaceutical manufacturers recommend different schemes for the systematic approach to visual analysis of A β PET data, all of which result in a binary conclusion ("A β -positive" or "A β -negative").
 - g) Experience shows that borderline findings are rare (<10%). For the interpretation of these borderline findings, reference is also made to the specific recommendations of the respective radiopharmaceutical providers.
1. Quantitative analysis
 - a) General
 1. Quantitative analysis methods can be integrated into routine clinical practice for A β PET.
 2. They can facilitate visual findings or increase confidence in visual findings.
 3. They are particularly recommended for follow-up assessments.
 4. Limit values depend on the radiopharmaceutical, PET system, reconstruction algorithm and method of analysis used and must be considered accordingly.
 5. The "centiloid scale" has now become widely established as a tool for improving the comparability of semi-quantitative A β PET data obtained with different A β radiopharmaceuticals and PET systems. The SUVRs are converted into radiopharmaceutical/PET scanner-specific centiloid units [19]. This concept is now available in software solutions with CE marking and can be used to implement the A β PET quantification included in the product information.



► **Fig. 1** Transverse [^{11}C]PIB β -amyloid PET slices showing, for the right frontal lobe, the typical non-specific radiopharmaceutical uptake only in the white matter consistent with an β -amyloid-negative finding (left), versus radiopharmaceutical uptake extending beyond the white matter into the grey matter consistent with a pathological (amyloid-positive) finding (right).

- b) Quantitative analysis
 1. Determination of an arterial input function is generally not required for absolute quantification of the A β -plaque load. Instead, what are known as reference tissue models [20, 21] can be used, generally using the cerebellar cortex or the whole cerebellum [22] as the reference region.
- c) Semi-quantitative analysis
 1. For this purpose, radiopharmaceutical uptake ratios between cortical target regions and the reference region, known as SUVRs, are calculated from static images acquired during the pseudo-equilibrium phase of brain uptake (timing differs between radiopharmaceuticals; ► **Table 1**).
 2. It has been shown for A β PET tracers that cortical SUVRs in the cerebrum correlate linearly and closely with binding parameters determined by the above-mentioned methods of absolute quantification. Therefore, SUVRs are the semi-quantitative parameters of choice for quantitative A β PET analyses. However, it should be noted that SUVRs only partially map quantitative binding parameters and are, for example, susceptible to perfusion and clearance effects (such as in the context of therapy studies with medications that influence brain circulation or renal and hepatic elimination of the radiopharmaceuticals).
- d) VOI-based analysis
 1. SUVRs are usually calculated for various VOIs, with particular interest – similar to visual analysis – in regions corresponding to the Thal phases of cerebral amyloidopathy in AD [5]. These are, in particular, the frontal cortex, posterior cingulate cortex/precuneus, lateral temporal and parietal cortices, and, in genetic forms of AD, the striatum.

2. In addition, “composite SUVR” can be determined – a volume-weighted mean of the SUVRs of, for example, the cortical VOIs mentioned above. This parameter is well suited as a measure of the average A β -burden of the whole brain. Newer methods are being tested, such as the so-called ‘fill-state’, a measure of the efficiency of A β pathology of the affected area/extent in the brain [23, 24].
3. In the centiloid concept, composite SUVR values are transformed into centiloid values via a linear transformation. The centiloid scale, on which the corresponding value for the individual patient can be plotted, has two anchor points: 0 = mean value in A β -negative healthy individuals and 100 = mean value in A β -positive affected patients. In the most recent literature, centiloid limit values of >30 are recommended for inclusion in therapeutic studies and, in the case of therapeutic monitoring, limit values of <11 (one-time) or <25 (twice) as evidence of response to anti-amyloid therapy [25].
- e) Voxel-based analyses
 1. The PET dataset to be analysed is stereotactically normalised and parameterised using various software solutions (e.g. SUVR normalisation using a reference region) and then compared voxel-by-voxel with a normal database. This yields “Z-score maps” in which the deviation from the norm of the relative radiopharmaceutical accumulation in the brain to be examined is parameterised and regionally quantified.
 2. It is recommended to use only procedures that are sufficiently clinically validated and published in the scientific literature.
2. The following clinical information should be included:
 - a) Clinical or suspected diagnosis of syndromes
 - b) Date and findings of prior morphologic brain imaging (CT, MRI), nuclear medicine brain examinations, and cerebrospinal fluid (CSF) examination
 - c) Whether prior brain morphologic imaging is present at time of diagnosis
 - d) Concrete questions, including suitability for anti-A β therapy
3. The following information on the examination technique should be included:
 - a) Type, dose and route of administration of the radiopharmaceutical
 - b) Time of acquisition post injection (p.i.) and scan duration
 - c) Imaging device and attenuation correction method used
4. The following information on the findings should be provided:
 - a) Description of any examination shortcomings:
 1. Deviations from the test protocol, e.g. a shortened effective acquisition time due to movements or changes in the time interval between injection and PET scan
 2. Potential problems/artefacts during acquisition, such as patient movement, and compensation if necessary
 - b) Visual description of the radiopharmaceutical uptake pattern:
 1. Prior training of the reader is required for this purpose (this is mandated by regulatory authorities for ^{18}F -labelled A- β radiopharmaceuticals and is offered by the manufacturers)
 2. Possible artefacts (movement, attenuation correction, incomplete detection of the brain in the field of view of the camera)
 3. Anatomical irregularities, especially when visible on structural imaging in the case of combined PET/CT or PET/MRI scans
 4. Atypical increased uptake in the grey matter of the cerebellum or in other brain structures used as reference regions. This is important because quantitative/voxel-based analysis can lead to false-negative findings.
 5. Only non-specific white matter uptake, or additional regional/global cortical uptake in the cerebrum? Which cerebral regions are affected? What is the pattern? Left/right symmetry or asymmetry?
 6. Is there increased uptake in the striatum?
 7. The key messages of the visual assessment should be consistent with the quantitative/software-based assessment.

I. Finding

1. General
 - a) In addition to the structured written reporting recommendation for A β PET examinations outlined below, it is recommended that the findings be discussed, for example in interdisciplinary case conferences with referring clinicians and neuroradiologists. The advantage of this is that a joint (clinical and biomarker-based) diagnosis can be established more quickly and easily, and that the nuclear medicine physician involved receives direct feedback on how the A β PET result should be interpreted in the context of other diagnostic findings and on the implications of the PET result for further diagnostic and therapeutic management.
 - b) The written findings should be accompanied by representative PET images, e.g. whole-brain series of selected transverse slices.

- c) In case of additional quantitative/software-based assessment:
 1. Regional SUVR (frontal cortex, posterior cingulate/precuneus, lateral temporal, parietal cortex) and composite SUVR or centiloid value, compared with radiopharmaceutical thresholds
 2. The result of voxel-based comparisons with standard databases, including regional Z-scores if necessary
- 5. The following assessment and conclusions should be provided:
 - a) PET findings should result in a binary evaluation (is the brain A β -positive or A β -negative?).
 - b) Interpretation of the visual and quantitative/voxel-based analysis results documented in the report on radiopharmaceutical uptake, in terms of cerebral A β -plaque presence, its intensity and extent, and – if present – any deviations from the typical A β -plaque distribution pattern within the brain
 - c) The A β PET provides information on the presence/absence or cerebral distribution of A β -plaques and not a disease diagnosis. Rather, as a neuropathology biomarker, it increases the certainty of clinical diagnosis.
 - d) In cases of MCI or dementia, a negative A β PET result effectively rules out AD with a high level of certainty. In this case, neurodegenerative dementia from the group of forms of frontotemporal lobar degeneration, dementia with Lewy bodies, or Parkinson's dementia may be considered. Vascular causes or a dementia syndrome associated with depression should also be considered in these cases (especially in view of the therapeutic implications).
 - e) In the case of MCI, particularly the amnesic subtype, or in the case of dementia that is clinically at least possibly attributable to AD, a positive A β PET finding strengthens the suspected clinical diagnosis, but does not exclude other forms of dementia (dementia with Lewy bodies, Parkinson's disease dementia, or rare disorders within the spectrum of frontotemporal lobar degeneration).
 - f) Differential diagnosis should take into account that in the case of dementia, mixed forms of different histopathological entities frequently occur.
 - g) The effect of brain atrophy/partial volume effects and structural lesions on the A β PET findings should be taken into account.
 - h) In the event of a difficult evaluation (e.g. findings that do not correspond with a common pattern according to the above criteria), this problem should be explicitly discussed.
 - i) If so requested, it should be specifically stated whether evidence for amyloid pathology as a prerequisite for anti-amyloid therapy was found.

J. Quality control of the PET device

1. Clinical investigations should be accompanied by a regular quality control programme.
2. Reference is also made to the DGN guidelines on the brain [^{18}F]FDG PET, the US guidelines published by the National Electrical Manufacturers Association (NEMA), and the European guidelines published by the International Electrotechnical Commission (IEC).

K. Pitfalls, artefacts, causes of errors

1. As already mentioned, no drugs or substances are currently known to affect the binding of the above-mentioned radiopharmaceuticals to A β -plaques. However, no systematic studies on this matter are available.
2. Patient movement during data acquisition, or resulting misalignment between emission and transmission measurements, as well as movement during the emission acquisition itself, can cause image artefacts and render meaningful interpretation of the examination impossible.

L. Issues requiring further clarification

1. Effect of brain atrophy/partial volume effects on the PET signal?
2. Definition of the best quantitative parameter in the context of follow-up/therapy monitoring?
3. Role of early post-radiopharmaceutical administration brain perfusion PET scans as an additional (without extra radiation exposure) biomarker of neurodegeneration? A number of clinical studies have been published in recent years on this aspect, which consistently show the potential of this method extension [26].

IV. Disclaimer

The German Society for Nuclear Medicine issues guidelines to promote the use of examination and treatment methods in nuclear medicine. This type of recommendation does not apply to all situations in practice. The guidelines are not intended to claim that they contain all the relevant procedures or that they exclude methods that lead to the same result. Whether an examination procedure is appropriate depends in part on the prevalence of the disease in the patient population. In addition, the diagnostic options available in different medical facilities may vary. For these reasons, guidelines must not be applied rigidly.

Advances in medicine are happening fast. Therefore, the date a guideline was created must be taken into account when applying it.

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Conflict of Interest

Declaration of financial interests

Receipt of research funding: no; receipt of payment/financial advantage for providing services as a lecturer: yes; paid consultant/internal trainer/salaried employee: yes; patent/business interest/shares (author/partner, spouse, children) in company: no; patent/business interest/shares (author/partner, spouse, children) in sponsor of this CME article or in company whose interests are affected by the CME article: yes.

Declaration of non-financial interests

COI declarations can be found in the AWMF guidelines report at <https://register.awmf.org/de/leitlinien/detail/031-052>.

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Scientifically responsible based on certification regulations

According to certification regulations, the person scientifically responsible for this article is Prof. Henryk Barthel, Leipzig

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Wir wünschen Ihnen viel Erfolg beim Beantworten der Fragen!

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Question 1

Beta-amyloid PET radiopharmaceuticals in Germany are

- A not yet approved for routine clinical use
- B approved but not yet generally available
- C approved, generally available, but not reimbursed as standard by the funding bodies
- D approved, generally available and reimbursed via the NUB system
- E approved, generally available and reimbursed as standard

Question 2

For the treatment of beta-amyloid pathology in Alzheimer's disease, in Germany

- A two medications have been approved recently
- B no medications have been approved yet
- C anticholinergics have been approved
- D there are no medications in the pipeline
- E two medications are fully reimbursed

Question 3

A beta-amyloid positive finding on PET imaging

- A confirms Alzheimer's dementia
- B excludes any form of frontotemporal lobar degeneration
- C does not fit a mild cognitive disorder
- D qualifies otherwise suitable patients for anti-amyloid therapy from a biological point of view
- E needs to be followed by FDG PET imaging

Question 4

Negative beta-amyloid findings of PET imaging rule out

- A frontotemporal lobar degeneration
- B Alzheimer's disease
- C dementia with Lewy bodies
- D vascular dementia
- E CBD

Question 5

The approved beta-amyloid PET radiopharmaceuticals

- A all have very high diagnostic accuracy
- B vary in terms of diagnostic accuracy
- C vary in terms of the frequency of adverse side effects
- D provide practically identical SUVR values
- E are all available in Germany

Question 6

The centiloid scale in beta-amyloid PET imaging

- A is not yet suitable for use in clinical routine
- B categorises "composite SUVRs" on a scale of 1 to 5
- C is used to predict tau status from beta-amyloid PET
- D quantitatively characterises the beta-amyloid load of the brain regardless of the beta-amyloid PET radiopharmaceutical and the PET system used
- E is not subject to risks

Question 7

The use of hybrid PET/MRI systems for beta-amyloid imaging is

- A not applicable, as the attenuation correction is unclear
- B not applicable, as co-registration of PET and MRI is unclear
- C applicable, just as that of PET/CT or dedicated brain PET systems
- D not applicable, since the magnetic field affects the binding of the radiopharmaceuticals to the beta-amyloid aggregates
- E only applicable in case of therapy monitoring

Question 8

The analysis of beta-amyloid PET images is currently performed

- A exclusively quantitatively
- B exclusively visually
- C primarily visually, supported by quantitative analyses
- D primarily with AI
- E centralized by the radiotracer manufacturers

► Additional questions on the next page...

Question 9

A key factor for interpreting beta-amyloid PET as pathological or normal is

- A the SUVR in the central region
- B the uptake of the radiopharmaceutical in the white matter of the brain
- C radiopharmaceutical uptake in the cerebellum
- D the contrast between grey and white brain matter in the cerebrum
- E radiopharmaceutical uptake in neck vessels

Question 10

Early PET images obtained immediately after intravenous bolus injection of the beta-amyloid radiopharmaceutical are a surrogate marker for

- A neurodegeneration
- B dopamine transporters
- C dopamine receptors
- D neuroinflammation
- E alpha-synuclein pathology