Comparison of Ictal Brain Perfusion SPECT With 99mTc-HMPAO Versus 99mTc-ECD for Identification of The Epileptic Seizure Onset Zone

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Abstract

Background: The chemical microspheres ^{99m}Tc-HMPAO and ^{99m}Tc-ECD are widely used as tracers in ictal brain perfusion SPECT for identification of the seizure onset zone (SOZ) in presurgical evaluation of patients with drug-resistant epilepsy and uncertainty of SOZ localization after standard diagnostic workup. For both tracers there are theoretical arguments to favor it over the other for this task. The aim of this study was to compare the performance of ictal brain perfusion SPECT between ^{99m}Tc-HMPAO and ^{99m}Tc-ECD in a rather large patient sample.

Methods: The study retrospectively included 196 patients from clinical routine in whom ictal perfusion SPECT had been performed with stabilized ^{99m}Tc-HMPAO (n = 110) or ^{99m}Tc-ECD (n = 86). Lateralization and localization of the SOZ was obtained by the consensus of two independent readers who visually inspected the SPECT images retrospectively.

Results: The ^{99m}Tc-HMPAO group and the ^{99m}Tc-ECD group were well matched with respect to age, sex, age at first seizure, duration of disease, seizure frequency, history of previous brain surgery, and findings of presurgical MRI. The tracer groups differed significantly with respect to the latency of tracer injection (median latency 4 s longer in the ^{99m}Tc-HMPAO group), duration of the seizure after tracer injection (25 s shorter in the ^{99m}Tc-HMPAO group), tracer dose (70 MBq higher in the ^{99m}Tc-HMPAO group), and delay of the SPECT acquisition after tracer injection (63 min longer in the ^{99m}Tc-HMPAO group). The fraction of lateralising ictal SPECT did not differ significantly between the ^{99m}Tc-HMPAO and the ^{99m}Tc-ECD group (65.5% versus 72.1%, p = 0.355). Sensitivity of ictal perfusion SPECT (independent of the tracer) for correct localization of the SOZ in 62 patients with temporal lobe epilepsy and at least worthwhile improvement (Engel scale ≤ III) 12 months after temporal epilepsy surgery was 63%.

Conclusions: This study does not provide evidence to favor ^{99m}Tc-HMPAO or ^{99m}Tc-ECD for identification of the SOZ by ictal perfusion SPECT in patients with drug resistant epilepsy.

Introduction

Brain surgery is a therapeutic option for patients with suspected focal epilepsy who do not respond sufficiently to drug therapy. A prospective, randomized, controlled trial of surgery for temporal-lobe epilepsy found 58% of the patients randomized to surgery to be free of seizures impairing awareness at one year after surgery compared to 8% of the patients randomized to optimal treatment with antiepileptic drugs (p < 0.001) [1]. The authors concluded that surgery is superior to prolonged medical therapy in drug-resistant temporal lobe epilepsy [1]. A systematic review for the Cochrane Collaboration concluded that "assessment for surgical selection should be offered to all people with a focal epilepsy where the first two antiepileptic drugs have failed" [2].

The aim of epilepsy surgery is to resect the "epileptogenic zone" (EZ) defined as the cortex area "whose removal (or disconnection) is necessary for complete abolition of seizures" [3]. Since the epileptogenic

zone obviously is not an operational concept for surgery planning, the combination of five different operationally defined cortical zones based on noninvasive methods is often used in presurgical evaluation [4]: the "irritative zone" that generates interictal spikes and can be localized by interictal scalp-EEG, the "seizure onset zone" (SOZ) that initiates seizures and can be localized by ictal scalp-EEG, the "symptomatogenic zone" that causes the initial ictal symptoms and can be localized by initial seizure semiology, the "epileptogenic lesion" defined as a single discrete macroscopic lesion causing the seizures that is visible on structural MRI, and the "functional deficit zone" that is not functioning normally in the interictal period and can be derived by neurological and neuropsychological examination. If all five zones can be reliably delineated and all point to the same brain region as EZ, additional presurgical investigation is usually not required [2]. If one or more of the zones cannot be identified reliably or if they point to different brain regions, further investigations might be useful, including nuclear imaging [5, 6] to clarify the localization of the SOZ or to plan intracranial placement of EEG electrodes to achieve this aim [2].

Brain perfusion SPECT with the ^{99m}Tc-labeled tracers hexamethyl-propyleneamine oxime (^{99m}Tc-HMPAO) [7, 8] or ethyl cysteinate dimer (^{99m}Tc-ECD) [9–11] is a nuclear imaging procedure widely used for presurgical evaluation of epilepsy patients with uncertain or discrepant standard pointers. After intravenous injection, ^{99m}Tc-HMPAO and ^{99m}Tc-ECD in reasonable approximation behave like a "chemical microsphere" that is fully extracted from arterial blood to tissue during a single capillary passage and then is locally retained in the tissue. Fixation of ^{99m}Tc-HMPAO in tissue is due to glutathione-dependent metabolism to hydrophilic forms and binding to non-diffusible cell components [12, 13]. Fixation of ^{99m}Tc-ECD in tissue is associated with cytosolic esterase activity that converts ^{99m}Tc-ECD into hydrophilic forms [14].

The microsphere pharmacokinetics of ^{99m}Tc-HMPAO and ^{99m}Tc-ECD allows an almost snapshot-like imaging of seizure-induced alterations of cerebral perfusion if the tracer is injected during the seizure. The aim of ictal brain perfusion SPECT is to identify the SOZ by regional hyperperfusion in the SOZ [15]. Regional hyperperfusion during the seizure is not only more sensitive for detection of the SOZ than regional hypoperfusion between seizures [16], it is also more specific, particularly in patients with any kind of lesion (including non-epileptogenic lesions) that may cause regional hypoperfusion independent of epileptic activity.

For both, ^{99m}Tc-HMPAO and ^{99m}Tc-ECD, there are theoretical arguments to favor it over the other for ictal brain perfusion SPECT. Intra-subject comparison in healthy subjects demonstrated significantly less extracerebral background activity and "easier to interpret images" with ^{99m}Tc-ECD, probably due faster elimination of ^{99m}Tc-ECD from blood compared to ^{99m}Tc-HMPAO [17]. In addition, grey-to-white matter contrast was found to be higher with ^{99m}Tc-ECD compared to ^{99m}Tc-HMPAO [18]. In line with these findings, comparison of ^{99m}Tc-HMPAO and ^{99m}Tc-ECD in patients with cerebrovascular or neurodegenerative diseases consistently showed higher contrast between lesions with reduced perfusion and normally perfused healthy tissue with ^{99m}Tc-ECD [19–21].

In contrast, preclinical [22] and human data [18, 23] demonstrated a higher single pass extraction fraction of ^{99m}Tc-HMPAO (about 70% at normal cerebral blood flow) compared to ^{99m}Tc-ECD (about 60%), particularly at higher cerebral blood flow, suggesting ^{99m}Tc-HMPAO to be superior to ^{99m}Tc-ECD for detection and localization of regional *hyper*perfusion (in contrast to regional *hypo*perfusion as in cerebrovascular and neurodegenerative diseases). ^{99m}Tc-HMPAO shows very little washout from the brain during the first 5 h after intravenous injection, while ^{99m}Tc-ECD is cleared from the brain with a rate of about 3% per hour (estimated from Fig. 4 in [17]). As a consequence, ^{99m}Tc-HMPAO might be superior to ^{99m}Tc-ECD when SPECT imaging is started more than 1 hour after tracer injection, for example due to transport of the patient from the neurology department to the nuclear medicine department. Furthermore, relative tracer uptake (scaled to the mean uptake in the whole brain) in the medial temporal cortex is higher for ^{99m}Tc-HMPAO [24], suggesting that ^{99m}Tc-HMPAO might be superior to ^{99m}Tc-ECD for the detection of a SOZ in the medial temporal cortex (e.g., associated with hippocampal sclerosis).

Furthermore, the only two previous studies that directly compared ^{99m}Tc-HMPAO and ^{99m}Tc-ECD for ictal perfusion SPECT [25, 26] appear to provide conflicting results. Lee and coworkers compared ictal ^{99m}Tc-HMPAO SPECT in 40 patients with ictal ^{99m}Tc-ECD SPECT in 14 different patients and concluded that ^{99m}Tc-HMPAO provides higher sensitivity than ^{99m}Tc-ECD in extratemporal epilepsy whereas the sensitivity is similar for both tracers in temporal epilepsy [25]. O'Brien and coworkers compared peri-ictal SPECT with unstabilized ^{99m}Tc-HMPAO in 49 patients with peri-ictal ^{99m}Tc-ECD SPECT in 49 different patients and concluded that ^{99m}Tc-ECD compares favourably with ^{99m}Tc-HMPAO as a radiopharmaceutical for peri-ictal SPECT studies [26].

Against this background, aim of the present study was to compare the performance of ictal brain perfusion SPECT between ^{99m}Tc-HMPAO and ^{99m}Tc-ECD in a rather large patient sample.

Methods

Subjects

For this retrospective study, the database of the Department of Nuclear Medicine of the University Medical Center Hamburg-Eppendorf was searched for patients in whom ictal brain perfusion SPECT had been performed for presurgical evaluation of suspected unifocal epilepsy. The only inclusion criterion was that the reconstructed SPECT image was available in digital form to allow retrospective image processing. Patients were excluded when the latency of the tracer injection after electrical seizure onset in EEG was > 120 s [27]. No further eligibility criteria were applied. The search identified 197 patients. One of these patients was excluded due to strong head motion during the SPECT acquisition (≥ 3 cm) that caused severe artefacts in the reconstructed image. The remaining 196 patients were included in the study. Ictal perfusion SPECT had been performed with stabilized ^{99m}Tc-HMPAO in 110 (56.1%) of these patients, with ^{99m}Tc-ECD in the remaining 86 (43.9%) patients. ^{99m}Tc-HMPAO and ^{99m}Tc-ECD had not

been used concurrently, but shifted in time: all SPECT with ^{99m}Tc-ECD had been performed before 2012, the majority of SPECT with ^{99m}Tc-HMPAO had been performed 2012 or later. However, all SPECT had been acquired with the same SPECT cameras and using the same acquisition and reconstruction protocol (described below) independent of the tracer.

Ictal perfusion SPECT

Ictal tracer injections had been performed during a seizure while the patient was undergoing video-EEG monitoring in the inpatient epilepsy unit of the Department of Neurology and Epileptology of the Protestant Hospital Alsterdorf. After the seizure, the patient was transported to the Department of Nuclear Medicine of the University Medical Center Hamburg-Eppendorf (20–30 min drive).

SPECT acquisition had been performed with a double-head camera (Siemens Symbia T2 or Siemens E.CAM) equipped with fanbeam or low-energy high-resolution collimators and angular steps of 2.8 or 3.0°. The radius of rotation was 15.4 ± 1.5 cm. Total acquisition time was 40 min. The projection data were reconstructed into transaxial SPECT images with 3.9 × 3.9 × 3.9 mm^3 voxel size using filtered backprojection implemented in the SPECT camera software with a Butterworth filter of order 5 and cutoff 0.6 cycles/pixel (= 1.5 cycles/cm). The resulting images were post-filtered with an isotropic Gaussian kernel with 8 mm full-width-at-half-maximum. Uniform post reconstruction attenuation correction was performed according to Chang (μ = 0.12/cm), no scatter correction was applied.

Individual SPECT images were stereotactically normalized (affine) to the anatomical space of the Montreal Neurological Institute using the statistical parametric mapping software package (version SPM12) and the SPM SPECT template as target.

SPECT interpretation

Standardized displays of the stereotactically normalized SPECT images were used for visual interpretation (Fig. 1). Visual interpretation was performed independently by two readers (IA and RB) blinded to all other data including clinical data, results of other presurgical tests, SPECT tracer and latency of tracer injection after seizure onset. The readers were asked to first lateralize the SOZ based on regional hyperperfusion (categories: left, right, both hemispheres, no hyperperfusion) and then to localize the SOZ within a brain lobe (temporal, frontal, parietal, occipital, no localization). In case of temporal hyperperfusion, additional hyperperfusion in ipsilateral insular cortex, putamen and/or thalamus was considered to be a propagation effect that supports ipsilateral temporal seizure onset [28]. Each reader interpreted all images twice. Images with discrepant interpretation with respect to lateralization and/or localization in the two reading sessions were assessed a third time to obtain an "intra-reader consensus". Finally, images with discrepant intra-reader consensus with respect to lateralization and/or localization between the two readers were assessed in a common reading session of the two readers to obtain an inter-reader consensus.

Ictal perfusion SPECT was considered "lateralising" when the inter-reader lateralization consensus was "left" or "right". It was considered "non-lateralising" when the inter-reader lateralization consensus was

"both hemispheres" or "no hyperperfusion".

Epilepsy surgery and clinical follow-up

Clinical follow-up data after epilepsy surgery following ictal perfusion SPECT was available in 97 of the 196 patients (the majority of the remaining patients did not undergo epilepsy surgery). Clinical follow-up of at least 12 months after surgery was available in 84 patients. The follow-up data at 12 months were categorized retrospectively according to the Engel Epilepsy Surgery Outcome Scale [29] based on the written reports in the patients' file. The Engel scores at 12 months were then combined as "good" (Engel IA-D), "improved" (Engel IIA-IIIB) or "worse" (Engel IVA-C) outcome [2].

Statistical analysis

Proportions are given as percentage and were compared between the ^{99m}Tc-HMPAO group and the ^{99m}Tc-ECD group using Fisher's exact test. Nominal variables with more than two possible values are given as percentages and were compared between groups using Pearson's Chi-Square test. Continuous variables are given as median and interquartile range and were compared using the non-parametric Mann-Whitney U test. All tests were two-sided. Probability values < 0.05 were considered significant. Cohen's kappa was used to characterize inter-reader agreement of visual SPECT interpretation.

Results

Demographical, clinical and SPECT data are summarized in Table 1.

Table 1

Demographical, clinical and SPECT data in the whole sample. Continuous variables are given as median [interquartile range]. If a variable was not available in all patients, the number of patients for that variable is given in parentheses. The p-values are not corrected for multiple testing.

	^{99m}Tc-HMPAO	^{99m}Tc-ECD	p
number of patients	110	86	
age at SPECT [y]	36.0 [25.3–49.3]	34.9 [26.0–45.0] (n = 84)	0.384
sex [% females]	44.5	44.2	1.000
age at first seizure [y]	15 [8–26] (n = 53)	14 [7–25] (n = 59)	0.560
duration of disease at SPECT [y]	22 [10–34] (n = 54)	19 [10–30] (n = 59)	0.374
mean seizure frequency in the last 12 months before SPECT [seizures/month]	8 [4–25] (n = 41)	9 [5–21] (n = 46)	0.740
with impairment of awareness in the majority of seizures during the last 12 months [%]	72.2 (n = 36)	72.7 (n = 44)	1.000
with history of brain surgery [%]	26.5 (n = 49)	16.7 (n = 60)	0.243
with one or more MRI lesions suspected to be epileptogenic [%]	71.3 (n = 108)	80.5 (n = 82)	0.175
MRI is lateralising (either left or right) [%]	64.8 (n = 108)	76.8 (n = 82)	0.081
latency of tracer injection relative to start of the seizure in EEG [s]	32 [25–40] (n = 95)	28 [23–35] (n = 77)	**0.026**
duration of seizure after tracer injection according to EEG [s]	48 [29–70] (n = 95)	73 [40–121] (n = 78)	**0.001**

	^{99m}Tc-HMPAO	^{99m}Tc-ECD	p
tracer dose [MBq]	590 [530–686]	520 [447–638]	**< 0.0005**
	(n = 109)	(n = 85)	
delay between tracer injection and scan start [min]	161 [123–227]	98 [78–135]	**< 0.0005**
		(n = 19)	
	(n = 91)		
with regional hyperperfusion in ictal SPECT [%]	70.9	74.4	0.631
ictal SPECT is lateralising (either left or right) [%]	65.5	72.1	0.355
proportion of temporal localization amongst the lateralizing ictal SPECT [%]	90.3	95.2	0.339
lateralization of ictal SPECT and MRI are contradictory (one left the other right) [%]	10.2	9.8	1.000
	(n = 108)	(n = 82)	
lateralization of ictal SPECT and EEG of the ictal SPECT seizure are contradictory (one left the other right) [%]	5.8	8.6	0.720
	(n = 52)	(n = 58)	
good/improved/worse outcome at 12 months after epilepsy surgery when lateralization and localization of surgery agreed with ictal SPECT [%]	33/50/17	66/28/6	0.145
	(n = 12)	(n = 32)	

The ^{99m}Tc-HMPAO group and the ^{99m}Tc-ECD group did not differ with respect to the age at ictal SPECT, sex, age at first seizure, duration of disease at ictal SPECT, mean monthly seizure frequency in the last 12 months before ictal SPECT, proportion of patients with impairment of awareness in the majority of seizures in the last 12 months, proportion of patients with history of brain surgery, and the proportion of patients with at least one possibly epileptogenic lesion in MRI.

There were significant group differences with respect to the latency of tracer injection after the electrical start of the seizure (median latency 4 s longer in the ^{99m}Tc-HMPAO group, p = 0.026), the remaining electrical duration of the seizure after tracer injection (25 s shorter in the ^{99m}Tc-HMPAO group, p = 0.001), the tracer dose (70 MBq higher in the ^{99m}Tc-HMPAO group, p < 0.0005), and with respect to the delay between tracer injection and the start of the SPECT acquisition (63 min longer in the ^{99m}Tc-HMPAO group, p < 0.0005). The latency of tracer injection was longer than 60 s in 4 of the 172 patients with known latency.

The two readers agreed with respect to the lateralization of the ictal SPECT in 171 of the 196 patients (87.2%). Cohen's kappa was 0.814 indicating substantial to almost perfect agreement. The frequency of discordant lateralization by the two readers did not differ between ^{99m}Tc-HMPAO and ^{99m}Tc-ECD (p = 0.397). In the majority of discordant cases (18 of 25, 9.2% of all 196 patients), the ictal SPECT was categorized as "no hyperperfusion" by one reader and as "left", "right" or "both hemispheres" by the other reader. In 5 of the 25 discordant cases (2.6% of all 196 patients), the lateralization of the ictal SPECT was categorized as "both hemispheres" by one reader and as "left" or "right" by the other reader. In the remaining 2 of the 25 discordant cases (1.0% of all 196 patients), one reader categorized the lateralization of the ictal SPECT as "left", the other reader as "right".

The fraction of lateralising ictal SPECT (according to the consensus of the two readers) in the whole sample did not differ significantly between the ^{99m}Tc-HMPAO and the ^{99m}Tc-ECD group (65.5% versus 72.1%, p = 0.355). The fraction of lateralising ictal SPECT was only slightly lower in the 57 patients with non-lateralising MRI (19 with ^{99m}Tc-HMPAO, 38 with ^{99m}Tc-ECD) and also did not differ significantly between ^{99m}Tc-HMPAO and ^{99m}Tc-ECD in this subgroup (63.2% versus 68.4%, p = 0.769). The MRI was considered non-lateralising if it did not show any potentially epileptogenic lesion (n = 46) or if it showed epileptogenic lesions in both hemispheres (n = 11).

Epilepsy surgery was performed in the other hemisphere than pointed to by ictal SPECT in 11 of the 97 patients with available surgery data (11.3%). The reason for this was an MRI lesion in the other hemisphere in the majority of these cases (n = 8, 72.7%).

In those patients in whom lateralization and localization of the resection area was in agreement with lateralization and localization of the ictal SPECT, the outcome at 12 months after surgery did not differ significantly between the ^{99m}Tc-HMPAO and the ^{99m}Tc-ECD group (good/improved/worse outcome 33/50/17% versus 66/28/6%, p = 0.145).

The proportion of patients with "worse" outcome at 12 months after surgery was higher in patients in whom the resection area did not agree with ictal perfusion SPECT with respect to lateralization and/or localization (n = 37, both tracers) compared to the patients in whom lateralization and localization agreed between surgery and ictal SPECT (n = 44, both tracers) (good/improved/worse outcome 54/16/30% versus 57/34/9%, p = 0.028).

When patients were grouped according to the latency of the tracer injection after start of the seizure in EEG independent of the tracer as "short latency" (latency ≤ 40 s, n = 138) or "relatively long latency" (40 s < latency ≤ 120 s, n = 34), the proportion of lateralizing ictal SPECT did not differ significantly between short and relatively long latency (73.2% versus 64.7%, p = 0.396).

The sensitivity of ictal perfusion SPECT (independent of the tracer) in temporal lobe epilepsy was estimated in the 62 patients with "good" or "improved" outcome at 12 months after temporal epilepsy surgery. Lateralization of the ictal perfusion SPECT was correct in 39 of the 62 patients. The SPECT

pointed towards the temporal lobe in all 39 patients with correct lateralization. Thus, sensitivity for correct lateralization and sensitivity for correct localization were both 63%. Ictal perfusion SPECT pointed to the wrong hemisphere in 5 patients (8%), to both hemispheres in 2 patients (3%), and did not show relevant hyperperfusion in 16 patients (26%).

Discussion

The primary finding of the present study is the lack of a significant impact of the tracer, 99mTc-HMPAO or 99mTc-ECD, on the performance of ictal brain perfusion SPECT for identification of the SOZ in patients with drug resistant epilepsy. Neither the proportion of lateralising ictal SPECT nor the 12 months outcome after resection in the lobe pointed to by ictal SPECT differed significantly between the 99mTc-HMPAO and the 99mTc-ECD group. These findings do not rule out small to medium sized (clinically relevant) differences, despite the fact that the sample size was considerably larger in the present study compared to the previous studies that directly compared 99mTc-HMPAO and 99mTc-ECD for ictal brain perfusion SPECT [25, 26]. The power of the present study to detect a difference of 5, 10, 15, 20 and 25% in the proportion of lateralising SPECT between 99mTc-HMPAO and 99mTc-ECD (65% versus 70, 75, 80, 85, and 90%) at the two-sided 5% level was 9%, 28%, 59%, 87% and 99%, respectively.

The lack of a significant tracer effect in the present study at first sight appears to be in conflict with the two previous studies that directly compared 99mTc-HMPAO and 99mTc-ECD for ictal perfusion SPECT and reported findings in favor of 99mTc-HMPAO [25] or in favor of 99mTc-ECD [26]. However, the sensitivity estimates reported in the study favoring 99mTc-HMPAO counted cases with temporal hyperperfusion in the wrong hemisphere (according to invasive EEG or surgical outcome as standard of truth) as true positive [25]. This approach resulted in significantly higher sensitivity with 99mTc-HMPAO compared to 99mTc-ECD (70% versus 29%, p = 0.03) in the 30 patients with extratemporal epilepsy (23 with 99mTc-HMPAO, 7 with 99mTc-ECD). When only cases with correct lateralization were counted as true positive, the sensitivity of 99mTc-HMPAO dropped to 35% and most likely did not differ significantly from the sensitivity of 99mTc-ECD (not reported in the publication). The study that reported results in favor of 99mTc-ECD included a significantly higher proportion of postictal scans (tracer injection after seizure activity had ended) for 99mTc-HMPAO than for 99mTc-ECD (57% versus 16%, p < 0.0001) [26]. This was caused by an additional average delay of 40 s for reconstitution of unstabilized 99mTc-HMPAO after seizure onset [26]. When the analysis was restricted to patients with ictal injections, there was no significant difference in the localization rate between 99mTc-HMPAO and 99mTc-ECD (85% versus 89%) [26]. Thus, closer inspection of the two previous comparisons of 99mTc-HMPAO and 99mTc-ECD for ictal perfusion SPECT reveals that they do not provide strong evidence for the superiority of 99mTc-ECD over 99mTc-HMPAO or vice versa. A meta-analysis of SPECT brain imaging in epilepsy reported that the performance of SPECT was not dependent on the tracer, but the meta-analysis did not include 99mTc-ECD SPECT studies but only 5 series with a total of 69 patients in whom an 123I-labelled tracer (123I-HIPDM or 123I-IMP) had been used for ictal perfusion SPECT instead of 99mTc-HMPAO [30].

A secondary finding of the present study was the 63% sensitivity of ictal perfusion SPECT (independent of the tracer) for correct localization (including correct lateralization) in 62 patients with "good" or "improved" outcome 12 months after temporal epilepsy surgery. This is lower than reported by most previous studies. For example, a prospective multi-center study initiated by the International Atomic Energy Agency in patients with temporal lobe epilepsy undergoing surgery found sensitivity of 86.5% and 83.8% for correct lateralization and localization (in the temporal lobe) of ictal ^{99m}Tc-ECD SPECT taking the surgical site as the gold standard [31]. The meta-analysis cited above reported the combined sensitivity of unifocal findings in ictal perfusion SPECT ipsilateral to the operative side among all good surgical outcomes to be 96.7% (95%-confidence interval 88.7–99.6%) [30]. Possible explanations of the lower sensitivity of ictal SPECT in the present study include differences in the patient population, particularly a lower proportion of patients with seizures that were already well localized by other presurgical methods (as expected in a sample from clinical routine patient care without specific eligibility criteria). In line with this, the proportion of patients with non-lateralizing MRI was rather high in the present study (Table 1).

Another possible explanation for the comparatively low sensitivity of ictal SPECT in the present study is the rather high cutoff of 120 s on the latency of tracer injection applied for exclusion of patients, although the latency was longer than 60 s in only 4 of the 172 patients with known latency. The rationale for the 120 s cutoff was that in temporal lobe epilepsy hyperperfusion in mesial temporal structures is observed up to 2 minutes after the ictus, whereas hypoperfusion of the whole temporal lobe ("postictal switch") is observed from 2–15 min after the ictus [27, 28]. However, after intravenous injection, the tracer takes about 40 s to reach the brain and to be metabolized to become locally fixed [5]. As a consequence, even with very early injection (latency ≤ 30 s) the SPECT image might primarily represent postictal perfusion in case of short seizures (≤ 30 s) [5]. In order to address this point, an additional analysis was performed in the subgroup of patients with "good" or "improved" outcome at 12 months after temporal epilepsy surgery with latency of tracer injection ≤ 60 s and electrical duration of the seizure after tracer injection ≥ 20 s (n = 50). Lateralization of the ictal perfusion SPECT was correct in 34 of the 50 patients, corresponding to 68% sensitivity, that is, slightly better than the 63% sensitivity of correct lateralization in all patients with "good" or "improved" outcome at 12 months after temporal epilepsy surgery.

The following limitations of the study should be mentioned. First, the study was retrospective, which explains the rather high fraction of missing data for some variables (Table 1). In order to avoid potential selection bias by the retrospective inclusion, only very liberal eligibility criteria were applied. As a consequence, the included patient sample should be representative of patients referred to ictal perfusion SPECT for presurgical evaluation of suspected focal epilepsy in clinical routine. Second, ^{99m}Tc-HMPAO and ^{99m}Tc-ECD had not been used concurrently, but ^{99m}Tc-HMPAO SPECT had been performed after ^{99m}Tc-ECD SPECT with only a few exceptions. In order to avoid a potential time effect (e.g., by varying experience of the personnel), processing and visual interpretation of all SPECT images was performed retrospectively by the same readers according to a standardized protocol (instead of using the original interpretation in the written report in the patients' files). All SPECT had been acquired with the same

SPECT systems and using the same acquisition and reconstruction protocol independent of the tracer. Third, the ^{99m}Tc-HMPAO group and the ^{99m}Tc-ECD group were well matched with respect to age, sex, age at first seizure, duration of disease, seizure frequency, history of previous brain surgery, and findings in presurgical MRI (Table 1). The tracer groups differed significantly with respect to the latency of tracer injection (median latency 4 s longer in the ^{99m}Tc-HMPAO group), the duration of the seizure after tracer injection (25 s shorter in the ^{99m}Tc-HMPAO group), the tracer dose (70 MBq higher in the ^{99m}Tc-HMPAO group), and with respect to the delay of the SPECT acquisition after tracer injection (63 min longer in the ^{99m}Tc-HMPAO group). The difference of the median latency of tracer injection between the groups of 4 s was rather small and probably would not have reached statistical significance with smaller sample size. However, it cannot be ruled out that it had a relevant impact on the results, although this appears unlikely. The difference in tracer dose also is not expected to have significantly affected the results [30]. The same is true for the difference in the delay of the SPECT acquisition after tracer injection, as repeat SPECT imaging at 30 min, 2 h and 4–7 h after a single injection of ^{99m}Tc-ECD in patients with temporal lobe epilepsy did not reveal a relevant impact of the delay between tracer injection and start of the SPECT acquisition on the perfusion pattern [25]. The rather large group difference with respect to the delay of the SPECT acquisition after tracer injection is explained by the fact that the transport from ictal tracer injection in the inpatient epilepsy unit of the Department of Neurology and Epileptology of the Protestant Hospital Alsterdorf to the SPECT acquisition in the Department of Nuclear Medicine of the University Medical Center Hamburg Eppendorf was by taxi in the majority of ^{99m}Tc-ECD cases versus ambulance patient transport in the majority of ^{99m}Tc-HMPAO cases. Finally, the two tracer groups comprised different patients instead of head-to-head comparison of the two tracers in the same patients. Head-to-head comparison of the two tracers in the same patients is limited by the fact that both tracers are radioactively labeled by the same isotope (^{99m}Tc) so that they cannot be used simultaneously during the same seizure. Sequential SPECT acquisition during different seizures of the same patient is affected by considerable intrasubject variability of the perfusion pattern in ictal SPECT between different seizures reflecting methodological differences (e.g., different injection latency) but also differences between seizures of the same patient [32, 33].

In conclusion, this study does not provide evidence to favor ^{99m}Tc-HMPAO or ^{99m}Tc-ECD for identification of the seizure onset zone by ictal perfusion SPECT in patients with drug resistant epilepsy.

List Of Abbreviations

^{99m}Tc-HMPAO ^{99m}Tc-hexamethyl-propyleneamine oxime

^{99m}Tc-ECD ^{99m}Tc-ethyl cysteinate dimer

EEG electroencephalography

EZ epileptogenic zone

MBq Megabequerel

MRI magnetic resonance imaging

SOZ seizure onset zone

SPECT single photon emission computed tomography

Declarations

Ethics approval and consent to participate: Waiver of informed consent for the retrospective analysis of the data was obtained from the ethics review board of the general medical council of the state of Hamburg, Germany.

Consent for publication: Not applicable.

Availability of data and materials: The datasets on which the conclusions of this article rely can be made available on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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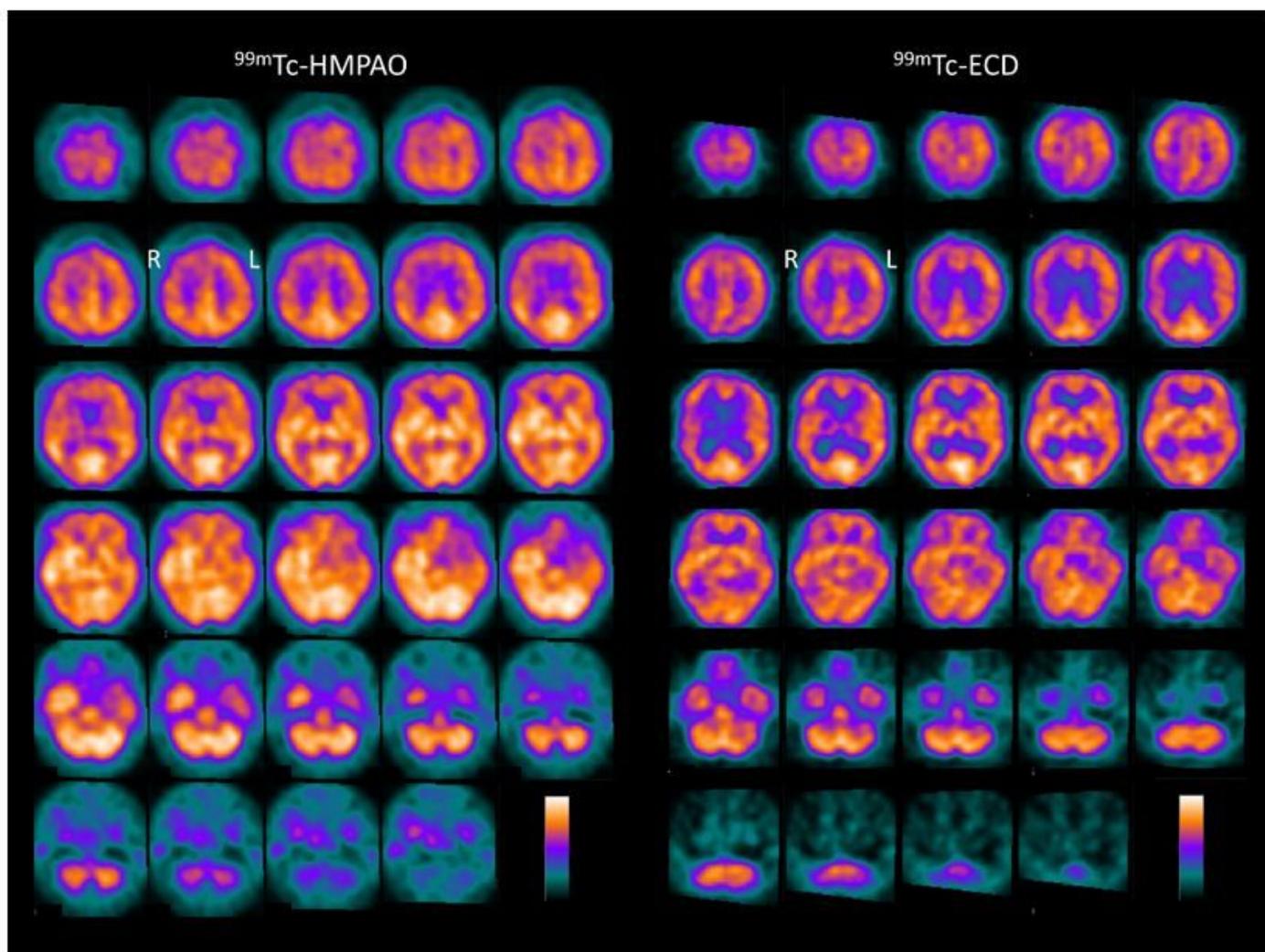
Figures

Figure 1

Standard display used for visual interpretation of ictal perfusion SPECT. The left example shows the ictal brain perfusion SPECT with 640 MBq 99mTc-HMPAO injected 20s after electrical start of the seizure in a 58 years old female patient with 17 years disease duration. The SOZ was localized in the right temporal lobe by both readers. The patient underwent epilepsy surgery with resection of the hippocampus and the anteromedial temporal lobe in the right hemisphere. Histology revealed focal cortical dysplasia. The patient was free of seizures (Engel IA) at 12 months follow-up. The right example shows the ictal brain perfusion SPECT with 393 MBq 99mTc-ECD injected 27s after electrical start of the seizure in a 44 years old male patient with 21 years disease duration. The SOZ was localized in the right temporal lobe by both readers. The patient underwent selective hippocampectomy in the right hemisphere. Histology showed gliosis. The patient was free of seizures (Engel IA) at 12 months follow-up.
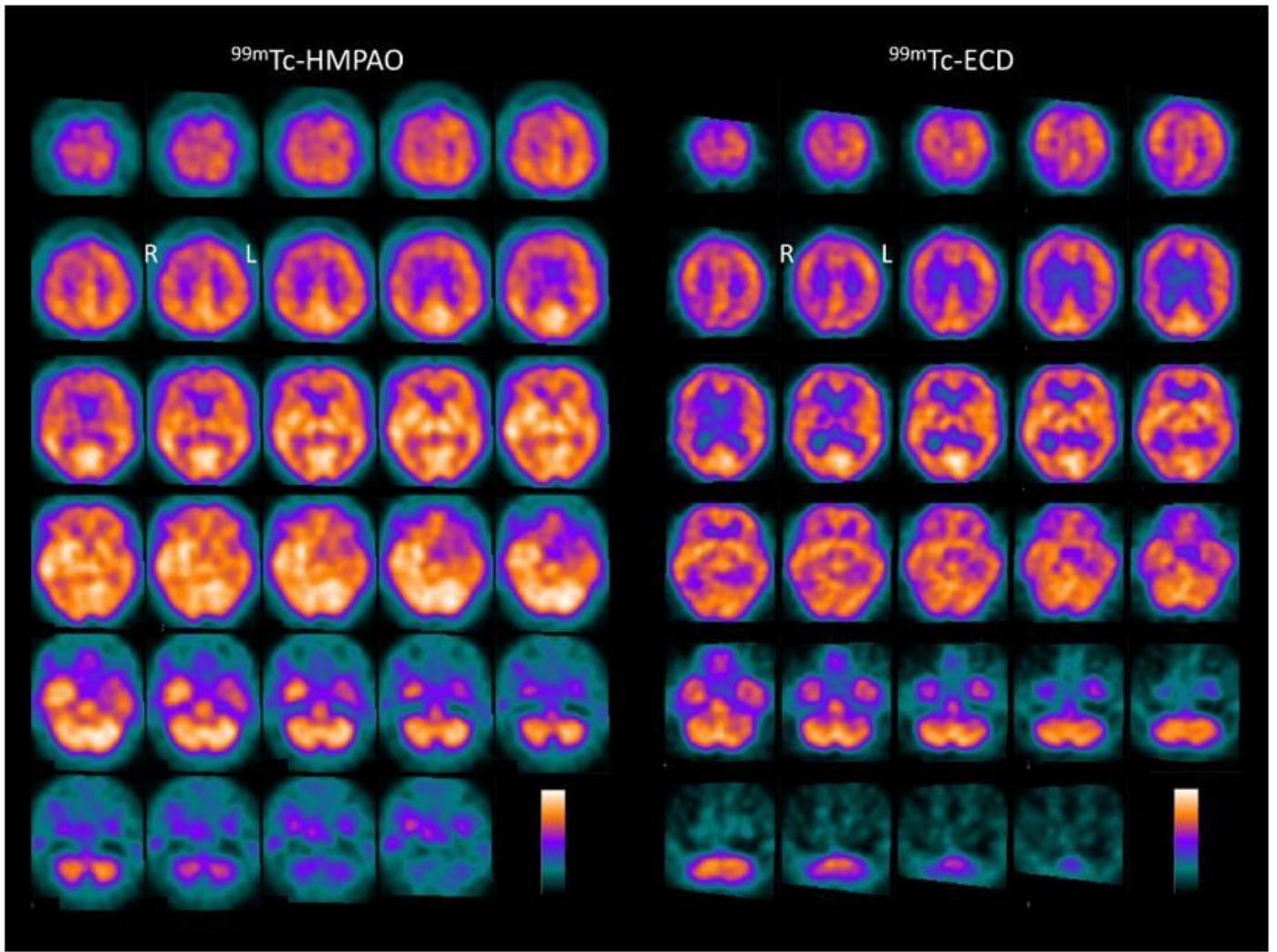
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Standard display used for visual interpretation of ictal perfusion SPECT. The left example shows the ictal brain perfusion SPECT with 640 MBq 99mTc-HMPAO injected 20s after electrical start of the seizure in a 58 years old female patient with 17 years disease duration. The SOZ was localized in the right temporal lobe by both readers. The patient underwent epilepsy surgery with resection of the hippocampus and the anteromedial temporal lobe in the right hemisphere. Histology revealed focal cortical dysplasia. The patient was free of seizures (Engel IA) at 12 months follow-up. The right example shows the ictal brain perfusion SPECT with 393 MBq 99mTc-ECD injected 27s after electrical start of the seizure in a 44 years old male patient with 21 years disease duration. The SOZ was localized in the right temporal lobe by both readers. The patient underwent selective hippocampectomy in the right hemisphere. Histology showed gliosis. The patient was free of seizures (Engel IA) at 12 months follow-up.