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Ictal SPECT in neocortical epilepsies: clinical usefulness and factors affecting the pattern of hyperperfusion

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Abstract *Introduction:* The aims of this analysis were to: (1) determine the value of ictal SPECT in the localization of neocortical epileptogenic foci, (2) evaluate the relationships between the results of ictal SPECT and other potential affecting factors, and (3) compare traditional visual analysis and the subtraction method. *Methods:* We retrospectively analyzed 81 consecutive patients with neocortical epilepsy who underwent epilepsy surgery and achieved a favourable surgical outcome, including 36 patients with normal MRI. Side-by-side visual analysis and subtraction images were classified as correctly localizing, correctly lateralizing, or non-localizing/non-lateralizing images according to the resected lobe. *Results:* Side-by-side visual analysis and subtraction SPECT correctly localized the epileptogenic lobe in 58.9% and 63.0% of patients, respectively. The two methods were complementary and the diagnostic sensitivity of ictal SPECT using the two methods was

79.0%. Ictal SPECT using the visual method correctly localized the epileptogenic lobe more frequently in patients with a localizing pattern of ictal scalp EEG at the time of radioligand injection. When using subtraction images, an injection delay of less than 20 s after seizure onset was significantly correlated with correct localization. The subtraction method was superior to the visual method for localizing frontal lobe epilepsy (FLE) and parietal lobe epilepsy (PLE), and in patients with non-localizing/non-lateralizing EEG at onset. *Conclusions:* Ictal SPECT analyses using visual and subtraction methods are useful and complementary for the localization of the epileptogenic foci of neocortical epilepsy. Early radioligand injection and ictal EEG patterns are related to ictal SPECT localization. The subtraction method may be more useful in some epileptic syndromes.

Keywords Ictal SPECT · Subtraction SPECT · Neocortical epilepsy

Introduction

The localization of neocortical epileptic foci for epilepsy surgery presents major challenges. The complete removal of a lesion and some surrounding cortex is well correlated with an excellent surgical outcome [1, 2]. However, in the absence of a structural lesion or in the presence of a widespread lesion, surgical resection of epileptogenic foci is often less successful [2].

Ictal SPECT has been shown to be a useful means of identifying seizure foci [3, 4], though most studies have concerned medial temporal lobe epilepsy (TLE). In TLE, ictal SPECT shows striking hyperperfusion in more than 90% of cases and the pattern of hyperperfusion is also clearly identified. Some studies, including some of neocortical epilepsy, have shown the potential usefulness of ictal SPECT with variable sensitivity [3, 5–9]. Beyond the temporal lobes, ictal SPECT has also been reported to

be able to localize seizure foci in the frontal, parietal, and occipital lobes. However, few studies have concentrated solely on patients with neocortical epilepsy, and studies regarding the value of ictal SPECT for the localization of epileptogenic foci especially in patients with a normal MRI are limited. Furthermore, most studies have included small numbers of patients.

Subtraction ictal SPECT coregistered with MRI (SISCOM) is known to be a worthwhile technique and is able to improve the specificity and sensitivity of seizure localization [8, 10–12]. Traditional side-by-side visual comparisons of interictal and ictal images may be difficult because of differences in the overall intensities of the two images or differences in slice level and orientation [10]. However, a recent report [13] questions the usefulness of ictal–interictal subtraction SPECT. Thus, the effectiveness of subtraction and visual analyses for the localization of neocortical epileptogenic foci need to be clearly assessed.

The standards used in previous studies have been variable. Ictal EEG or invasive EEG have been used in many studies as standards for the localization of epileptogenic foci. However, ictal rhythms on scalp EEG in neocortical epilepsies are unclear in many cases, and intracranial electrodes placed on the basis of ictal SPECT are likely to give localizing information that coincide with SPECT. The true value of ictal SPECT should be not only to confirm ictal EEG and MRI localization, but to independently localize epileptogenic foci. For this purpose, resected areas in patients showing at least a worthwhile improvement seems to be more suitable as a standard. If ictal SPECT is useful for neocortical epilepsy localization, in cases where other localizing techniques including MRI are less effective, then outcome may be improved.

The diagnostic sensitivity of ictal SPECT in neocortical epilepsy has not been well described in relation to other potential factors affecting the results of ictal SPECT, such as EEG, the presence of a structural lesion, injection time, and seizure pattern. The identification of potential factors affecting the pattern of hyperperfusion is very important for the correct interpretation of ictal SPECT.

The aims of this analysis were to: (1) determine the value of ictal SPECT for the localization of neocortical epileptogenic foci using a large series of surgical patients including many patients with a normal MRI, (2) evaluate the relationships between the results of ictal SPECT and other potential affecting factors, and (3) compare traditional visual analysis and the subtraction method. For these purposes, we retrospectively assessed the results of ictal and interictal SPECT images using subtraction and visual methods in patients who had undergone focal resective surgery on other than the medial temporal lobe.

Patients and methods

Patients

We retrospectively analyzed 81 consecutive patients (55 male and 26 female) with neocortical epilepsy who had undergone epilepsy surgery and had achieved a favourable surgical outcome (i.e., were seizure-free or with at least 90% seizure reduction after surgery). Their average age at surgery was 27.5 years (range 8–56 years), and the mean duration of epilepsy was 13.4 years (range 2–32 years). Presurgical evaluation included brain MRI, FDG-PET, long-term video-EEG monitoring, ictal and interictal SPECT, amobarbital procedure, and intracranial EEG recording. All patients had undergone focal resection other than resection of the medial temporal lobe. Of the 81 patients, 45 had a localized lesion on MRI (41 focal and 4 diffuse lesions), and 36 had no identifiable lesion on MRI. We excluded patients with evidence of hippocampal sclerosis on MRI.

Video-EEG monitoring

Ictal scalp recordings were obtained using a full complement of scalp electrodes placed according to the international 10–20 system with additional anterior temporal electrodes (T1 and T2). Video-EEG monitoring was performed after withdrawing antiepileptic drugs, except phenobarbital. EEGs were reviewed using bipolar and referential montages. Localized pattern classifications at onset and at radioligand injection were defined as follows:

1. Localized initial ictal rhythm: the initial ictal rhythm was confined to one lobe or to two adjacent electrodes.
2. Lateralized patterns: the initial ictal rhythm was lateralized to one hemisphere.
3. Others: the initial ictal rhythm occurred bilaterally or started at lobes not in the epileptogenic area or the ictal rhythm could not be identified.

MR imaging

Standard MRI was performed on a 1.0-T or a 1.5-T unit (Signa Advantage; General Electric Medical Systems, Milwaukee, Wis.) with conventional spin-echo T1-weighted sagittal and T2-weighted axial and coronal sequences. The section thickness was 5 mm and the conventional image gaps were 1 mm. To evaluate the hippocampus and subtle cortical abnormalities, T2-

weighted fast spin-echo sequences with 3-mm thick sections, and T1-weighted 3D magnetization prepared rapid acquisition gradient-echo sequences with 1.5-mm sections, were obtained in the oblique coronal plane of the temporal lobe. The angle of the oblique coronal imaging was perpendicular to the long axis of the hippocampus. We also acquired a fluid-attenuated inversion recovery sequence in the coronal plane.

Interictal and ictal SPECT

Ictal SPECT was performed during video-EEG monitoring. ^{99m}Tc was mixed with hexamethylpropylene amine oxime (HMPAO) and injected as soon as a seizure started. The brain SPECT image was acquired within 2 h of the injection using a triple-head rotating gamma camera (Prism 3000, Picker International, Cleveland, Ohio) with a high-resolution fan beam collimator. Brain perfusion SPECT was acquired using the step and shoot method at 3° intervals and a 128×128 matrix. The whole acquisition lasted 15 min. Interictal SPECT was also performed to identify perfusion changes to be used as the basal perfusion image for subtraction.

Subtraction method

SPM 99 (Statistical Parametric Mapping 99; Institute of Neurology, University College London, London, UK) implemented in Matlab 5.3 (MathWorks, Natick, Mass.) was used to realign ictal and interictal SPECT images and for the spatial normalization of these SPECT images into standard templates. First, ictal and interictal SPECT images were aligned with each other, and then individual ictal and interictal SPECT images were spatially normalized into the SPECT template provided by the SPM software. Parameters for the spatial normalization were obtained from the interictal SPECT images and applied on both the ictal and the interictal SPECT images. Spatially normalized images were smoothed by convolution using an isotropic Gaussian kernel. Pixel counts of SPECT images were normalized to the mean pixel count of gray matter in each SPECT image, which was measured using a probabilistic map of gray matter using the following equation:

$$\frac{\sum_{i,j,k} I_{i,j,k} \times G_{i,j,k}}{\sum_{i,j,k} G_{i,j,k}}$$

where $I_{i,j,k}$ and $G_{i,j,k}$ are the pixel counts in the SPECT images and the probabilistic map of gray matter at the (i, j, k)th pixel, respectively. The probabilistic map provided by SPM was also used.

A perfusion change map was calculated using the following equation:

$$\frac{I_{ic} - I_{in}}{I_{in}} \times 100(\%)$$

where I_{ic} and I_{in} are normalized ictal and interictal SPECT images, respectively.

Perfusion changes >20% were regarded as significant, and perfusion change maps with significant pixels were superimposed on the appropriate T1 MRI template.

Tracer injection time

Delay from seizure onset to tracer injection was calculated. Seizure onset was defined as the onset of an initial ictal rhythm or the onset of clinical seizure. (We defined the faster of these two as the onset.) The relationship between tracer injection and the start of secondary generalized tonic-clonic seizure (2GTCS) was also analyzed.

Image interpretation and evaluation of localizing values

Side-by-side analysis of interictal and ictal SPECT, and analysis of subtraction SPECT images were reviewed independently by one experienced physician who was unaware of the clinical histories or the results of the other presurgical evaluations.

The standard for correctly localized neuroimages was defined as the resected lobe (“epileptogenic lobe”). Side-by-side visual analysis and subtraction images were classified as either correctly localizing, correctly lateralizing (including the resected lobe), or non-localizing/non-lateralizing images.

Invasive study and surgery

We used intracranial electrodes for every patient with a normal MRI to identify the ictal onset zone and the resection margin. Intracranial electrodes were subdural grids and strips in various combinations, but always including multiple strips reaching the parahippocampal gyrus to sample mesial temporal activity. Intracranial initial ictal rhythm was defined as a sustained rhythmic change in EEG that was clearly differentiable from the background EEG and the interictal waves. The surgical resection margin was defined by the intracranial ictal onset zones. We did not remove the mesial temporal structures because the ictal onset zone was located outside the hippocampus and the parahippocampal gyrus.

All patients had a seizure onset categorized as focal, regional, or widespread. Focal onset was defined as an

onset involving fewer than five adjacent electrode contacts, regional onset as one involving five or more adjacent contacts, and widespread onset as one involving more than 20 adjacent electrodes. All patients underwent focal neocortical resections.

Pathological diagnosis

Sections from resected cortical tissue were immersion-fixed in 10% buffered formalin, embedded in paraffin, and stained with haematoxylin and eosin, Bielschowsky, and cresyl violet stains. A diagnosis of pathological cortical dysplasia (CD) was made according to the grading system of Mischel et al. [14]. Specimens were evaluated for the presence of nine specific microscopic and other abnormal features. The nine microscopic features were: (1) cortical laminar disorganization, (2) single heterotopic white matter neurons, (3) neurons in the cortical molecular layer, (4) persistent remnants of the subpial granular cell layer, (5) marginal glioneuronal heterotopia, (6) polymicrogyria, (7) white matter neuronal heterotopia, (8) neuronal cytomegaly with associated cytoskeletal abnormalities, and (9) balloon cell change. Criteria 1 to 5 were classified as mild CD, and 6 and 7 as moderate CD. Pathological findings of 8 or 9 were regarded as severe CD.

Statistical analysis

The McNemar test was used to compare the sensitivity of visual analysis and subtraction SPECT. The factors potentially affecting the result of ictal SPECT were examined using the χ^2 -test or Fisher's exact test depending on the sample size.

Results

Side-by-side visual analysis and subtraction ictal SPECT correctly localized the epileptogenic lobe in 47 patients (58.9%) and 51 patients (63.0%), respectively. No significant difference was found in the localization of the epileptogenic lobe between these two methods ($P=0.59$, McNemar test; Table 1). However, subgroup analysis according to the epileptogenic lobe revealed that the subtraction method was superior in frontoparietal lobe

Table 1 Diagnostic sensitivity of ictal SPECT by the two methods

Localization pattern	Visual analysis	Subtraction	<i>P</i> value
Localizing	47 (58.9%)	51 (63.0%)	0.59
Lateralizing	16 (19.8%)	11 (13.6%)	
Bilateral or normal	14 (17.3%)	17 (21.0%)	
Falsely lateralizing	4 (4.94%)	2 (2.47%)	

Table 2 The relationship between epileptogenic zone location and the diagnostic sensitivity of ictal SPECT

Location of epileptogenic zone	Correct localization		<i>P</i> value
	By visual analysis	By subtraction	
Frontal lobe (<i>n</i> =20)	6 (30.0%)	14 (70.0%)	0.001
Parietal lobe (<i>n</i> =14)	5 (35.7%)	8 (57.1%)	
Temporal lobe (<i>n</i> =36)	30 (83.3%)	24 (66.7%)	0.016
Occipital lobe (<i>n</i> =11)	6 (54.5%)	5 (45.5%)	
<i>P</i> value ^a	<0.0001	0.515	

^a*P* value was calculated between frontoparietal lobe and temporo-occipital lobe

epilepsy localization ($P=0.001$, McNemar test) and visual analysis was superior in temporooccipital lobe epilepsy localization ($P=0.016$, McNemar test; Table 2). The two methods were complementary in terms of localization of the epileptogenic foci. Localization of the epileptogenic foci was possible in 30 patients by only one of these two methods. The results of these two methods were concordant with correct localization in 34 patients (Table 3, Fig. 1).

The mean delay in injection of radioligand was 29.6 ± 18.6 s, and the mean duration of seizure was 77.8 ± 31.3 s. When using subtraction images, an injection delay of <20 s after seizure onset was significantly correlated with correct localization of the epileptogenic zone ($P=0.02$; Table 4; χ^2 -test).

Successful localization by ictal SPECT was observed more frequently in patients without 2GTCS than in those with 2GTCS, which was nearly significant by the visual method ($P=0.052$, Fisher's exact test). Successful localization was also observed more frequently when the radioligand was injected prior to the start of 2GTCS than during 2GTCS, though this was not statistically significant (Table 5).

Correct localization was even possible in patients without localizable EEG, especially by the subtraction method. A trend was noted for the correct localization of ictal SPECT by the visual method to be more frequent in patients with localizing ictal scalp EEG at onset, than in those without ($P=0.09$, χ^2 -test). However, this effect was not observed for subtraction images. The subtraction method localized well even in patients with non-localizing EEG onset. The correct localization of ictal SPECT by the visual method was observed significantly more frequently

Table 3 The complementary nature of the two methods

Visual analysis	Subtraction	
	Localizing	Non-localizing
Localizing	34	13
Non-localizing	17	17

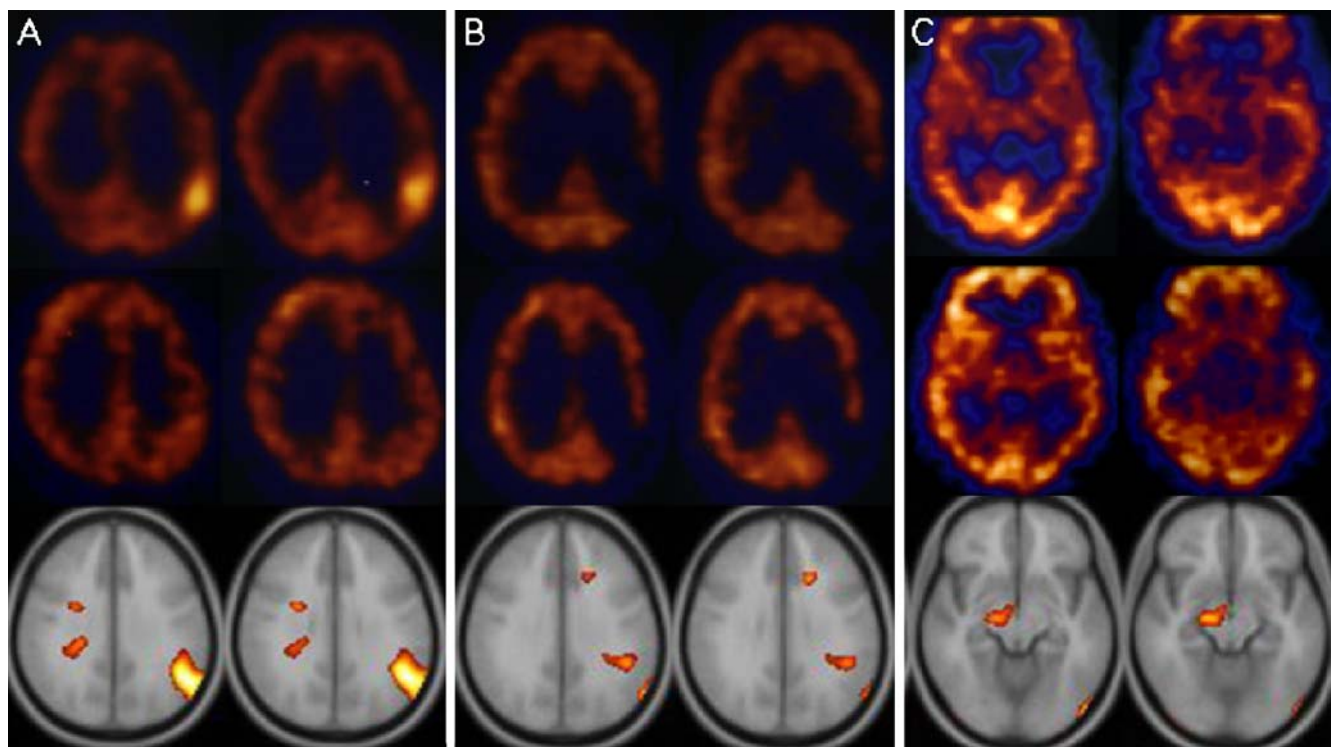


Fig. 1 The complementary roles of the two methods: *top to bottom* ictal SPECT, interictal SPECT, and subtraction SPECT. **a** Both methods localized the epileptogenic foci correctly. **b** Subtraction SPECT localized and visual analysis failed to localize the epilep-

togenic foci. **c** Visual analysis detected the increased ictal perfusion in the left temporal lobe. Subtraction SPECT failed to localize the epileptogenic foci

in patients with localizing or lateralizing ictal scalp EEG during radioligand injection ($P=0.003$, χ^2 -test). However, this effect was not observed for subtraction images. Regional ictal invasive EEG was significantly correlated with the correct localization of ictal SPECT using subtraction images ($P=0.013$, χ^2 -test; Table 6).

The presence of a lesion did not affect the diagnostic sensitivity of ictal SPECT analyzed by either method. However, visual analysis localized the epileptogenic zone in only one of four patients with a diffuse lesion, while the subtraction method successfully localized the epileptogenic zone in three of these patients (Table 7). The pathology of the epileptogenic zone was not related to the diagnostic sensitivity of ictal SPECT (Table 7).

Ictal SPECT localization did not affect the surgical outcome (Table 8).

Table 4 The relationship between injection delay of radioligand after seizure onset and the diagnostic sensitivity of ictal SPECT

Injection delay	Correct localization	
	By visual analysis	By subtraction
Less than 20 s ($n=31$)	21 (67.7%)	25 (80.6%)
More than 20 s ($n=50$)	26 (52.0%)	26 (52.0%)
<i>P</i> value	Not significant	0.02

Discussion

Recent studies have demonstrated that the clinical utility of peri-ictal SPECT can be enhanced by using subtraction images [10–12, 15]. Traditional side-by-side visual comparisons of interictal and ictal images may be difficult because of differences in the overall intensities of images or differences in slice level and orientation. In our series, the localization of epileptogenic foci was possible more frequently using the subtraction method, but this difference

Table 5 The relationship between the presence of a secondary generalized tonic-clonic seizure (2GTCS) and the diagnostic sensitivity of ictal SPECT

Presence of 2GTCS	Correct localization	
	By visual analysis	By subtraction
Present ($n=38$)	18 (47.4%)	21 (55.3%)
Ligand injected prior to 2GTCS ($n=21$)	11 (52.4%)	13 (61.9%)
Ligand injected during 2GTCS ($n=17$)	7 (41.2%)	8 (47.1%)
Absent ($n=43$)	29 (67.4%)	30 (69.8%)
<i>P</i> value	0.052	Not significant

Table 6 The relationship between ictal EEG and the diagnostic sensitivity of ictal SPECT

	Correct localization	
	By visual analysis	By subtraction
Ictal scalp EEG at onset		
Localizing (<i>n</i> =44)	29 (65.9%)	24 (54.5%)
Lateralizing (<i>n</i> =19)	11 (57.9%)	14 (73.7%)
Others (<i>n</i> =18)	7 (38.9%)	13 (72.2%)
<i>P</i> value	0.09	Not significant
Ictal scalp EEG at injection		
Localizing (<i>n</i> =3)	3 (100.0%)	3 (100.0%)
Lateralizing (<i>n</i> =23)	18 (78.3%)	15 (65.2%)
Others (<i>n</i> =55)	26 (52.0%)	30 (60.0%)
<i>P</i> value	0.003	Not significant
Invasive EEG at onset		
Focal (<i>n</i> =25)	14 (56.0%)	11 (44.0%)
Regional (<i>n</i> =35)	17 (48.6%)	27 (77.1%)
Widespread (<i>n</i> =12)	7 (58.3%)	7 (58.3%)
<i>P</i> value	Not significant	0.013

was not significant. Moreover, these methods were complementary in terms of the localization of epileptogenic foci. The subtraction method is not always superior to visual analysis for several reasons. Interictal SPECT may not actually be interictal, and this discrepancy may occur in as many as 5% of interictal scans, probably due to injection during the subclinical ictal period [13]. Our recent investigation has shown that even interictal injection of radiotracer several hours after an ictal episode cannot guarantee true interictal images [16]. In addition, because a perfusion change just more than 20% was regarded as significant, subtle perfusion change could be ignored.

Although no significant difference was found in terms of the localizing value of these two methods, the subtraction method was able to more frequently localize the epileptogenic zone in the frontal and parietal lobes than visual analysis. The subtraction method showed significant blood flow change in 14 of 20 patients with frontal lobe epilepsy

Table 7 The relationship between lesion characteristics and the diagnostic sensitivity of ictal SPECT

	Correct localization	
	By visual analysis	By subtraction
Presence of lesion on MRI		
Present (<i>n</i> =45)	27 (60.0%)	28 (62.2%)
Focal (<i>n</i> =41)	26	25
Diffuse (<i>n</i> =4)	1	3
Absent (<i>n</i> =36)	20 (55.8%)	23 (63.9%)
Pathology		
Cortical dysplasia (<i>n</i> =52)	29 (55.8%)	34 (65.4%)
Tumour (<i>n</i> =16)	11 (68.8%)	7 (43.8%)
Others (<i>n</i> =13)	7 (53.8%)	10 (76.9%)

Table 8 Surgical outcomes and the localization of ictal SPECT

Surgical outcome	Correct localization	
	By visual analysis	By subtraction
Seizure-free (<i>n</i> =42)	23 (54.8%)	26 (61.9%)
Not seizure-free (<i>n</i> =39)	24 (61.5%)	25 (64.1%)

(FLE) whereas visual analysis could do so in only six patients. The frontal lobe is the largest lobe and it may be difficult to see subtle blood flow changes by side-by-side visual analysis. Thus, the subtraction method may be more useful for localization in FLE. Our results show that the localizing value of ictal SPECT is higher in lateral TLE and occipital lobe epilepsy (OLE) by visual analysis. One possible explanation for this is the relatively slow propagation of lateral TLE and OLE compared with FLE or parietal lobe epilepsy (PLE). Our previous study demonstrated that the localizable ictal rhythm on scalp EEG is more prolonged in lateral TLE and OLE than in FLE and PLE [17]. This means that the ictal rhythm has a tendency to remain in one lobe for a longer time in lateral TLE and OLE. However, this effect was not confirmed by subtraction analysis. Subtraction analysis more frequently localized the epileptogenic zone in FLE and PLE than visual analysis. The subtraction method seems to be particularly useful for the localization of epileptogenic foci when there is a subtle blood flow difference of foci due to rapid propagation of the ictal rhythm.

Considering the spreading nature of ictal discharges with time, the early injection of radioligand after seizure onset is indispensable for the correct localization of epileptogenic foci [18, 19]. Injections within less than 20 s clearly showed a higher rate of correct localization in our series. If the radioligand is injected during the earlier part of a seizure, ictal propagation might be limited to structures surrounding the epileptogenic focus and subsequent ictal hyperperfusion might also be limited to this area. The epileptogenic focus is more often correctly localized by SPECT in patients without 2GTCS than in those with 2GTCS. Injection prior to the start of 2GTCS also enhanced the localizing ability of ictal SPECT compared with injection during 2GTCS. 2GTCS means a widespread ictal rhythm over the whole brain, which produces the widespread perfusion change.

In this study ictal SPECT correctly localized epileptogenic foci in patients with non-localized EEG at seizure onset or at radioligand injection. This means that increased perfusion after neuronal activity undetected by scalp EEG can be captured by ictal SPECT. In this sense, ictal SPECT is fundamentally an independent presurgical evaluation tool. The subtraction method was found to be superior to the visual method for the localization of FLE and PLE, and in conditions with non-localizing/non-lateralizing EEG at onset. The subtraction method may have an advantage in

terms of localizing an epileptogenic zone with a subtle blood flow change.

Regional ictal invasive EEG onset was found to be significantly correlated with the correct localization of ictal SPECT using subtraction images. Regional patterns may be more suitable in terms of blood recruitment for correct localization than focal patterns, because focal onset patterns may not recruit enough blood flow due to restricted neuronal firing.

The presence of a structural lesion may hamper correct localization by ictal SPECT. In the presence of a relatively large structural lesion or cerebromalacia, a relatively small proportion of neurons of the true epileptogenic zone can fire. Restricted neuronal firing in the true epileptogenic zone may recruit less blood to the area, which can cause false epileptogenic zone localization. Visual analysis could not detect the difference and subtraction showed subtle perfusion difference in two patients with a diffuse lesion of our series.

This study did not seek to predict surgical outcome according to the localization of ictal SPECT because we only included patients with a worthwhile improvement (90% seizure reduction or more). However, we compared the localization of ictal SPECT between the seizure-free patients and those with only worthwhile improvement. The localization of ictal SPECT was not found to predict seizure freedom (Table 8). One previous study has shown the predictive value of SISCOM SPECT in extratemporal lobe epilepsy [15]. In that study concordance of the SISCOM focus with the site of surgery was associated with a significantly higher rate of excellent postoperative seizure control than nonconcordant or nonlocalizing SISCOM studies. This contradictory result may have been caused by our inclusion criteria, as we included only patients with a favourable surgical outcome. Further analysis is needed to clarify this issue.

Conflict of interest statement We declare that we have no conflict of interest.

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