Epilepsy Research (2013) **106**, 173—180

journal homepage: www.elsevier.com/locate/epilepsyres

# Statistical parametric mapping of interictal 123I-iomazenil SPECT in temporal lobe epilepsy surgery

**Shigeru Fujitani** [a,*], **Kazumi Matsuda** [b], **Fumihiro Nakamura** [b], **Koichi Baba** [b], **Naotaka Usui** [b], **Takayasu Tottori** [b], **Tadahiro Mihara** [b], **Kiyohito Terada** [b], **Keiko Usui** [b], **Yushi Inoue** [b], **Yasukazu Kajita** [c], **Toshihiko Wakabayashi** [c]

[a] *Japanese Red Cross Nagoya First Hospital, Michishita-cho 3-35, Nakamura-ku, Nagoya City, Aichi, Japan*
[b] *National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Urushiyama 886, Aoi-ku, Shizuoka City, Shizuoka, Japan*
[c] *Department of Neurosurgery, Nagoya University, Graduate School of Medicine, Tsurumai-cho 56, Showa-ku, Nagoya City, Aichi, Japan*

Received 28 September 2012 ; received in revised form 4 February 2013; accepted 20 March 2013
Available online 11 April 2013

**KEYWORDS**
Temporal lobe epilepsy;
Epileptogenic foci;
Single photon emission computed tomography;
123I-iomazenil;
Benzodiazepine receptor;
Statistical parametric mapping

**Summary** Brain single photon emission computed tomography (SPECT) for epilepsy is divided into two types (using three radionuclide tracers)—perfusion SPECT (123I-IMP or 99 mTc-ECD), identifying epileptogenic foci by detecting abnormality in regional cerebral blood flow, and 123I-iomazenil SPECT, identifying epileptogenic foci based on distribution of central benzodiazepine receptors. This study aimed to statistically evaluate and compare the SPECT effectiveness for the three tracers. Statistical parametric mapping (SPM) analysis was performed on 30 mesial temporal lobe epilepsy (mTLE) patients. The radionuclide and patient data were categorized as follows: abnormality in the medial temporal lobe on the operated hemisphere (AAA), in the entire temporal lobe on the operated hemisphere (AA), in the dominantly affected temporal lobe on the operated hemisphere (A), in bilateral temporal lobes (B), with no abnormalities in bilateral temporal lobes (C), and with abnormality in the temporal lobe on the nonoperated hemisphere (D). For analyses of (AAA), (AA), and (A), examining the hemisphere containing epileptogenic foci, IMP-SPECT was significantly superior to ECD-SPECT ($P < 0.05$). For (AAA), indicating localization, IMZ-SPECT was significantly superior to the other two ($P < 0.05$).

* Corresponding author at: Japanese Red Cross Nagoya First Hospital, 453-8511, Michishita-cho 3-35, Nakamura-ku, Nagoya City, Aichi, Japan. Tel.: +81 52 481 5111; fax: +81 52 482 7733.
*E-mail address:* shigeru_f717@nyc.odn.ne.jp (S. Fujitani).


http://dx.doi.org/10.1016/j.eplepsyres.2013.03.008

IMP-SPECT was superior for lateralizing and IMZ-SPECT was useful for localizing epileptogenic foci in mTLE patients though the applicability of the results in extratemporal lobe epilepsy is unknown.


## Introduction

Successful seizure outcome following epilepsy surgery depends on how accurately the location and extent of the epileptogenic focus is identified preoperatively (Wiebe et al., 2001). While EEG and MRI greatly contribute to presurgical evaluation, recent developments in neurofunctional imaging techniques allow better assessment of the epileptogenic focus preoperatively (Goffin et al., 2008; la Fougère et al., 2009). 123I-iodamphetamine (123I-IMP), 99 mTc-ethyl cysteinate dimer (99 mTc-ECD), and 123I-iomazenil (123I-IMZ) are the most frequently used radionuclide tracers for presurgical evaluation of patients with refractory partial epilepsy (Tanaka et al., 1997; Kaneko et al., 2006; Van Paesschen et al., 2007; Barba et al., 2009).

123I-IMP and 99 mTc-ECD are brain perfusion SPECT techniques that measure regional cerebral blood flow (rCBF). Their application to clinical practice for epilepsy is based on the assumption that decreased interictal neuronal activity is associated with decreased metabolism and rCBF (O'Brien et al., 1998). Recently, a computer-aided subtraction method called subtraction ictal SPECT coregistered to MRI (SISCOM) was reported to be sensitive and specific in the detection of the seizure onset zone. However, ictal SPECT has several technical difficulties. It is difficult and too cumbersome to obtain spontaneous seizures because the seizures always occur unexpectedly. Accurate localization of the seizure onset zone can be achieved only when a radionuclide tracer is injected as quickly as possible before the neuronal activity is propagated from the seizure onset zone to other sites. Even if the radionuclide tracer is promptly injected during the seizure, it is impossible for the tracer to immediately reach the brain when injected through an arm vein; it usually takes 15—20 s to reach the brain (Goffin et al., 2008; Kaneko et al., 2006; Barba et al., 2009; Bartolini, 1981; Shuke et al., 2004).

The radionuclide tracer 123I-IMZ can detect reduction in the central-type benzodiazepine receptor (BZR). It is applied to clinical practice for epilepsy on the basis that the BZR density is decreased in the epileptogenic tissue of patients with partial epilepsy (Savic et al., 1988; Sata et al., 2002).

Correct identification of the functional deficit area on SPECT examination leads to a better surgical outcome (Tanaka et al., 1997; Van Paesschen et al., 2007; Morimoto et al., 2005). Despite previous observations that the result of each SPECT method usually does not coincide (Shuke et al., 2004; Venz et al., 1998), no study has compared the sensitivity and diagnostic values of all the three SPECT techniques in the same patient.

In the present study, we retrospectively evaluated the ability of these three types of SPECT techniques to identify the epileptogenic focus in patients with mesial temporal lobe epilepsy (mTLE) during the interictal state, using statistical parametric mapping (SPM), a statistical brain imaging analysis technique.

## Methods

### Participants

Selective amygdalohippocampectomy was performed in 152 patients with mTLE at National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders between July 2004 and September 2008. In 46 of these patients, IMP-, ECD-, and IMZ-SPECT were all performed preoperatively in the interictal state. A group of 20 healthy volunteers also consented to participate, with their SPECT images used to create the healthy brain template for each radionuclide. These databases were used as control for SPM analysis. Sixteen of the 46 patients were excluded for the following reasons: one patient was too young to be compared with the adult-specific database, one patient died for an unknown reason within two years of surgery, six patients achieved poor postoperative seizure outcomes, and eight patients' SPECT data were unavailable for review. In total, 30 patients were included in this study. The clinical characteristics of participants are shown in Table 1.

The patient group consisted of 15 male and 15 female individuals with age ranging from 17 to 56 years (mean age, 30 years) at surgery. Histopathological diagnosis was mesial temporal sclerosis in 21 cases, glioma in one case, hamartoma in the amygdala in one case, and unavailable in the others. The postoperative outcome was evaluated using Engel's classification, and only patients with class I and II were selected for the study to confirm that the surgically resected area encompassed the epileptogenic focus. In these 30 patients with mTLE, we retrospectively investigated SPECT findings for the aforementioned three radionuclides using SPM analysis.

### Scanning protocol

SPECT studies were conducted using 123I-IMP, 99 mTc-ECD, and 123I-IMZ while the patient was in the interictal state. IMZ-SPECT technique was routinely performed in two separate phases: early scanning was performed for 30 min starting at 5 min after the intravenous injection of 222 MBq of IMZ (Nihon Medi-Physics Co. Ltd, Hyogo, Japan) and delayed scanning was performed for 30 min starting at 165 min after the injection. It was reported that delayed SPECT images reflect better distribution of the benzodiazepine receptor than early images (Onishi et al., 1996). Early SPECT images were considered to be influenced by the distribution of cerebral blood flow. Therefore, the delayed IMZ-SPECT scans were analyzed in the present study. For the other two SPECT techniques, SPECT scanning was performed

**Table 1** Clinical features of patients and results of stratification of images for each radionuclide tracer.

| Case | Age | Sex | Lat | Engel | Patho | IMP | ECD | IMZ |
|---|---|---|---|---|---|---|---|---|
| 1 | 30 | F | R | Ia | MTS | AAA | A | C |
| 2 | 41 | M | L | Ia | MTS | C | C | AA |
| 3 | 24 | M | L | Ia | MTS | AA | A | C |
| 4 | 21 | F | L | Ib | MTS | AA | C | C |
| 5 | 56 | F | R | Id | MTS | AA | AA | AAA |
| 6 | 19 | F | R | Ib | UA | AA | C | AAA |
| 7 | 22 | F | L | Ia | MTS | AA | C | C |
| 8 | 26 | F | L | Ia | MTS | AA | AA | AA |
| 9 | 35 | F | L | I | MTS | AA | AA | AA |
| 10 | 25 | F | L | Ia | Glioma | C | AAA | AAA |
| 11 | 32 | M | L | Ia | UA | B | C | C |
| 12 | 34 | M | R | II | MTS | B | AA | AAA |
| 13 | 22 | M | R | Ic | MTS | AAA | C | AAA |
| 14 | 43 | M | R | Ia | MTS | A | C | AAA |
| 15 | 31 | F | L | Ic | MTS | AA | C | D |
| 16 | 46 | M | R | Ia | UA | AAA | AAA | AAA |
| 17 | 31 | M | L | IIb | MTS | AA | D | C |
| 18 | 36 | M | L | Ia | MTS | C | C | B |
| 19 | 27 | F | R | Ib | MTS | AA | A | AAA |
| 20 | 21 | F | R | I | MTS | AA | C | A |
| 21 | 36 | F | L | IId | MTS | A | B | AAA |
| 22 | 35 | F | L | I | UA | A | AA | C |
| 23 | 17 | M | L | Ia | MTS | A | AA | A |
| 24 | 17 | M | L | Ia | MTS | AA | AA | A |
| 25 | 39 | F | L | II | UA | AA | C | D |
| 26 | 23 | M | R | Ia | MTS | AA | C | AAA |
| 27 | 20 | F | R | Ia | UA | B | AA | AA |
| 28 | 30 | M | L | Ib | MTS | AA | C | C |
| 29 | 30 | M | L | I | Hamar | A | B | AA |
| 30 | 40 | M | R | Ia | UA | D | A | C |

Abbreviations: Engel, Engel's classification; F, female; Hamar, hamartoma; Lat, laterality; L, left; M, male; MTS, mesial temporal sclerosis; Patho, pathology; R, right; UA, unavailable.

for 30 min starting at 20 min after intravenous injection of 222 MBq of IMP (Nihon Medi-Physics Co. Ltd, Hyogo, Japan) and 740 MBq of 99 mTc-ECD (Daiichi Radioisotope Laboratories, Tokyo, Japan). All SPECT techniques were performed using the same two-detector rotating gamma camera system equipped with ultrahigh-resolution fan beam collimators at an acquisition matrix of $128 \times 128$ pixels and a zoom factor of 1.4, with a step-and-shoot acquisition that had $5^{\circ}$ per step, 45 s per view, and 72 views (Millennium VG SPECT machine, General Electric Medical Systems). A filtered back-projection method was applied for image reconstruction, with a Butterworth ramp filter after preprocessing (order 10) and a cutoff of 0.45 cycles/pixel. Slice thickness was 3.16 mm, and no attenuation was corrected.

## Statistical parametric mapping analysis

We used SPM5 under MATLAB version 6.5 (MathWorks, Inc., Natick, MA, USA). The control MRI atlas images (constructed from scans of 20 healthy participants) were converted from DICOM to Analyze file format using the software MRIcro. A unique original standard brain MRI was created on SPM5 using a signal averaging procedure on all MRI data from 20 normal people. For all participants, SPECT data for each of the three nuclides was converted to Analyze with MRIcro. SPECT data for each healthy control were standardized to be appropriate for morphological assessment of standard brain MRI using the algorithm that appeared when our own standard brain MRI had been created. Morphologically standardized SPECT data for the 20 healthy controls were averaged for each nuclide to produce a normalized, standardized database.

Similarly, for the 30 mTLE patients, raw SPECT data were converted from DICOM to Analyze format using MRIcro. Similar to controls, patient brains were standardized and normalized to the database.

Jackknife analysis using SPM was performed to compare each voxel between patients' standardized SPECT data and the control template. The easy *Z*-score imaging system (eZIS; National Center of Neurology and Psychiatry, Tokyo, Japan) was used to outline statistically significant low uptake regions.

## Image interpretation

Three independent, experienced examiners who were blinded to patients' pre- and postsurgical outcomes assessed

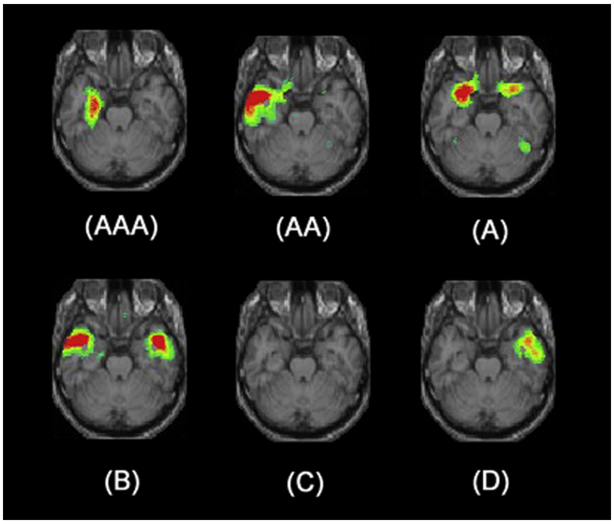


**Figure 1** Example of the eZIS images (SPM Tomography: Axial) stratified into the six stages. A case of an epileptogenic focus on the right mesial temporal lobe. (AAA) Decreased uptake in the medial temporal lobe on the operated hemisphere, (AA) Decreased uptake in the entire temporal lobe on the operated hemisphere, (A) Decreased uptake dominantly in temporal lobe on the operated hemisphere, (B) Decreased uptake in bilateral temporal lobes, (C) No Decreased uptake in bilateral temporal lobes, and (D) Decreased uptake in the temporal lobe on the nonoperated hemisphere.

the eZIS images. For each radionuclide and patient, data were categorized as follows: abnormality in the medial temporal lobe on the operated hemisphere (AAA), in the entire temporal lobe on the operated hemisphere (AA), in the dominantly affected temporal lobe on the operated hemisphere (A), in bilateral temporal lobes (B), with no abnormalities in bilateral temporal lobes (C), and with abnormality in the temporal lobe on the nonoperated hemisphere (D) (Fig. 1). In cases of disagreement between the examiners, a discussion was conducted and consensus was reached for all cases.

## Statistical analysis

The data sets mentioned above were evaluated between the three radionuclide tracers using a Wilcoxon signed rank test. We defined two lines—one between (AAA) and (AA) and the other between (A) and (B). We created a line between (AAA) and (AA) to divide the stages into the groups from the viewpoint that only (AAA) provides useful information on accurate localization of the epileptogenic focus, and the other between (A) and (B) to divide the stages into the groups from the viewpoint that (AAA), (AA), and (A) provide useful information for determining the side of surgery. That is, analyses related to focus localization and lateralization were performed using the Wilcoxon signed rank test. Statistical significance was set as $P < 0.05$. All statistical analyses were performed using SPSS (versions 17.0, SPSS Inc.)

**Table 2** Summary of the results of stratification and comparison of findings of localization and lateralization for each radionuclide tracer.

| | IMP | ECD | IMZ |
|---|---|---|---|
| AAA | 3 | 2 | 10 |
| AA | 15 | 8 | 5 |
| A | 5 | 4 | 3 |
| B | 3 | 2 | 1 |
| C | 3 | 13 | 9 |
| D | 1 | 1 | 2 |

| | AAA | | AAA, AA and A | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| IMP | 3/30 | 10.0 | 23/30 | 76.7 |
| ECD | 2/30 | 6.7 | 14/30 | 46.7 |
| IMZ | 10/30 | 33.3 | 18/30 | 60.0 |

## Results

We retrospectively investigated IMP-, ECD-, and IMZ-SPECT techniques for 30 patients with mTLE. Some patients had mesial temporal atrophy or hyperintensity, and no patient had obvious tumorous or vascular lesions on presurgical MRI. Tables 1 and 2 show the results of each SPECT technique analyzed using SPM. Findings were categorized as previously described.

Decreased radionuclide tracer uptake in the mesial temporal lobe ipsilateral on the operation side (AAA) was observed in three patients using IMP-SPECT, two using ECD-SPECT, and 10 using IMZ-SPECT. Decreased radionuclide tracer uptake in the entire temporal lobe on the operated hemisphere (AA) was observed in 15 patients using IMP-SPECT, eight using ECD-SPECT, and five using IMZ-SPECT. Decreased radionuclide tracer uptake dominantly located in the temporal lobe contralateral to the operated hemisphere (D) was observed in one patient by both IMP-SPECT and ECD-SPECT, and in two patients by IMZ-SPECT. Of note, many extratemporal regions also demonstrated minor low-uptake findings for all the three radionuclide tracers in all patients. In this study, we primarily focused on the extent of abnormally reduced radionuclide tracer uptake in the temporal lobes compared with the epileptogenic focus as confirmed by surgical resection.

## Diagnostic performance of IMP-, ECD-, and IMZ-SPECT in lateralizing the epileptogenic focus

Decreased 123I-IMP uptake in the temporal lobe ipsilateral of the operated hemisphere was observed in 26 (86.7%) of the 30 patients. Abnormalities in the ipsilateral temporal lobe were observed in 16 (53.3%) using ECD-SPECT and in 19 (63.3%) using IMZ-SPECT. Of these, decreased radionuclide tracer uptake in the contralateral temporal lobe was observed in eight using IMP-SPECT, six using ECD-SPECT, and four using IMZ-SPECT. However, five of the eight patients using IMP-SPECT, four of the six using ECD-SPECT, and three of the four using IMZ-SPECT demonstrated dominant laterality of the ipsilateral temporal lobe. Therefore, diagnostic performance with respect to focus lateralization was 23 (76.7%) using IMP-SPECT, 14 (46.7%) using ECD-SPECT, and 18 (60.0%) using IMZ-SPECT. All the three techniques showed similar results with respect to laterality in seven patients (23.3%). IMP-SPECT and ECD-SPECT corresponded to the surgically resected side in 10 patients. IMP-SPECT and IMZ-SPECT corresponded to the surgically resected side in 14 patients. ECD-SPECT and IMZ-SPECT corresponded to the surgically resected side in 10 patients. Three patients had decreased 123I-IMP uptake in the contralateral temporal lobe despite decreased tracer uptake observed in the ipsilateral temporal lobe with the other two tracers. Seven patients had decreased 99 mTc-ECD uptake and three patients had decreased 123I-IMZ uptake in the contralateral temporal lobe despite showing decreased tracer uptake located in the ipsilateral temporal lobe using the other two tracers.

### Diagnostic performance of IMP-, ECD-, and IMZ-SPECT in localizing the epileptogenic focus

Decreased 123I-IMZ uptake localized in the mesial temporal lobe ipsilateral to the operated hemisphere was observed in 10 (33.3%) of the 30 patients. Exact localization in the ipsilateral mesial temporal lobe was found in three (10%) using IMP-SPECT and in two (6.7%) using ECD-SPECT. Of the three cases with localized findings in the ipsilateral mesial temporal lobe using IMP-SPECT, two also demonstrated localized findings using IMZ-SPECT, but one demonstrated no apparent findings on either temporal lobe using IMZ-SPECT. The two cases with localized findings in the ipsilateral mesial temporal lobe using ECD-SPECT also demonstrated ipsilaterally localized findings using IMZ-SPECT. Only one patient (no. 16) had an exact co-localization in the ipsilateral mesial temporal lobe using all three radionuclide tracers.

### Lateralization and localization

IMP-SPECT was statistically superior to ECD-SPECT in lateralizing the epileptogenic focus in mTLE patients (IMP 76.7% vs. ECD 46.7%; $P = 0.029 < 0.05$). Lateralization of the focus to the correct temporal lobe was achieved more often using IMP-SPECT than IMZ-SPECT. However, this was not significantly different (IMP 76.7% vs. IMZ 60.0%; $P = 0.166 > 0.05$). On the other hand, IMZ-SPECT correctly localized the focus significantly more often than the other two perfusion SPECT techniques (IMZ 33.3% vs. IMP10.0%, $P = 0.020 < 0.05$; IMZ 33.3% vs. ECD 6.7%, $P = 0.003 < 0.01$). There was no significant difference between IMP-SPECT and ECD-SPECT in localizing the epileptogenic focus in mTLE patients (IMP 10.0% vs. ECD 6.7%; $P = 0.157 > 0.05$) (Table 2 and Fig. 2).

### Case study (Fig. 3)

A 23-year-old male presented with a history of intractable epileptic seizures. He had no remarkable medical history (e.g., febrile convulsions or head trauma). He reported an episode with sudden onset at age 20, in which he lost consciousness and convulsed for several minutes. Following that episode, he suffered from monthly complex partial seizures, which involved repeating nonsensical phrases followed by lack of response. MRI did not reveal obvious hippocampal sclerosis. With respect to the SPECT techniques, IMZ-SPECT demonstrated an apparent decrease in the BZR density restricted to the right mesial temporal lobe, which was compatible with high frequency rhythmic activity appearing predominantly at the right sphenoidal electrode on ictal EEG. According to IMP-SPECT, regional blood flow was decreased in the right mesial temporal lobe accompanied by wider area, including the ipsilateral lateral temporal lobe and bilateral orbitofrontal region. On the contrary, ECD-SPECT yielded no apparent decrease in rCBF, even in the right mesial temporal lobe. Based on presurgical evaluation, which included examination of these SPECT techniques, right amygdalohippocampectomy was performed. Pathological examination of the resected surgical specimens revealed hippocampal sclerosis. The patient suffered no neurological deficit following surgery and remained seizure free at follow up 24 months later (Engel Class Ia).

## Discussion

In the present study of patients with mTLE, IMP-SPECT demonstrated decreased uptake in the temporal lobe ipsilateral to epileptogenic focus more frequently than the other two radionuclide tracers. In this study, findings were observed in the temporal lobe ipsilateral to the epileptogenic focus using IMP-SPECT in more than 75% of cases, while rates for IMZ-SPECT and ECD-SPECT were <60% and <50%, respectively. Our results suggest that when lateralization of the epileptogenic focus is necessary for surgical intervention, IMP-SPECT may be valuable. If the aim of examination was to confirm laterality in conjunction with other examinations, such as EEG and MRI, IMP-SPECT would be most useful of the three radionuclide tracers. However, IMP-SPECT could not accurately localize the focus. Decreased 123I-IMP uptake localizing to the resected area was no more than 10.0% of cases. The area identified on IMP-SPECT often extended beyond the surgically resected area. The decreased 123I-IMP uptake represents not the epileptogenic area but the hypoperfused or hypometabolic area, which includes the surrounding region with depressed neuronal function. This is the reason behind more frequently observed decreased uptake using IMP-SPECT than IMZ-SPECT, which makes it an unsuitable tracer for localizing the focus.

Because 99 mTc-ECD can be retained in the brain without redistribution for a sufficient time to permit image acquisition, it is currently the most frequently used tracer for ictal SPECT (Goffin et al., 2008; la Fougère et al., 2009; Kazemi et al., 2010). It has been well established that ictal subtraction technique improves the ability to evaluate the epileptogenic focus. However, ictal subtraction technique has several disadvantages. This method routinely requires two images, i.e., ictal and interictal. Moreover, we could not always obtain successful ictal SPECT images. Radionuclide tracer injection is performed briefly after the seizure starts, but delay must be overcome before the tracer reaches the brain. That indicates the possibility of propagation from epileptogenic focus, which results in false localization or lateralization. Patients with fast propagation are profoundly

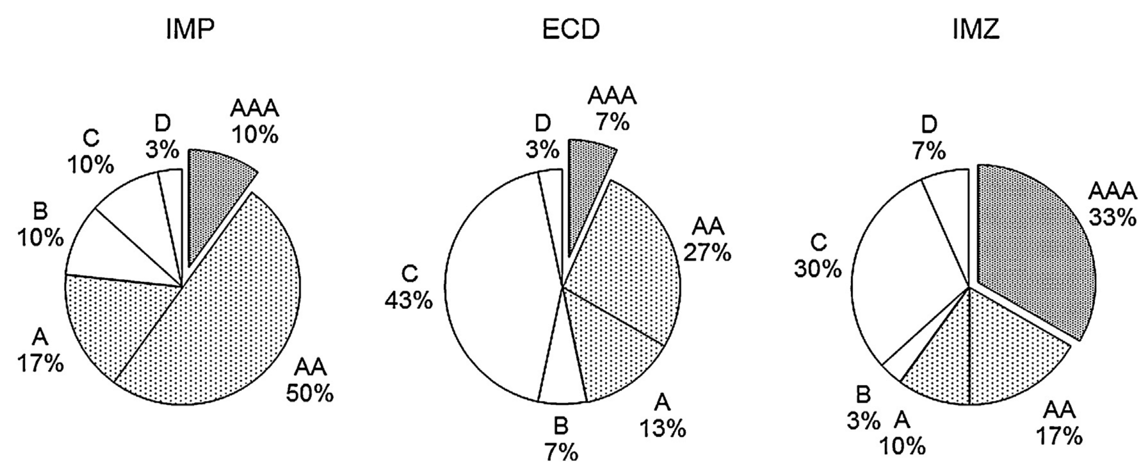


**Figure 2** Comparison of findings of localization and lateralization for each radionuclide tracer with circle graphs Lateralization: IMP vs. ECD, $P = 0.029^*$; IMP vs. IMZ, $P = 0.166$; IMZ vs. ECD, $P = 0.248$ Localization: IMZ vs. IMP, $P = 0.020^*$; IMZ vs. ECD, $P = 0.003^*$; IMP vs. ECD, $P = 0.157$.

affected by the time lag between seizure onset and tracer application. Although ictal subtraction technique is highly useful, it is fraught with uncertainty. SPECT examination becomes useful only after we obtain successful images. Some patients could never get the successful image no matter how many times we repeated the studies. Although we cannot realize the importance, it is an advantage of interictal SPECT that we can always obtain the image with certainty.

Interictal ECD-SPECT can be used to detect the epileptogenic focus by identifying the hypoperfused area, this finding was less frequently observed using ECD-SPECT than

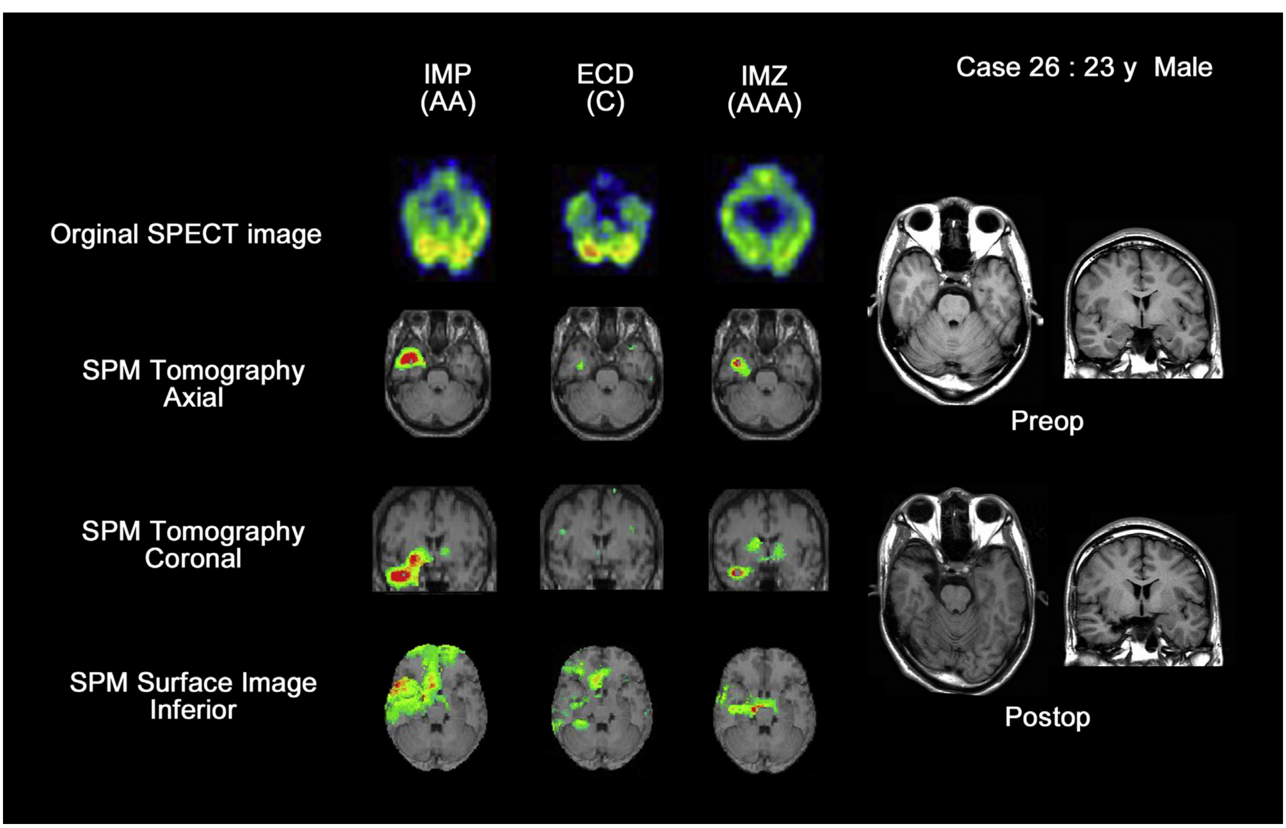


**Figure 3** SPECT images of a 23-year-old patient with mesial temporal lobe epilepsy due to mesial temporal sclerosis on the right hemisphere (case 26 in Table 1). Axial raw data and tomography with eZIS of IMP, ECD, and IMZ SPECT images. The decreased area on IMZ SPECT was restricted to the right mesial temporal lobe. MRI indicated pre- and postamygdalohippocampectomy in the right hemisphere.

IMP-SPECT. This discrepancy in findings regarding cerebral blood flow distribution between IMP-SPECT and ECD-SPECT is well established and not specific to epilepsy. Although ECD-SPECT demonstrates high diagnostic accuracy in cerebrovascular disease, its image contrast is not as high as that of IMP-SPECT (Moretti et al., 1994; Tsuchida et al., 1994). 123I-IMP has higher first pass extraction and smaller back diffusion, resulting in a linear relationship between tissue activity and rCBF. In contrast, 99 mTc-ECD has been reported to have a lower extraction fraction and back diffusion of the unmetabolized tracer during the initial phase after intravenous injection (Walovitch et al., 1989). Retention of 99 mTc-ECD is reported to occur because of the metabolism of polar acid products that are trapped in the brain. Such differences in the mechanism of uptake, as specific enzyme reactions responsible for conversion, may modify the images (Moretti et al., 1994; Matsuda et al., 1993). Though enzymatic transformation of 99 mTc-ECD in neuronal cells in epilepsy patients is unspecified, the present study demonstrated that ECD-SPECT delineates lesser prominent image contrast than IMP-SPECT in interictal epilepsy patients.

Some studies reported an advantage conferred by IMZ-SPECT compared to other SPECT techniques and PET radionuclide tracers. A multicenter European study of 89 epilepsy cases revealed a sensitivity of 93% for IMZ-SPECT and 80% for cerebral blood flow SPECT for identification of epileptogenic foci (Schubiger et al., 1991). Shuke et al. (2004) reported a case of temporal lobe epilepsy with discordant findings observed between IMZ-SPECT, IMP interictal, and ECD ictal cerebral blood flow SPECT. The authors advocated the use of IMZ-SPECT because it determines the location of seizures based on the BZR density, which in turn reflects neuronal tissue integrity and could not be influenced by temporal changes in electrical neuronal activity or cerebral blood flow. Kaneko et al. (2006) compared the efficacy of IMZ-SPECT, IMP-SPECT, and FDG-PET in seven patients with temporal lobe epilepsy. The authors suggested that IMZ-SPECT was more useful than FDG-PET and IMP-SPECT because it had the highest level of agreement with the operative findings.

Although our data is concordant with these previous studies in terms of demonstrating the advantage of IMZ-SPECT, the present study has addressed two potential limitations of the previous studies. Firstly, these previous studies may have included not only mesial but also lateral temporal lobe epilepsy cases. Because most studies performed anterior temporal lobectomy, not selective amygdalohippocampectomy, there is a possibility that the epileptogenic focus may have been located in the lateral temporal lobe in the case diagnosed as mTLE preoperatively in their studies. That is, because the resected area investigated in their studies might be much wider and extended than the actual epileptogenic focus, their studies have a limitation in terms of determining the exact location of the epileptogenic zone. Therefore, it is difficult to argue about focus localization with their study.

The present study included only mTLE cases that were confirmed by successful selective amygdalohippocampectomy. The present study confirmed that the decreased uptake area of 123I-IMZ was more restricted to the ipsilateral mesial temporal lobe than those observed using 123I-IMP or 99 mTc-ECD. Our results suggest that IMZ-SPECT is more valuable than cerebral perfusion SPECT if the purpose of the SPECT study was the precise presurgical localization of the epileptogenic focus in mTLE. It may invite the criticism that IMZ-SPECT is not so useful since only 33% of IMZ-SPECT studies showed the (AAA) pattern and the rest of the patients, as much as 67%, comprised the false-negative group. However, it is not even possible to determine the exact location of epileptogenic focus with SPECT examination alone. The clinical usefulness depends on whether SPECT examination could have additional diagnostic value on EEG and MRI in presurgical evaluation at present. Once IMZ-SPECT image shows the (AAA) pattern, we have a great chance of finding the focus on ipsilateral mesial temporal lobe because the false positive rate is considered to be low. We can know it from the low rate of (B) and (D) of IMZ-SPECT reflecting the finding in the temporal lobe on the nonoperated hemisphere. Therefore, if discrimination between mesial and lateral temporal lobe epilepsy is the aim of SPECT examination, IMZ-SPECT has a greater advantage over the other radionuclide tracers examined in this study.

Secondly, previous studies have made evaluations primarily using visual assessment. It can be difficult to identify the focus using traditional visual interpretation of SPECT scans. Even if images are assessed by the same doctor, there may be some variability in assessment. Furthermore, if brain volume decreases with atrophy, partial volume effects reduce radioactivity on the SPECT image even if the cerebral blood flow remains unchanged. Therefore, diagnosing the focus localization with raw SPECT data alone may merely reflect the atrophy of the concerned brain. We were able to rule out this variability by using SPM-based computed statistical brain imaging analysis. Our results suggest that IMZ-SPECT is less likely to delineate the finding than IMP-SPECT. However, once abnormality in the mesial temporal lobe is identified, IMZ-SPECT may be useful in terms of localization (Umeoka et al., 2007).

The principal limitation of our study is that it included only mTLE cases. Further examinations are required to judge the applicability of the results of the present study in extratemporal lobe epilepsy.

In conclusion, IMZ-SPECT was superior to IMP-SPECT and ECD-SPECT in accurate evaluation of the focus localization in mTLE patients. IMP-SPECT was superior to IMZ-SPECT and ECD-SPECT in sensitive evaluation of the focus lateralization in mTLE patients. Although SPECT examination is only an aid to EEG or MRI in preoperative evaluation at present, the appropriate radionuclide tracers should be selected as the situation demands to maximize its value.

## References


Barba, C., Di Giuda, D., Fuggetta, F., Colicchio, G., 2009. Provoked ictal SPECT in temporal and extratemporal drug-resistant epileptic patients: comparison of statistical parametric mapping and qualitative analysis. Epilepsy Res. 84, 6—14.

Bartolini, A., 1981. Regional arm-brain mean transit time in the diagnostic evaluation of patients with cerebral vascular disease. Stroke 12, 241—245.

Goffin, K., Dedeurwaerdere, S., Van Laere, K., Van Paesschen, W., 2008. Neuronuclear assessment of patients with epilepsy. Semin. Nucl. Med. 38, 227—239.

Kaneko, K., Sasaki, M., Morioka, T., et al., 2006. Pre-surgical identification of epileptogenic areas in temporal lobe epilepsy by 123I-domazenil SPECT: a comparison with IMP SPECT and FDG PET. Nucl. Med. Commun. 27, 893—899.

Kazemi, N.J., Worrell, G.A., Stead, S.M., et al., 2010. Ictal SPECT statistical parametric mapping in temporal lobe epilepsy surgery. Neurology 74, 70—76.

la Fougère, C., Rominger, A., Förster, S., Geisler, J., Bartenstein, P., 2009. PET and SPECT in epilepsy: a critical review. Epilepsy Behav. 15, 50—55.

Matsuda, H., Li, Y.M., Higashi, S., et al., 1993. Comparative SPECT study of stroke using Tc-99 m ECD, I-123 IMP, and Tc-99 m HMPAO. Clin. Nucl. Med. 18, 754—758.

Moretti, J.L., Tamgac, F., Weinmann, P., et al., 1994. Early and delayed brain SPECT with technetium-99 m-ECD and iodine-123-IMP in subacute strokes. J. Nucl. Med. 35, 1444—1449.

Morimoto, K., Tamagami,.H., Matsuda, K., 2005. Central-type benzodiazepine receptors and epileptogenesis: basic mechanisms and clinical validity. Epilepsia 46 (Suppl. 5), 184—188.

O'Brien, T.J., So, E.L., Mullan, B.P., et al., 1998. Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. Neurology 50, 445—454.

Onishi, Y., Yonekura, Y., Mukai, T., et al., 1996. Delayed image of iodine-123 iomazenil as a relative map of benzodiazepine rectptor binding: the optimal scan time. Eur. J. Nucl. Med. 23, 1491—1497.

Sata, Y., Matsuda, K., Mihara, T., Aihara, M., Yagi, K., Yonekura, Y., 2002. Quantitative analysis of benzodiazepine receptor in temporal lobe epilepsy: [(125)I]iomazenil autoradiographic study of surgically resected specimens. Epilepsia 43, 1039—1048.

Savic, I., Persson, A., Roland, P., Pauli, S., Sedvall, G., Widén, L., 1988. In-vivo demonstration of reduced benzodiazepine receptor binding in human epileptic foci. Lancet 2, 863—866.

Schubiger, P.A., Hasler, P.H., Beer-Wohlfahrt, H., et al., 1991. Evaluation of a multicentre study with Iomazenil — a benzodiazepine receptor ligand. Nucl. Med. Commun. 12, 569—582.

Shuke, N., Hashizume, K., Kiriyama, K., et al., 2004. Correct localization of epileptogenic focus with I-123 iomazenil cerebral benzodiazepine receptor imaging: a case report of temporal lobe epilepsy with discordant ictal cerebral blood flow SPECT. Ann. Nucl. Med. 18, 541—545.

Tanaka, F., Yonekura, Y., Ikeda, A., et al., 1997. Presurgical identification of epileptic foci with iodine-123 iomazenil SPET: comparison with brain perfusion SPET and FDG PET. Eur. J. Nucl. Med. 24, 27—34.

Tsuchida, T., Nishizawa, S., Yonekura, Y., et al., 1994. SPECT images of technetium-99 m-ethyl cysteinate dimer in cerebrovascuar diseases: comparison with other cerebral perfusion tracers and PET. J. Nucl. Med. 35, 27—31.

Umeoka, S., Matsuda, K., Baba, K., et al., 2007. Usefulness of 123I-iomazenil single-photon emission computed tomography in discriminating between mesial and lateral temporal lobe epilepsy in patients in whom magnetic resonance imaging demonstrates normal findings. J. Neurosurg. 107, 352—363.

Van Paesschen, W., Dupont, P., Sunaert, S., Goffin, K., Van Laere, K., 2007. The use of SPECT and PET in routine clinical practice in epilepsy. Curr. Opin. Neurol. 20, 194—202.

Venz, J., Hierholzer, S., et al., 1998. Quantitative estimation of I-123-Iomazenil receptor binding in temporal lobe epilepsies using two SPECT acquisitions — comparison with the regional cerebral blood flow and a compartment model. Nuklearmedizin 37, 49—56.

Walovitch, R.C., Hill, T.C., Garrity, S.T., et al., 1989. Characterization of technetium-99 m-L,L-ECD for brain perfusion imaging, Part 1: pharmacology of technetium-99 m ECD in nonhuman primates. J. Nucl. Med. 30, 1892—1901.

Wiebe, S., Blume, W.T., Girvin, J.P., Eliasziw, M., 2001. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N. Engl. J. Med. 345, 311—318.