Utility of Ictal Single Photon Emission Computed Tomography in Mesial Temporal Lobe Epilepsy With Hippocampal Atrophy: A Randomized Trial

Tonicarlo R. Velasco, MD*
Lauro Wichert-Ana, MD†
Gary W. Mathern, MD‖
David Araújo, MD‡
Roger Walz, MD*
Marino M. Bianchin, MD*
Charles L. Dalmagro, MD
Joao P Leite, MD*
Antonio C. Santos, MD‡
Joao A. Assirati, Jr, MD§
Carlos G. Carlotti, Jr, MD§
Americo C. Sakamoto, MD*

Departments of *Neurology, †Nuclear Medicine, ‡Radiology, and §Neurosurgery, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirao Preto, Brazil; ‖Department of Neurosurgery, The Intellectual and Developmental Disabilities Research Center, and The Brain Research Institute; David Geffen School of Medicine, University of California, Los Angeles, California

Correspondence:
Tonicarlo Rodrigues Velasco, MD, PhD,
710 Westwood Plaza,
Room 2123,
Los Angeles, CA 90095-1769.
E-mail: tonicarlo@gmail.com

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BACKGROUND: The development of newer diagnostic technologies has reduced the need for invasive electroencephalographic (EEG) studies in identifying the epileptogenic zone, especially in adult patients with mesial temporal lobe epilepsy and hippocampal sclerosis (MTLE-HS).

OBJECTIVE: To evaluate ictal single photon emission computed tomography (SPECT) in the evaluation and treatment of patients with MTLE-HS.

METHODS: MTLE patients were randomly assigned to those with (SPECT, n = 124) and without ictal SPECT (non-SPECT, n = 116) in an intent-to-treat protocol. Primary end points were the proportion of patients with invasive EEG studies, and those offered surgery. Secondary end points were the length of hospital stay and the proportion of patients with secondarily generalized seizures (SGS) during video-EEG, postsurgical seizure outcome, and hospital cost.

RESULTS: The proportion of patients offered surgery was similar in the SPECT (85%) and non-SPECT groups (81%), as well as the proportion that had invasive EEG studies (27% vs 23%). The mean duration of hospital stay was 1 day longer for the SPECT group ($P < 0.001$). SGS occurred in 51% of the SPECT and 26% of the non-SPECT group ($P < 0.001$). The cost of the presurgical evaluation was 35% higher for the SPECT compared with the non-SPECT group ($P < 0.001$). The proportion of patients seizure-free after surgery was similar in the SPECT (59%) compared with non-SPECT group (54%).

CONCLUSION: Ictal-SPECT did not add localizing value beyond what was provided by EEG-video telemetry and structural MRI that altered the surgical decision and outcome for MTLE-HS patients. Ictal-SPECT increased hospital stay was associated with increased costs and a higher chance of SGS during video-EEG monitoring. These findings support the notion that a protocol including ictal SPECT is equivalent to one without SPECT in the presurgical evaluation of adult patients with MTLE-HS.

KEY WORDS: Clinical utility, Diagnostic test, Epilepsy surgery, Ictal SPECT, Presurgical evaluation, Randomized, Temporal lobe epilepsy

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ABBREVIATIONS: **EEG**, electroencephalographic; **EZ**, epileptogenic zone; **MTLE-HS**, mesial temporal lobe epilepsy and hippocampal sclerosis; **SGS**, secondarily generalized seizures; **SPECT**, single photon emission computed tomography

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Selection of candidates for epilepsy surgery relies on the identification of the epileptogenic zone (EZ), the brain area that generates seizures.[1] In the past, the EZ was identified based on the clinical and electroencephalographic (EEG) characteristics, frequently by use of invasive intracranial EEG.[2] The development of newer diagnostic technologies such as MRI, fluorodeoxyglucose positron emission tomography (FDG-PET), magnetoencephalography (MEG), and single photon emission computed tomography (SPECT) has reduced

the need for invasive EEG studies in identifying the EZ, especially in adult patients with mesial temporal lobe epilepsy and hippocampal sclerosis (MTLE-HS).

Despite the large number of articles evaluating these presurgical tests, the assessment of diagnostic techniques used in epilepsy surgery is far from being as developed as the evaluation of treatments. Unlike antiepileptic drugs, imaging techniques require few regulatory approvals to be implemented as a routine and class I evidence supporting the clinical benefit of an imaging procedure for patients with epilepsy is limited. Most studies have addressed the diagnostic accuracy of tests, with little information about the impact of imaging protocols on clinical management, outcome, and costs.[3]

Ictal SPECT is considered a reliable noninvasive tool to lateralize complex partial seizures in patients with medically refractory MTLE. Most studies have reported high rates of correct localization with few false-positives scans.[4-10] One study advocated that ictal SPECT should be a routine test in the presurgical evaluation of patients with refractory epilepsy.[11] However, these studies did not address whether the results of ictal SPECT provided additional knowledge about the epileptogenic zone beyond what was already known by ictal scalp EEG and MRI. Moreover, there is a lack of information on if the test had an impact on clinical management for MTLE patients.[3]

To address this question, we performed a randomized trial to determine whether ictal SPECT added value over other diagnostic tests in the clinical management of patients with MTLE. Our initial hypothesis was that ictal SPECT would reduce the need for invasive EEG studies and increase the probability of offering surgery to MTLE patients compared with those not having ictal SPECT scans. That hypothesis turned out to be incorrect. We found evidence that the use of ictal SPECT had no impact on the chance of patients becoming seizure free after surgery. In addition, secondary measures found that the incidence of secondary generalized seizures during video-EEG evaluation, length of hospital stay, and hospital costs were higher in patients who had ictal SPECT scans.

PATIENTS AND METHODS

Study Recruitment

The trial was conducted at the University of São Paulo, Ribeirao Preto, Brazil, and patients were enrolled from 2002 to 2004. Subjects were identified at the time of admission for inpatient EEG-video monitoring and had to be at least 18 years of age. Patients were considered eligible if they had a medical history, seizure semiology as described by the family, routine outpatient interictal EEG, and MRI results consistent with refractory MTLE-HS. The clinical picture usually consisted of patients with complex partial seizures with epigastric, autonomic, or psychic auras; focal slowing, interictal spikes, and sharp waves over the anterior, inferior, and mesial temporal regions on routine scalp EEG; and hippocampal atrophy on T1 and increased hippocampal signal on T2 MRI sequences. However, we included all patients with features of the MTLE-HS syndrome. This included patients without an aura, patients with normal routine EEGs or bilateral interictal spikes, and patients with bilateral hippocampal atrophy on MRI. In addition, we included 2 patients whose clinical history and routine EEG strongly suggested the MTLE-HS syndrome, but the MRI results were normal (also called Paradoxical TLE[12]). We excluded patients with extrahippocampal lesions, focal motor-sensory abnormalities on physical examination, and generalized and extratemporal interictal spikes because such features place the diagnosis of MTLE in doubt.[13] Refractoriness was defined as failure to respond to at least 2 antiepileptic drugs in adequate trials.[14]

Protocol Approvals, Registrations, and Consents

The study was approved by the National Ethics Committee for Experiments Using Human Subjects and by our Hospital Ethics Committee (HCRP N6773/2002). If the patients were deemed eligible, an information brochure was provided to them; an informed written consent was obtained from all participating patients.

Experimental Design and Randomization

Those who agreed to participate were randomly assigned, using a computer-generated list, to those undergoing standard presurgical evaluation including ictal and interictal SPECT (SPECT group) or the same protocol without SPECT (non-SPECT group). Allocation concealment was performed until interventions were assigned to prevent selection bias. The staff member responsible for seeing the patient allocated the next available number only after hospital admission to the Video-EEG monitoring unit and the informed consent was obtained. The patient remained in the assigned group throughout the study (intent-to-treat protocol). For both groups, the presurgical workup included detailed clinical history and neurological examination, interictal and ictal video-EEG monitoring, neuropsychological examination, and, when appropriate, intracarotid amobarbital testing for memory and speech representation. Neuroimaging studies included high-resolution MRI with special protocols to visualize the hippocampus and mesial temporal structures (see Methods, Supplemental Digital Content 1, http://links.lww.com/NEU/A351). Ictal perfusion changes were analyzed by a nuclear medicine physician blinded to the other presurgical evaluation tests.

The Surgical Decision Process

The data from the presurgical evaluation were discussed at a weekly multidisciplinary meeting and a treatment plan was formulated. At the time of the discussion, the team knew if an ictal SPECT study had been performed and its results. The group designed a treatment plan using all available information for each patient. If the combined results of noninvasive investigation suggested that one temporal lobe was responsible for the seizures and the risk of increased postoperative memory deficit was low, we offered surgery. If the studies suggested bitemporal MTLE based on MRI or EEG studies, and additional information from ictal SPECT or neuropsychology studies did not help to lateralize the epileptogenic zone, we recommended invasive or semi-invasive EEG studies. If invasive or semi-invasive evaluation revealed unilateral ictal onsets and the risk of memory deficit was low, we offered surgery. For those with a risk of postoperative memory deficit (eg, bilateral hippocampal atrophy or bilateral memory deficits on neuropsychological evaluation), we performed amobarbital intracarotid memory (WADA) tests. For the WADA, approximately 30 to 45 seconds after amobarbital injection, 16 items were presented for 4 to 5 seconds each (4 abstract figures, 4 pictured objects, 4 words, and 4 real objects). If, after the injection of the hemisphere of the planned surgery, the patient recalled or recognized at least 9 objects, the patient was considered to have passed the Wada test and was offered surgery.

Study End Points

The primary end points were (1) the proportion of patients offered surgery and (2) proportion of patients submitted to invasive EEG investigations. Secondary end points included (1) postsurgical seizure outcomes, (2) hospital costs for the presurgical evaluation, (3) length of hospital stay during presurgical evaluation, and (4) the percentage of patients who had secondarily generalized seizures during EEG-video monitoring with reduced antiepilepsy drugs. Investigators assessing primary and secondary end points were blinded to ictal SPECT group assignment.

Statistical Analysis

We used an intention-to-treat analysis and all randomly assigned patients were included in the statistical analysis. The null hypothesis was that the primary and secondary end points would be similar for the SPECT and non-SPECT groups. SPSS package (release 13.0) was used. We computed absolute differences and 95% confidence intervals for the event rates in both groups. An a priori power analysis concluded that 120 patients were necessary per group to detect a 10% absolute difference of primary end points between SPECT and non-SPECT groups with a 70% power or a 20% absolute difference with an 80% power, at a level of significance of.05. These calculations assumed that an absolute difference of 10 to 20% on the primary outcome measures would be clinically relevant. To evaluate the contribution of multiple variables on dependent dichotomous variables we used binary logistic regression. To evaluate the diagnostic accuracy of ictal SPECT we used the localization by EEG-video monitoring as the reference standard.

RESULTS

Cohort Characteristics

From January 2002 to June 2004, 521 patients were screened for eligibility, 243 met age and clinical inclusion criteria, and 240 agreed to participate and signed informed consent. After randomization, the SPECT group consisted of 124 patients and the non-SPECT group consisted of 116 patients (Figure 1). Once enrolled, 10 patients did not complete the study. Seven patients did not complete the presurgical evaluation process and 3 patients did not have seizures during video-EEG monitoring. In addition, 5 patients from the ictal SPECT group had scans with movement artifact (n = 3) and uneven distribution of radiopharmaceutical (n = 2). In the SPECT group, the mean (±SD) time from the EEG seizure onset to radiotracer injection was 40.7 ± 16.8 seconds. The clinical and neuroimaging features were similar in the comparison of the SPECT with the non-SPECT group (Table 1).

Primary End Points

In this randomized trial, the proportion of MTLE patients offered surgery or who had invasive EEG studies was similar in the ictal SPECT compared with the non-SPECT group (Table 1).

Secondary End Points

The mean hospital stay for video-EEG monitoring was 1 day longer in the SPECT compared with the non-SPECT group (Table 2). Hospital costs for the ictal SPECT group were 35% higher (US $3200) compared with the non-SPECT group ($2300; $P < .001$, Student t test). The increase in cost was due to the SPECT study and the longer hospital stay. The proportion of patients who had secondarily generalized seizures (SGS) during video-EEG monitoring was higher in the SPECT group compared with the non-SPECT group (Table 2).

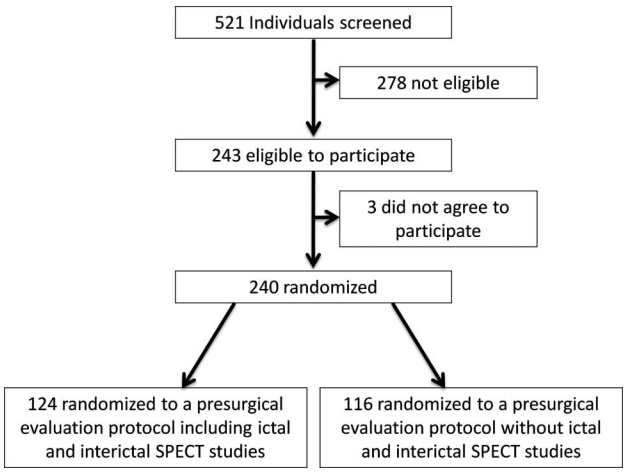

FIGURE 1. *Enrollment and outcomes of patients randomly assigned to the SPECT and non-SPECT groups.*

To evaluate which variables could explain why patients in the SPECT group had a higher chance of having SGS, we performed multivariate analysis (binary logistic regression). The dependent variable was SGS during video-EEG monitoring and the independent variables were group assignment (SPECT vs non-SPECT), lateralization of ictal EEG onsets, MRI, and ictal and interictal EEG, previous frequency of SGS, and sex. The results showed that only video-EEG duration was associated with the probability of having secondary generalized seizures during the presurgical evaluation ($P < .01$).

Accuracy of Ictal SPECT

Consistent with prior studies, ictal SPECT scans were accurate in detecting the epileptogenic region in MTLE-HS patients. The accuracy of ictal SPECT, however, overlapped with the results of EEG-video monitoring and MRI information. Ictal SPECT was concordant with ictal EEG results in 80% of MTLE-HS cases (95% CI = 72% to 87%). Subgroup analysis revealed that the accuracy of ictal SPECT was higher in patients whose ictal EEG was ipsilateral to the side of hippocampal atrophy (85%) compared with those with bilateral and contralateral ictal EEG onsets (65%, $P = .017$, Fisher exact test). The accuracy of ictal SPECT was lower in patients with bilateral interictal spikes (68%) compared with those with unilateral interictal spikes (90%, $P = .01$, Fisher exact test). The time of radiotracer injection was similar between those in which the ictal SPECT was accurate (39.4 ± 14.0 s) and nonaccurate (40.1 ± 27 s, $P = .871$, Student t test).

TABLE 1. Demographic and Clinical Features of the Study Participants at Baseline[a,b]

Variable	SPECT n = 124	Non-SPECT n = 116	*P* Value
Age, y			
Age at randomization	38.1 ± 9.3	38.7 ± 8.7	.635[c]
Range	(19-57)	(22-59)	
Age at IPI	3.1 ± 3.9	4.4 ± 4.5	.107[c]
Range	(0.1-27)	(0.6-25)	
Age at seizure onset	11.0 ± 8.1	10.4 ± 6.8	.587[c]
Range	(1-36)	(1-33)	
Epilepsy duration, y	27.1 ± 11.1	28.2 ± 9.4	.361[c]
Range	(5-40)	14-45	
Sex (female),- n (%)	65 (52.4%)	67 (57.8%)	.437[d]
Presence of IPI,- n (%)	53 (45.7%)	41 (41.0%)	.495[d]
Presence of aura, n (%)	63 (50.8%)	55 (47.4%)	.608[d]
Frequency of SGS, seizures/y	2.7 ± 4.9	3.1 ± 5.4	.477[c]
History of status epilepticus, n (%)	15 (12.1%)	13 (11.2%)	.844[d]
Family history of epilepsy, n (%)	74 (58.7%)	61 (52.6%)	.229[d]
MRI findings, n (%)			
Unilateral hippocampal sclerosis	104 (83.9%)	104 (89.7%)	
Bilateral hippocampal sclerosis	18 (14.5%)	12 (10.3%)	.230[d]
Normal MRI (cryptogenic MTLE)	2 (1.6%)	0 (0.0%)	
Intelligence quotient	82.1 ± 9.8	81.4 ± 8.1	.570[c]
Range	(62-100)	(69-103)	
Years of education, y	6.7 ± 3.6	6.5 ± 3.7	.671[c]
Range	(1-11)	(1-11)	

[a]SPECT, single photon emission computed tomography; IPI, initial precipitating injury; SGS, secondarily generalized seizures; MTLE, mesial temporal lobe epilepsy.
[b]Plus-minus values are mean ± SD.
[c]Independent sample *t* test.
[d]Fisher exact test.

Surgical Outcomes

Based on presurgical evaluation, surgery was considered in 199 patients, and was performed in 163 patients at the time of manuscript preparation. Sixteen patients declined surgery, 5 had medical or psychiatric comorbidities, and 6 patients were not submitted to surgery because the team was concerned about the risk of memory deficit after WADA memory testing. Nine other cases are awaiting surgery. The standard operation consisted of anterior resection of the temporal tip followed by microsurgical resection of the mesial temporal structures.[15]

The median follow-up after surgery was 56.7 ± 13.3 months (range, 14-73 months). The intention-to-treat analysis showed that, overall, 57.1% of patients were seizure-free at the completion of the study (95% CI = 50.8-63.2). The proportion of seizure-free patients was similar between the SPECT and non-SPECT groups (Table 2).

All patients had pathologically confirmed hippocampal sclerosis, with the exception of 2 patients with endfolium sclerosis, both in the SPECT group. No deaths were reported. Nine patients (5.6%) had complications including infection (n = 3), 4th cranial nerve palsy (n = 1), temporary hemiparesis (n = 1), mania (n = 1), psychosis (n = 1), cerebrospinal fluid fistula (n = 1), and deep vein thrombosis (n = 1).

DISCUSSION

This study found that ictal SPECT did not add additional localizing value over standard ictal scalp EEG-video telemetry and high-quality MRI in the presurgical evaluation of patients with MTLE-HS. The percentages of patients who were offered surgery and had invasive EEG studies were similar between the SPECT and non-SPECT groups. Moreover, ictal SPECT studies increased (1) the length of hospital stay during inpatient video-EEG telemetry, (2) the chance of having generalized seizures during EEG monitoring, and (3) the cost of the presurgical evaluation in MTLE-HS patients. In addition, the percentage of MTLE-HS patients with Engel class I outcomes after surgery was similar in the SPECT and non-SPECT groups. Taken together, these results support the notion that ictal SPECT studies provide redundant information in the

TABLE 2. Primary and Secondary End Points Comparison Between SPECT and non-SPECT groups: Intent-to-Treat Analysis[a,b]

Variable	SPECT (n = 124)	Non-SPECT (n = 116)	Absolute Difference (95% CI)	*P* value
Offered surgery				
Overall	105 (84.7%)	94 (81.0%)	3.7% (−6.0 to 13.5)	.495[c]
Without invasive electrodes	86 (69.4%)	80 (69.0%)	0.4% (−11.5 to 11.9)	1.000[c]
Invasive electrodes	34 (27.4%)	27 (23.3%)	4.1% (−6.9 to 14.9)	.556[c]
Foramen ovale	33 (26.6%)	26 (22.4%)	4.2% (−6.7 to 14.9)	.545[c]
Depth electrodes	7 (5.6%)	8 (6.9%)	−1.2% (−5.2 to 5.6)	.894[c]
Engel class I	74 (59.7%)	63 (54.3%)	5.4% (−7.1 to 17.6)	.435[c]
Generalized seizures during VEEG	63 (50.8%)	30 (25.9%)	24.9% (12.7 to 36.1)	<.001[c]
Length of stay during VEEG, d	5.6 ± 2.1	4.6 ± 2.2	1.01 (0.46 to 1.6)	<.001[d]
Hospital costs of VEEG (× 1000 U$)	3.2 ± 1.1	2.3 ± 1.1	697 (441.0 to 954.0)	<.001[d]

[a]SPECT, single photon emission computed tomography; VEEG, Video-EEG.
[b]Plus-minus values are mean ± SD.
[c]Fisher exact test.
[d]Independent sample *t* test.

presurgical evaluation of refractory MTLE patients. Furthermore, elimination of ictal SPECT for MTLE-HS patients would reduce hospital cost and length of stay.

When designing this study we hypothesized that in MTLE-HS patients, the results of ictal SPECT would reduce the need for invasive EEG electrodes and shorten the presurgical evaluation process. However, this was not the case. Our results indicate that the findings of video-EEG monitoring had more impact in our decision-making process than we expected. In other words, if a patient had bilateral independent seizure onsets, we became concerned about bilateral disease, and submitted the patients to invasive evaluation, even if the SPECT findings were ipsilateral to the side of hippocampal atrophy. In addition, we offered surgery to patients whose MRI and EEG were concordant but the ictal SPECT data were nonlateralizing. If the video-EEG results were clearly ipsilateral to the side of hippocampal atrophy, the nonconcordant results of ictal SPECT were not enough to prompt us to use intracranial electrodes, because it is known that ictal SPECT may reveal unusual perfusion patterns due to propagated seizure activity.[16] On the other hand, if the results were clearly bilateral, similar to other centers, we performed invasive studies. The group of patients in which ictal SPECT might have been useful in our study were those with unilateral hippocampal atrophy and ipsilateral interictal EEG, but bilaterally synchronous ictal EEG findings. In this group, 7 of 8 patients had ictal SPECT findings in agreement with the MRI, and they were offered surgery. However, there were 6 similar cases in the non-SPECT group, and they were also referred to surgery without ictal SPECT results, if the MRI and interictal EEG were lateralized and concordant and the ictal EEGs were not contradictory. Ictal SPECT in our hands was not useful in any subgroup of MTLE-HS patients in deciding which cases were offered surgery or invasive EEG studies.

Patients submitted to ictal SPECT had a higher chance of having secondarily generalized seizure compared with the non-SPECT group. The longer length of hospital stay in the SPECT group, associated with the reduction of antiepileptic drugs, could explain why patients in this group had a higher chance of SGS.

One could argue about the reason to conduct a randomized controlled trial to evaluate the clinical utility of ictal SPECT in MTLE patients. The answer relies on the evidence-based paradigm for the health care system, which involves the use of the best evidence to provide the care to patients. Ictal SPECT studies have been performed in patients with temporal lobe epilepsy by several centers around the world without a critical evaluation of its utility and impact on clinical decision making. Diagnostic accuracy studies of imaging techniques in the workup for epilepsy surgery are inappropriate to examine clinical utility.[17,18] For such purposes, randomized comparisons have several advantages over other methods. The random assignment of patients should prevent selection bias. This basic principle opens up the application of experimental statistical design, such as testing for significance and calculating confidence intervals. Randomized controlled trials are also attractive from a pragmatic point of view: if randomization coincides with a choice between 2 management strategies, trial design closely mimics existing clinical dilemmas.[19,20]

The reader should be aware of the limitations of our study. During the multidisciplinary surgery decision meeting, investigators were aware of which patients had ictal SPECT studies. This issue is inherent to trials enrolling patients to study diagnostic techniques. In addition, ictal SPECT patterns are not specific of seizure onset zone. They may result from propagated seizure activity. Thus, in our surgical decision process, patients with bilateral independent ictal EEG patterns or ictal onsets contralateral to the side of hippocampal atrophy on MRI required intracranial monitoring to confirm the site of ictal EEG onsets, regardless of other studies. In other words, similarly to other groups, we gave more weight to ictal EEG in comparison with ictal SPECT.[21] The results of this trial might be different using a decision process that accepted ictal SPECT with equal or more weight than ictal EEG. Furthermore, our conclusions are applicable to adult patients with MTLE-HS. Our results should not be generalized to all types of patients with refractory epilepsy undergoing presurgical evaluation or pediatric patients with temporal lobe epilepsy. It is important to remember, however, that MTLE-HS is the most common surgically remediable epilepsy syndrome in adults worldwide. At our institution, 47% (243/521) of our screened patients had MTLE-HS when admitted for presurgical evaluation.

In surgical epilepsy centers where there are limited financial resources, the results of our trial may be used to decide which patients with medically refractory epilepsy would benefit from ictal SPECT studies. This knowledge will allow us to offer presurgical evaluation for more patients because we can utilize our limited video-EEG bed capacity more efficiently and effectively.

Disclosure

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COMMENT

The authors present their results of a prospective randomized study that assesses the utility of ictal SPECT in a large cohort of patients with medically refractory unilateral temporal lobe epilepsy. Primary end points were (1) proportion of subjects who were offered resective surgery and (2) proportion of subjects that were offered invasive studies. There was no difference between groups for these primary end points, and the authors conclude that ictal SPECT did not provide additive value over standard telemetry and MRI. This is a valuable study, because there are no guidelines available for the inclusion of ictal SPECT in the diagnostic evaluation for medically refractory epilepsy.

In consideration of the validity of this study, one should assess the patient population, use of an independent gold standard, and selection of objective outcome criteria. The study population is sizeable and representative of a clinical population of patients with medically refractory mesial temporal epilepsy. The appropriate gold standard for a diagnostic study intended to localize epileptic foci is invasive recordings. Therefore, blinding clinicians to the results of the SPECT study with subsequent comparison with the results of electrocorticography would have strengthened this study. Instead, the SPECT study was used here as a factor in the decision to proceed with invasive monitoring. In terms of objective outcome criteria, offering an invasive study or surgical resection were primary end points of the study. These are objective, but systematically biased by the results of the diagnostic test under study, the ictal SPECT.

Considering how these results are applicable to patient care, this study indicates that indiscriminant use of ictal SPECT in unilateral temporal lobe epilepsy does not have clinical value. Therefore, this study may influence epilepsy centers to be more selective with ictal SPECT, thus reducing patient isotope exposure and clinical resources. Unfortunately, this study does not identify clinical situations where ictal SPECT provides diagnostic value. Our center uses ictal SPECT in scenarios where lateralization or localization of epilepsy is uncertain to either guide our placement of invasive electrodes, or to identify patients with bilateral epileptic foci. Because ictal SPECT can, at best, only identify a single seizure onset zone, a strong argument may be made that it is inferior to invasive recordings. Therefore, design of a study with blinding of clinicians to SPECT results in patients appropriate for invasive studies would be an opportunity to provide data on the utility of SPECT in a more complex epilepsy population. This is likely where the value of ictal SPECT lies.

Adam O. Hebb
Seattle, Washington