through a failure to provide a normal level of protection against initiation and spread. Although the thalamus plays a role in the initiation, propagation and/or symptoms of seizures, it is uncertain whether thalamic dysfunction is related to alterations in thalamic blood flow, and thalamic perfusion is reduced in an interictal state. Further investigation of thalamic dysfunction and alterations in blood flow is needed.

CONCLUSION

Although ipsilateral thalamic hypoperfusion on interictal SPECT is too small to assist in seizure localization, it may aid in the localization of seizure foci. This finding occurs ipsilateral to epileptic foci in the temporal lobe, not in the contralateral thalamus. This finding may reflect either thalamic hypometabolism secondary to decreased efferent activity from the temporal lobe structures or functional alteration of thalamic metabolism by the regulation of cortical excitability and seizure propagation or both.

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SPECT Brain Imaging in Epilepsy: A Meta-Analysis

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A meta-analysis of SPECT brain imaging in epilepsy was performed to derive the sensitivity and specificity of interictal, postictal or ictal rCBF patterns to identify a seizure focus in medically refractory patients. **Methods:** Papers were obtained by pooling all published articles identified by two independent literature searches: (a) Dialnet (EMBASE) or Radline by CD-ROM and (b) Current Contents searched manually. Literature inclusion criteria were: (a) patients had a localization-related epileptic syndrome; (b) more than six patients were reported; and (c) patients had at least an interictal EEG-documented epileptiform abnormality. Of 46 papers meeting these criteria, 30 contained extractable data. SPECT results were compared to localization by standard diagnostic evaluation and surgical outcome. Meta-analytic sensitivities for SPECT localization in patients with temporal lobe seizures relative to diagnostic evaluation were 0.44 (interictal), 0.75 (postictal) and 0.97 (ictal). Similar results were obtained relative to surgical outcome. False-positive rates were low relative to diagnostic evaluation (7.4% for interictal and 1.5% for postictal studies) and surgical outcome (4.4% for interictal and 0.0% for postictal studies). **Results:** The results were not dependent on tracer used (or dose), the presence of CT-identified structural abnormalities, blinding of image interpretation or camera quality (although data were more variable with low-resolution cameras). There were insufficient data for conclusions regarding extratemporal-seizure or pediatric epilepsy populations. **Conclusion:** Insights gained from reviewing this literature yielded recommendations for minimal information that should be provided in future reports. Additional recommendations regarding the nature and focus of future studies also are provided. The most important of these is that institutions using SPECT imaging in epilepsy should perform ictal, preferably, or postictal scanning in combination with interictal scanning.

Key Words: epilepsy; meta-analysis; SPECT

J Nucl Med 1998; 39:285–293

Epilepsy surgery increasingly is considered the treatment of choice for people with medically refractory partial seizures of temporal lobe origin (*1*). Recently, Rougier et al. (*2*) reported a longitudinal assessment of seizure outcome after temporal lobectomy. Of 76 patients, 49 were seizure-free 5 yr postsurgery. A review by Engel et al. (*3*) of more than 6,000 epilepsy surgeries from 1986–1990 showed that 68% of the patients having limbic resections became seizure-free, and a further 24% had seizure frequency reduced by at least 90%. It has been suggested that more than 200,000 patients in the U.S. might benefit from surgical treatment, but the need for multiple, complex, preoperative investigations to accurately localize the seizure focus limits the use of surgical treatment.

EEG monitoring, using scalp, cortical or depth electrodes, is the current gold standard used for accurate focus localization (*4*). However, the interictal EEG often does not adequately localize the epileptic focus (*5*). Seizure monitoring combining ictal scalp EEG with simultaneous videotaping of behavior during seizures also is often inadequate for the anatomic localization of epileptic foci (*6,7*). Thus, the use of intracranial electrodes during seizure monitoring was developed for more precise seizure focus localization (*8*). This method derives spatial sampling capability only from precise surgical placement of the electrodes. Unfortunately, intracranial monitoring is invasive, with definite morbidity and mortality, as well as expensive. In recent years, growing recognition of the characteristic clinical features of the mesial temporal lobe epilepsy syndrome (*9*) and improved MRI technique and interpretation for detecting mesial temporal sclerosis (*10*) have reduced reliance on invasive electrode studies in many patients.

PET with ^{18}F-fluorodeoxyglucose (FDG) has shown that, during the interictal period, areas of decreased glucose metabolism may be identified that correspond to the depth electrode EEG (and ultimately pathological) localization of the seizure focus. Several authors (*11,12*) report an incidence of 60%–90% of temporal lobe hypometabolism in groups of patients with complex partial seizures. Interictal PET-FDG imaging may replace the need for depth electrode recording for selected patients at some institutions, but clinical utility is limited by its restricted availability and high cost (*13*). Regional cerebral blood flow (rCBF) also has been demonstrated to be abnormal at the site of the epileptic focus (*14*). During seizures, rCBF may increase at the site of the epileptic event (*15,16*). Interictally, the epileptic focus may demonstrate either regional hypoperfusion (commonly) or hyperperfusion (rarely) (*17*). SPECT is a widely available tool that may be used to measure rCBF noninvasively. Thus, SPECT may be useful for investigating and localizing epileptic foci in patients suffering from medically refractory epileptic seizures.

Despite a large number of interictal SPECT studies in the literature (*18,19*), there are few with large patient cohorts, and there is large variation in the stated sensitivity of this technique. Tracer injection at the time of a seizure appears to significantly improve the accuracy and sensitivity of seizure localization with SPECT, though the number of published ictal or postictal studies is small. Consequently, the true sensitivity for SPECT rCBF imaging is yet to be established for either interictal, postictal or ictal scans. Also, the relationship between SPECT and surgical outcome has not been established, nor has the efficacy of interictal or ictal SPECT to localize seizure foci been determined when the EEG is nonlocalizing.

This meta-analysis (*20*) of SPECT brain imaging in epilepsy was performed to address these issues to the degree possible with existing literature. Our purpose was to review the available published literature and to combine, where possible, studies from different institutions to improve the understanding of the contribution of SPECT brain imaging to the management of patients with medically refractory epilepsy.

MATERIALS AND METHODS

Papers initially selected for review were obtained by pooling all published articles identified by two independent literature searches: (a) Dialnet (EMBASE) or Radline through CD-ROM and (b) Current Contents searched manually. The reference sections of three comprehensive literature reviews on SPECT imaging in epilepsy (*18,19,21*) were examined for any additional papers missed in the process. All conference abstracts, case history reports and narrative reviews were rejected from this initial pool and the final list was reviewed for completeness by one of the authors. This process identified 53 papers for review. One of these papers was not reviewed as it was not obtainable through normal channels (British Lending Library, London).

Eligible papers were reviewed next against the following inclusion criteria, which were established a priori by consensus discussion of the authors: (a) patients had a localization-related epileptic syndrome; (b) patient number $\geq$ 6 reported; and (c) patients had at least an interictal EEG-documented epileptiform abnormality. Each paper was reviewed and included or rejected by consensus on the sole basis of these predetermined criteria. Forty-six papers met these criteria.

Wherever possible, patient-level information was used to classify results rather than summaries provided in the manuscripts (*22*). Patient-level information was reviewed on a patient-by-patient basis by the authors as a group to classify the inclusion status and outcome of each patient. Sixteen of the 46 papers meeting the initial inclusion criteria were subsequently excluded because they did not contain sufficiently detailed descriptions of results to permit data extraction (e.g., no data on EEG localization). Papers included in the analysis are listed in Appendix A. A full list of the papers reviewed but not included in the meta-analysis is available on request.

Patients were categorized in several ways, as: (a) medically refractory or medically responsive (if not explicitly stated in manuscript, then patients were assumed to be *not* refractory); (b) adult or pediatric (<13 yr); and (c) of general or special patient populations (e.g., included only patients with normal CT scans, only patients with unilateral EEG findings, exclusion of patients with ambiguous EEG or SPECT results). Also, because most reports used ^{99m}Tc-HMPAO, those SPECT studies using other radiopharmaceuticals were analyzed as a separate group.

The electroencephalographic data were classified as unilateral, bilateral, localizing or nonlocalizing. Surgical outcome was classified as good or poor (accepted for this analysis only with a minimum of 12 mo surgical follow-up and defining outcome as good if the patient was either seizure-free or had > 90% reduction in seizure frequency).

SPECT images were classified as unifocal ipsilateral to EEG, unifocal contralateral to EEG, multifocal ipsilateral, multifocal bilateral and normal. Data related to interictal, ictal and postictal SPECT were entered separately. Ictal SPECT was defined as a tracer injection during an observed clinical seizure or within 30 sec of the seizure completion during seizure monitoring. Therefore, postictal SPECT was defined as an injection later than 30 sec postseizure completion with seizure monitoring, but in association with a seizure (typically not more than 5 min postictal).

Some manuscripts provided information relevant to more than one of these imaging time frames. Therefore, data were organized by "series." That is, a collection of results from a single manuscript

comprising findings from a particular patient population. The main distinctions among series were adult/pediatric and ictal/interictal/ postictal. Thus, a paper reporting data on both ictal and interictal seizures would result in two series in the database. When possible, efforts were made to exclude any studies that might report duplicated subject information. Consequently, not all series entered in the database were usable ultimately.

Three additional characteristics of reported results were recorded: (a) the site of focus as temporal, extratemporal or mixed (papers that reported temporal and extratemporal patients combined); (b) whether image interpretation was blinded to other patient data (especially EEG); and (c) whether image resolution was low (camera resolution > 12 mm), medium (8–12 mm) or high ($\leq$8 mm).

For each data series, we analyzed SPECT findings with respect to unilateral EEG findings. Sensitivity (sens1) was defined to be the fraction of unifocal ipsilateral SPECT findings among all unilateral EEGs. A second, broader definition of sensitivity also was evaluated (sens2), defined as unifocal or multifocal SPECT findings ipsilateral to EEG localization. Similarly, discordant SPECT was defined as a unifocal SPECT finding contralateral to EEG (false1), and unifocal or multifocal SPECT findings contralateral to EEG (false2).

With respect to surgery, sensitivity was defined as the fraction of unifocal SPECT findings ipsilateral to the operative side, among all good surgical outcomes. As with the comparison to EEG, both narrow (unifocal SPECT finding) and broad (unifocal or multifocal SPECT findings) definitions were used for sensitivity (sens3, sens4) and false localization rate (false3, false4).

The method of DerSimonian and Laird (23) was used to calculate meta-analytic estimates of sensitivity (μ) based on the combined reports and to assess possible heterogeneity across series (Q). Exact confidence intervals were calculated using the method described by Brownlee (24). Multiple logistic regression was used to assess factors affecting the determination of SPECT sensitivity relative to diagnostic evaluation. Factors included series type (interictal/postictal/ictal), dose, camera resolution and blinding.

Six questions that potentially could be addressed by the meta-analytic process were established by consensus discussion before any of the papers were reviewed. The first two questions represent our primary focus:

1. What are the sensitivity and false-positive rate of interictal, postictal or ictal SPECT *relative to diagnostic evaluation* in (a) localization and (b) lateralization of a seizure focus?
2. What are the sensitivity and false-positive rate of interictal, postictal or ictal SPECT *relative to surgical outcome* in localization of a seizure focus?

In addition, we thought it would be useful to attempt to use extant literature to address the following secondary questions:

3. What is the differential relationship to surgical outcome among unifocal, multifocal-ipsilateral and multifocal-bilateral SPECT abnormalities?
4. What are the sensitivity and false-positive rate of interictal, postictal or ictal SPECT in pediatric epilepsy?
5. Are sensitivity or false-positive measures a function of technical factors such as instrumentation quality or radiopharmaceutical dose?
6. With what frequency is *hyper*perfusion seen in the interictal state?

RESULTS

Patient Accountability

Table 1 provides information on patient accountability for each

TABLE 1
Patient Accountability

Criterion	Series	No. of patients	EEG	Surgery
Interictal				
Inclusion criteria/extractable	31	624	592	184
Medically refractory	24	471	445	184
Adult	22	453	427	178
Nonspecial population*	15	290	280	99
99mTc-HMPAO	13	256	247	99
Postictal				
Inlcusion criteria/extractable	5	101	73	53
Medically refractory	5	101	73	53
Adult	4	81	69	51
Nonspecial population*	4	81	69	51
99mTc-HMPAO	4	81	69	51
Ictal				
Inclusion criteria/extractable	7	136	120	49
Medically refractory	7	136	120	49
Adult	7	136	120	49
Nonspecial population*	4	62	51	12
99mTc-HMPAO	4	62	51	12

*Special populations were defined as having unusual inclusion/exclusion [e.g., mentally retarded (n = 13), exclusively unilateral EEG (n = 24), only unambiguous SPECT findings (n = 40) and purely CT normal (n = 65)].

seizure population. Because a single paper may, in principle, give rise to as many as six series (interictal, ictal and postictal series for both adult and pediatric populations), and because some of the patients from a single paper could appear in more than one series (same patient studied under both ictal and interictal conditions), it is not possible to construct a table showing patient accountability in the aggregate, but this can be done by series type. For example, paper 36.2 reported on EEG versus SPECT findings for 12 patients whose surgical outcomes were reported in a later paper (44.2). These are counted as two series, but the 12 patients are counted only once in the totals.

The first column of each table lists a series of criteria applied in sequence. For instance, the series recorded in the row labeled "adult" are composed of medically refractory adult patients for which data were extractable from a paper that met our inclusion criteria. The second column represents the total number of patients reported in the papers, whether or not those patients were evaluable in the meta-analysis. The next two columns give, respectively, the number of patients from the papers that were evaluable with respect to EEG findings and evaluable with respect to surgical results.

The series listed in the bottom rows (for interictal, postictal and ictal) of Table 1 are those included in our principal analyses. Table 2 lists extracted data from each of these series for the variables used in our analyses.

Insufficient data were available to enable meta-analysis of the accuracy of SPECT in pediatric patients or to evaluate the impact of variations in rCBF tracers other than 99mTc-HMPAO. Three series from two papers (43.1, 43.3, 101.1) involving pediatric patients meeting all inclusion criteria and having extractable data were identified. This represents only 18 interictal and four postictal patients. Similarly, only six series in five studies reported data from tracers other than 99mTc-HMPAO (101.1, 101.11, 105.1, 106.2, 108.1, 110.1). Three of these reported data from special populations. Among papers concerned with special populations, four series reported on CT-

TABLE 2
SPECT Versus EEG: Extracted Variable by Series*

	No. of patients[†]	Sens1	Sens2	False1	False2	Dose	Camera	Blind
Interictal series								
1.1	5	0	0.4	0	0.6	High	Low	No
4.1	8	0.375	0.375	0.125	0.125	—	—	No
5.1	5	0.800	0.800	0	0	High	Med	Yes
9.1	10	0.4	0.9	0.1	0.1	High	Med	No
16.1	28	0.464	0.571	0.214	0.393	High	Low	No
22.1	6	0.5	0.5	0	0	Low	Med	No
28.1	29	0.31	0.517	0.069	0.069	High	Med	Yes
34.1	46	0.391	0.391	0.065	0.109	High	Med	Yes
39.1	5	0.4	0.6	0	0	High	High	Yes
43.11	5	0.6	0.6	0.2	0.2	High	Med	Yes
44.1	12	0.667	0.667	0	0	High	Med	Yes
48.1	7	0.714	0.714	0	0.286	Low	Low	Yes
201.1	23	0.435	0.522	0	0.043	High	High	Yes
Postictal series								
13.3	28	0.786	0.786	0	0.071	High	Med	Yes
22.3	2	0.5	0.5	0.5	0.5	Low	Med	No
44.3	12	0.75	0.75	0	0	High	Med	Yes
201.3	23	0.739	0.783	0	0.043	High	High	Yes
Ictal series								
22.2	3	1	1	0	0	Low	Med	No
36.2	40	1	1	0	0	High	Med	No
39.2	6	0.667	0.833	0	0	High	High	Yes

*The index number xx.yz identifies the series within paper xx;y = 1, 2 or 3 for interictal, ictal and postictal, respectively, and z is added to distinguish multiple series from the same paper and observation period.

[†]No. of patients = number of patients in the series with unilateral EEG findings.

normal subjects. Two series were non-^{99m}Tc-HMPAO (105.1, 110.1) and two (14.1, 40.1) reported data using ^{99m}Tc-HMPAO.

Relationship of SPECT to EEG

A survey of Table 2 suggests that the ictal and postictal results for sensitivity, especially the definition sens1, are strikingly better than for the interictal findings, as expected. Multiple logistic regression analysis indicated that series type was a statistically significant determinant of sensitivity. The effects of dose, resolution and blinding did not reach statistical significance. The odds of SPECT correctly identifying a unifocal lesion on the ipsilateral hemisphere (when EEG findings were unilateral) were 45 times larger using ictal rather than interictal observations, and four times larger using postictal rather than interictal. "Odds" can be thought of as the number of correctly diagnosed patients for every incorrectly diagnosed patient.

Table 3 lists the combined sensitivity measures (μ for sens1) derived from meta-analysis for all series. These results are compared to results from individual series in Figure 1. The only

TABLE 3
Combined Sensitivities: SPECT Versus Diagnostic Evaluation

	μ*	95% CI[†]	Q[‡]	df[§]
Interictal	0.438	0.323–0.553	31.80	12
Postictal	0.754	0.631–0.852	0.707	3
Ictal	0.967	0.887–0.996	2.989	3

*μ is the meta-analytic derived combined sensitivity across all series (23).
[†]95% CI = 95% confidence intervals for μ.
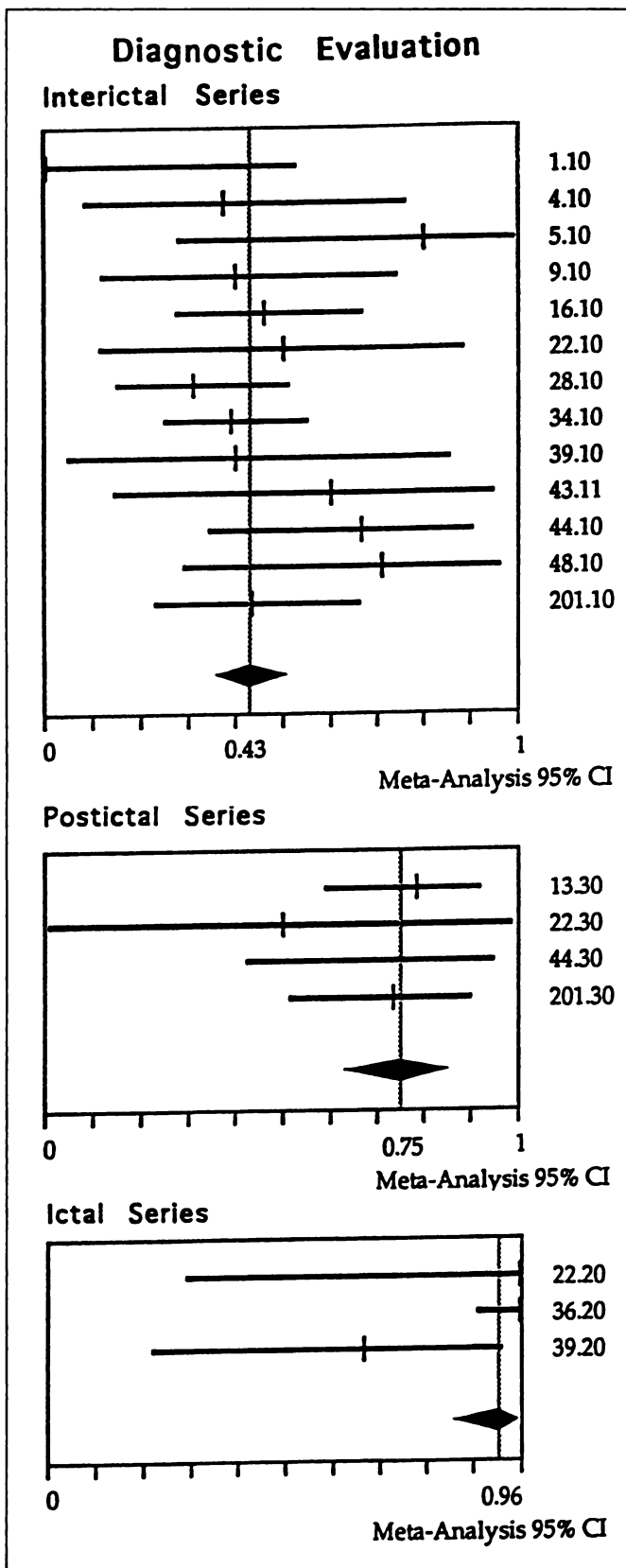[‡]Q is a measure of homogeneity (23).
[§]df = degrees of freedom.

significant heterogeneity was found in the interictal series (Q = 31.8, df = 12, p < 0.01). This heterogeneity is completely accounted for by removing the three series with low-resolution cameras (1.1, 16.1, 48.1). These three studies had observed sensitivities ranging from 0% to 72%. Among the medium- and high-resolution studies, there was no evidence of heterogeneity (Q = 10.4, df = 9, p > 0.5). However, removing the three low-resolution series had little effect on interictal sensitivity (μ = 0.430) or confidence intervals (95% CI = 0.349–0.513). None of the ictal or postictal studies used low-resolution cameras.

A broader definition of sensitivity (sens2) includes, as positive findings, the presence of a SPECT lesion at the EEG positive site in addition to SPECT lesions at other sites in the same hemisphere (multifocal ipsilateral). The combined sensitivity (μ for sens2) was 0.582 (95%CI = 0.480–0.684) for interictal data, 0.769 (0.648–0.865) for postictal data and 0.980 (0.891–0.999) for ictal data.

While the majority of patients analyzed had seizures of temporal lobe origin, one series (39.1) reported on patients of purely extratemporal seizures and four others reported on populations of mixed temporal and extratemporal seizures. To determine if a purely temporal lobe seizure population would be associated with a different sensitivity, our data were reanalyzed without these five series. The resultant combined sensitivity was 0.46 (0.36–0.54). This result is not different from the original analysis.

Data that relate to generating misleading results (contralateral unifocal) are found also in Table 2. The rates of misleading findings are quite low in the ictal and postictal settings (the 50% rate from series 22.3 is based on a sample size of 2). The estimated rate of this type of error is 7.4% for interictal and

FIGURE 1. Individual and meta-analytic (μ) sensitivities (sens1) for SPECT data relative to diagnostic evaluation. Median values are noted by vertical bars and 95% confidence intervals (CI) are noted by horizontal bars.

1.5% for postictal studies, based on the combined data, and these differences are statistically significant (p = 0.026). The optimistic observed rate of 0% in the ictal category may be due to the relatively small combined sample sizes, as the confidence intervals suggest (the upper end of the 95% confidence interval

TABLE 4
Variables Relating SPECT to Surgical Outcome*

	Outcome	Sens3	Sens4	False3	False4
Interictal series					
28.1	20/23	0.2	0.5	0.05	0.05
34.1	38/41	0.447	0.447	0.053	0.053
43.11	2/3	0.5	0.5	0.5	0.5
44.1	12/12	0.667	0.667	0	0
201.1	19/20	0.474	0.526	0	0.053
Postictal Series					
13,3	16/19	0.812	0.812	0.000	0.062
44.3	12/12	0.750	0.750	0.000	0.000
201.3	19/20	0.737	0.789	0.000	0.053
Ictal series					
44.2	12/12	1.000	1.000	0.000	0.000

*Outcome = number of patients with good outcome/series total.

based on all of the data in this group is 5.9%). The broader definition of misleading results (unifocal contralateral + multifocal bilateral) was slightly higher: interictal = 9.5%; postictal = 6.2%.

Relationship of SPECT to Surgical Outcome

Data extracted from the series reporting surgical cases are reported in Table 4. The data are again consistent with increased accuracy being associated with ictal and postictal observations. Table 5 lists the combined sensitivity measures (μ for sens3) derived from meta-analysis for all series. The differences between groups are statistically significant (p < 0.01). These results are compared to results from individual series in Figure 2.

A broader definition of sensitivity (unifocal ipsilateral + multifocal ipsilateral) also was constructed to relate SPECT to surgical outcome data. The combined sensitivity (μ for sens4) was 0.505 (CI = 0.399–0.612) for interictal data, and 0.787 (0.643–0.893) for postictal data. Combined data for ictal studies cannot be obtained since surgical outcome and ictal SPECT data were only available from a single series.

SPECT results that were misleading relative to surgical outcome were rare for either the conservative definition (unifocal contralateral) or the broader definition (unifocal contralateral + multifocal bilateral). For interictal series, they were 4.4% and 5.5%. For postictal series, they were 0.0% and 4.3%. Again, combined results for ictal studies cannot be obtained since these come from only a single series.

Other Analyses

We next analyzed two subsets of papers that were not used in our principal analysis. One set focused on the sensitivity of SPECT relative to diagnostic evaluation when radiopharmaceuticals other than ^{99m}Tc-HMPAO were used. As previously

TABLE 5
Combined Sensitivities: SPECT Versus Surgical Outcome

	μ*	95% CI†	Q‡	df§
Interictal	0.429	0.325–0.537	9.656	4
Postictal	0.766	0.620–0.877	0.323	2
Ictal	1.00	0.737–1.00	0.000	0

*μ is the meta-analytic derived combined sensitivity across all series (23).
†95% CI = 95% confidence intervals for μ.
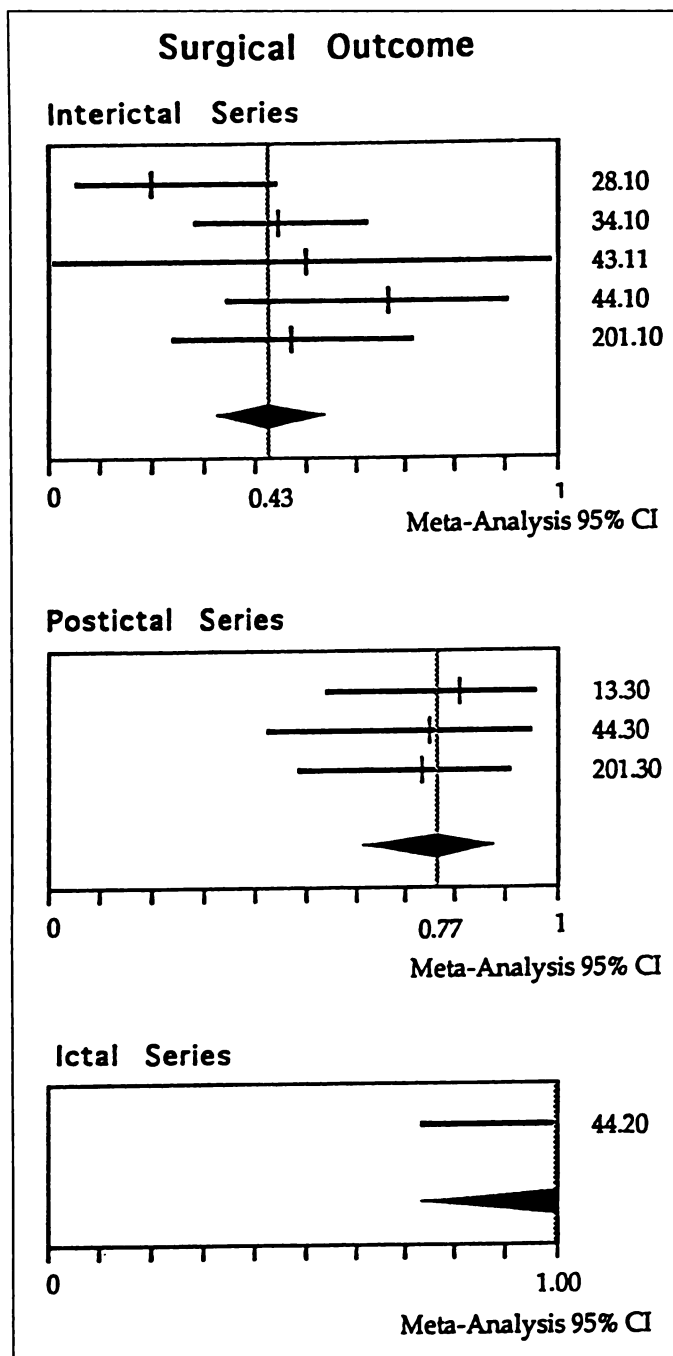‡Q is a measure of homogeneity (23).
§df = degrees of freedom.

Surgical Outcome

Interictal Series

	28.10
	34.10
	43.11
	44.10
	201.10

0   0.43   1

Meta-Analysis 95% CI

Postictal Series

	13.30
	44.30
	201.30

0   0.77   1

Meta-Analysis 95% CI

Ictal Series

	44.20

0   1.00

Meta-Analysis 95% CI

FIGURE 2. Individual and meta-analytic (μ) sensitivities (sens1) for SPECT data relative to surgical outcome. Median values are noted by vertical bars and 95% confidence intervals (CI) are noted by horizontal bars.

mentioned, these data did not exclude special populations. The second analysis concerned the sensitivity of SPECT relative to diagnostic evaluation in papers reporting on patients who were required to have a normal CT scan. This analysis included data for any tracer.

Non-^{99m}Tc-HMPAO. Five series were entered into the analysis, giving a total patient count of 69. There was little heterogeneity in the group (Q = 9, df = 4), and μ = 0.422 (0.248–0.597). This sensitivity was not significantly different from that obtained in studies using ^{99m}Tc-HMPAO (0.438).

CT Normal. Little heterogeneity was observed in this group of interictal studies (Q = 3, df = 3) and μ = 0.426 (0.282–0.569). This sensitivity is similar to that of the major series, although the confidence interval is broader at the lower end.

This value is derived from a relatively small patient pool, and three of the four series report sensitivities > 0.500.

CONCLUSION

Most literature suggests that the primary role of SPECT imaging in seizure disorders is the presurgical evaluation of medically refractory epileptic patients (*18,19*). However, there is no single, large clinical study that definitively supports this position. This meta-analytical review of the published literature combined the available data to address this issue and other questions of clinical interest.

Meta-analysis is a statistical method of combining data from several different studies (*20*). It allows clinical or scientific hypotheses to be retrospectively addressed through a rigorous methodological analysis of published work, imparting a degree of objectivity that is generally lacking in a standard narrative literature review. It also requires that all criteria for inclusion and exclusion of data be stated in advance (*25,26*). It does not have universal acceptance as a genuine research tool and its limitations should be well understood (*27*). One criticism frequently voiced about data selection for the meta-analytical procedure is the inherent bias of using published data only, thus excluding all studies which were not accepted or submitted for publication. These studies may well arrive at different conclusions to those available in the literature and theoretically should be available for inclusion (*28*). However, in reality, medical decisions are made based on published experiences and meta-analysis can give a quantitative estimate to the weight of the available published evidence. In this respect, it is superior to the narrative literature review but clearly less desirable than a prospective, well-controlled, randomized large cohort clinical trial.

Table 1 illustrates the effect on our patient pool as we applied first our inclusion criteria and then initially excluded from analysis all papers that reported patients who were medically responsive or who had been systematically studied as a special population. Excluding papers that studied medically responsive patients or those that did not specify whether their patients were refractory led to a total loss of 153 patients. A second major reduction in patient numbers occurred when special populations were excluded.

Relationship of SPECT to Diagnostic Evaluation

Four of our questions (Questions 1, 4, 5, 6) concern the role of SPECT relative to diagnostic evaluation.

Question 1. What are the sensitivity and false-positive rate of interictal, postictal or ictal SPECT relative to diagnostic evaluation in (a) localization and (b) lateralization of a seizure focus? The sensitivity of ^{99m}Tc-HMPAO SPECT in localizing an epileptic focus increases in the order interictal ⇒ postictal ⇒ ictal. For the 13 series included in the interictal analysis (total patient count = 256, of whom 247 were evaluable), a mean sensitivity value of 0.44 was obtained. When we examine the accuracy of SPECT observations for postictal imaging, sensitivity increases to 0.75 and for ictal imaging to 0.96. True ictal scanning is difficult to achieve (due to methodological problems with existing tracers), consequently this aggregate is based on only three series with a total patient count of 62. It is also important to keep in mind that 42 of 69 evaluable postictal patients and 42 of 51 evaluable ictal patients are derived from a single center (Rowe et al.: *13.3; 36.2; 44.2; 44.3*).

It can be inferred from these values that with current techniques and methodology, an interictal scan alone is not a sensitive determinant of the site of an epileptic focus. In contrast, interictal imaging with a PET tracer such as ^{18}F-FDG

is reported in the literature by several authors to have localization sensitivities of about 0.70. Our findings suggest that a combination of interictal imaging with ictal or postictal scanning is more sensitive than an interictal PET study. In fact, many of the reviewed ictal/postictal studies reported results only relative to the interictal state. It is important to combine interictal and either ictal or postictal imaging because an ictal or postictal image could appear normal if read independently, but may reflect increased perfusion at the seizure focus relative to interictal hypoperfusion at the same site.

To determine if a gain in sensitivity is achieved when lateralized SPECT findings are included with localized findings, we compared sens2 (lateralized) to sens1 (localized). These did not differ for postictal or ictal data, likely related to the common practice of only referring to "change from interictal" when reporting postictal/ictal abnormalities. However, for interictal data sens2 was somewhat greater than sens1 (0.582 versus 0.438).

Two false-positive rates were determined. The estimated rate for false1 was 7.4% for interictal and 1.5% for combined ictal and postictal data. These differences are statistically significant (p = 0.026). Again, the false-positive postictal data are based on little published information and further studies are needed to confirm that these rates of error are indeed so low. False2 (9.5%) is somewhat greater than false1 only for interictal data. Thus, the increase in sensitivity obtained with sens2 is obtained at the cost of a modest increase in false-positive findings.

Question 4. What are the sensitivity and false-positive rate of interictal, postictal or ictal SPECT in pediatric epilepsy? Few reviewed papers described pediatric patients, precluding meta-analysis. Table 1 shows that, for the two papers meeting our inclusion criteria, there are reports of only 18 children who have had interictal scans, of whom six have surgical follow-up reports. Four children are reported with postictal scans, of whom two have had surgical follow-up. One paper (43.1) that contributed to this small sample reports a 53% interictal sensitivity and false-positive rate of 9%. Postictal sensitivity was 73%.

Question 5. Are sensitivity or false-positive measures a function of technical factors such as instrumentation quality or radiopharmaceutical dose? Camera resolution and administered dose did not significantly affect sensitivity (only evaluable in studies using ^{99m}Tc-HMPAO). However, there was significant heterogeneity (p < 0.01) in the interictal data which was not present (p > 0.5) when the three papers reporting data collected with low-resolution systems were removed from the analysis. Therefore, it appears that findings are likely to be more variable with low-resolution systems (FWHM > 12 mm).

Question 6. With what frequency is hyperperfusion seen in the interictal state? We examined the database for the number of instances that interictal hyperperfusion was reported in the 624 patients for whom data were collected. Seven papers reported interictal hyperperfusion in a total of 31 patients (approximately 5%). These reports did not monitor preinjection EEG. All but one of these observations were made using low-resolution cameras. This incidence is similar to earlier reports (*18*).

Relationship of SPECT to Surgical Outcome

Two of our questions (Questions 2 and 3) concern the role of SPECT relative to surgical outcome.

Question 2. What are the sensitivity and false-positive rate of interictal, postictal or ictal SPECT relative to surgical outcome in localization of a seizure focus? There are relatively few SPECT studies reporting on patients with surgical follow-up of

at least 1 yr. Sensitivity of SPECT relative to surgical outcome shows a similar trend to that relative to diagnostic evaluation: interictal ⇒ postictal ⇒ ictal (Table 5). However, all of the ictal/surgical outcome data are derived from a single report. It is encouraging to note that this one paper (44) reports surgical outcomes for all three scan conditions and the sensitivity increases as expected from 0.67 to 0.75 to 1.00.

Misleading results were somewhat less common relative to surgical outcome than relative to diagnostic evaluation, likely because EEG can be falsely localizing. False3 and false4 were not substantially different. However, postictal and ictal data included only a small number of subjects. Consequently, our results should be interpreted cautiously.

Question 3. What is the differential relationship to surgical outcome among unifocal, multifocal unilateral and multifocal bilateral SPECT abnormalities? The expanded definition of sensitivity, in other words unifocal or multifocal SPECT findings ipsilateral to the side of surgery, resulted in a slightly higher interictal sensitivity (0.51 versus 0.43 for unifocal SPECT) without an increase in false localization. No difference was found for the postictal data, but most studies were not presented in a way that would lead to a report of multifocal "hot spots." That is, such data are primarily interpreted relative to interictal data with a specific focus on finding regions of relative rCBF increase.

Most SPECT findings are compared to interictal or ictal EEG. Neither is an absolute gold standard and, in some instances, will be nonlocalizing when SPECT is positive. In order for SPECT (or PET and MRI) to be validated as a useful clinical procedure, there is a need for good outcome measures after surgery. Poor surgical outcome can be a result of poor surgical technique or incomplete removal of the focus rather than the inaccurate localization of the focus by the diagnostic modalities. However, if SPECT is to play a clinical role in presurgical evaluation of patients and complement or replace invasive EEG procedures, there must be significant correlation between SPECT findings and surgical outcome. In this regard, it was surprising how few investigators reported the surgical outcome of their patients. Of the 624 patients reported in all papers meeting our inclusion criteria, surgical outcome data were available on 99 with interictal SPECT studies (16%), 51 with postictal data (8%) and only 12 with ictal SPECT (2%).

Other Questions

Non-^{99m}Tc-HMPAO. There were five non-^{99m}Tc-HMPAO series analyzed. The sensitivity of these series (0.422) was not significantly different from that obtained in studies using ^{99m}Tc-HMPAO (0.438). There were insufficient data to determine if postictal or ictal data from other tracers were comparable to that from ^{99m}Tc-HMPAO.

CT Normal. Some investigators excluded patients with CT evidence of structural abnormalities. The combined interictal sensitivity determined from these papers is comparable to that of the major series, indicating that the presence or absence of structural lesions (at least as observed on CT) has little to do with the likelihood of observing a SPECT abnormality.

Extratemporal Seizures. The majority of evaluable data concern patients with seizures of temporal lobe origin. Only one paper reported a pure population of extratemporal foci (39) and this report does not include results of surgical outcome. Interictal and ictal sensitivities were 0.400 and 0.667, respectively. However, the patient numbers were small (6/12 evaluable). Four further papers reported data from populations that mixed patients with temporal and extratemporal seizures. When the respective papers (1, 16, 39, 201) were excluded from the

principal analysis, the resulting pure population of temporal lobe seizure patients showed reasonable homogeneity (Q = 12.9, df = 8), with μ = 0.46 (sens1), within confidence limits of 0.36–0.54. This compares to 0.44 for the mixed temporal/extratemporal group. There are insufficient published data to draw any definitive conclusions about SPECT in patients with extratemporal seizures.

In this review, we made no attempt to compare the accuracy of SPECT to CT and MRI. The ability of structural imaging with CT and MRI to localize/lateralize epileptic foci has steadily improved. It is likely that sensitivities for detecting structural lesions reported in the pre-1990 papers would have little relationship to the current sensitivity of MRI. However, MRI may identify structural lesions that are not connected to the epileptic disorder. Therefore, it is possible that sensitivity of lesion identification would increase with evolving MRI technology, while specificity for identifying the epileptic focus might not. In a retrospective study published in 1991, 78% correct lateralization was achieved using MRI, with a false-positive rate of 5% (29). Prospective comparative studies are required to define the relationship between SPECT and MRI.

It became evident in reviewing the literature that there is great variability in the methods and standards of reporting of these data. As a consequence of our experience, we recommend that the following information be included in future reports in order to improve the applicability of reported data to interested readers and the eventual implementation of this technique by other institutions:

1. Describe results of EEG, SPECT and CT/MRI (especially mesial temporal MRI evaluation) on a patient-level basis.
2. Report EEG before, during and after all radiopharmaceutical injections.
3. Indicate, on a patient-level basis, the degree of concordance or disagreement between EEG and SPECT for both ictal and interictal studies.
4. Describe criteria used to define ictal, postictal or interictal states (including determination of seizure onset for ictal/postictal studies, determination of interictal status, and length of required seizure-free time preceding interictal studies).
5. Describe EEG morphology and semiology (behavior) at the time of ictal injections.
6. Describe all criteria used to determine localization on a patient-level basis.
7. Provide status of medications at time of imaging.
8. Report image analysis, evaluation or interpretation techniques.
9. Provide detailed results for patients not referred for surgery.
10. Provide data on the clinical decision-making impact of SPECT.

Gaps in the current literature also became evident during this review. Though not all-inclusive, we identified a need for the following future studies:

1. Studies using SPECT imaging in epilepsy that include ictal (preferably) or postictal scanning in addition to interictal studies in all patients (though difficult with current tracers, upcoming availability of tracers that are stable in vitro and automated delivery devices should do much to enhance this opportunity).
2. Studies that report surgery follow-up data, particularly to clarify, in patients with EEG "false localizations" (poor

outcome), the relationship between functional imaging and surgical outcome.
3. Surgical outcome studies that determine whether SPECT can provide data additional to MRI and EEG, in terms of outcome prediction and ability to identify EEG-nonlocalizing patients who can benefit from surgery.
4. Studies in large cohorts of patient populations with extratemporal seizures, pediatric epilepsies and new-onset patients.
5. Studies that clarify the relationship between timing of injection for ictal/postictal scans and sensitivity and specificity of localization (perhaps leading to widely-accepted standards regarding the duration of ictal and postictal stages).
6. Natural history studies of the evolution of rCBF abnormalities in new-onset patients, their relationship to prognosis and their response to medical therapy.

There is little doubt that SPECT imaging can play an important role in patient management for problem epilepsy. SPECT uniquely offers the possibility of visualizing rCBF at all stages of a seizure, which our results suggest leads to an accuracy of localization of the focus of approximately 90% in temporal lobe epilepsy. However, the current literature is not conclusive in its support behind this claim, primarily due to inadequate ictal SPECT data.

APPENDIX A

The following articles were included in this review. The index number xx.yz identifies the series within paper xx, where y = 1, 2 or 3 for interictal, ictal and postictal, respectively, and z is added to distinguish multiple series from the same paper and observation period.

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Paradoxical Hippocampus Perfusion in Mild-to-Moderate Alzheimer's Disease

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The purpose of this study was to clarify the changes in hippocampal perfusion in mild-to-moderate Alzheimer's disease using PET and ^{15}O-labeled water. **Methods:** Sixteen patients with probable mild-to-moderate Alzheimer's disease (age: 68.1 ± 11.3 yr; MMSE: 21.1 ± 4.5) and 10 normal volunteers (age: 65.1 ± 8.2 yr) were studied. Regional cerebral blood flow (CBF) and cerebral blood volume (CBV) were measured using ^{15}O-labeled water autoradiographic method, C[15]O-gas inhalation technique and PET. **Results:** Although the mean CBF in the parietotemporal region was signifi-cantly lower in the patient group than in the control group, the mean CBF in the hippocampus did not show significant reduction between the two groups, both in absolute and relative values. There was no significant regional CBV difference between the two groups. Parietotemporal perfusion correlated well with cognitive scores, both in absolute and relative values, in Alzheimer's disease, but hippocampal perfusion did not correlate well. **Conclusion:** Hippocampal perfusion was preserved in mild-to-moderate Alzheimer's disease.

Key Words: PET; Alzheimer's disease; Oxygen-15-labeled water; hippocampus; cerebral blood flow