Objective: To gain information on the predictive and prognostic value of magnetic source imaging (MSI), 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (18FDG-PET), and ictal single-photon emission computed tomography (SPECT) as compared with intracranial electroencephalography (ICEEG) localization in epilepsy surgery.

Methods: This work was part of a cohort study of epilepsy surgery candidates not sufficiently localized with noninvasive studies. Of 160 patients enrolled over 4 years, 77 completed ICEEG seizure monitoring. Sensitivity, specificity, and predictive values relative to ICEEG were computed for each modality.

Results: Seizures were not captured in five patients. Of the 72 diagnostic ICEEG studies, seizure localization results were 74% localized, 10% multifocal, and 17% nonlocalized. Sixty-one percent were localized to neocortical regions. Depending on patient subgroup pairs, sensitivity ranged from 58 to 64% (MSI), 22 to 40% (PET), and 39 to 48% (SPECT); specificity ranges were 79 to 88% (MSI), 53 to 63% (PET), and 44 to 50% (SPECT). Gains in diagnostic yield were seen only with the combination of MSI and PET or MSI and ictal SPECT. Localization concordance with ICEEG was greatest with MSI, but a significant difference was demonstrated only between MSI and PET. Moderate redundancy was seen between PET and ictal SPECT ($\kappa = 0.452; p = 0.011$).

Interpretation: Conclusively positive MSI has a high predictive value for seizures localized with ICEEG. Diagnostic gain may be achieved with addition of either PET or ictal SPECT to MSI. Diagnostic values for imaging tests are lower than "true values" because of the limitations of ICEEG as a gold standard.

Advances in technology to localize focal epileptogenic tissue, especially that of high-resolution structural imaging with magnetic resonance imaging (MRI), have considerably improved the cost and success of surgical treatment. The large problem that remains is in regard to the 60 to 70% of intractable partial epilepsy patients who do not benefit from the identification of a unifocal epileptogenic lesion on MRI. At most epilepsy surgery centers in the United States and abroad, the majority of these patients undergo long-term intracranial electroencephalographic (ICEEG) monitoring with surgically implanted electrodes. And in the United States, ICEEG procedures add tens of thousands of dollars to the presurgical evaluation. Furthermore, this cost is highlighted by seizure-free outcomes that often do not exceed 50%. In addition to these extra costs, a 1 to 4% risk for complications ranging from infections to intracranial bleeding to even death from brain edema and herniation is associated with ICEEG.

Once justification for ICEEG is demonstrated and accepted, critical for the success of the recordings is optimal electrode coverage such that limited sampling of the brain does not yield false-negative or incorrect localization of the epileptogenic zone. The development and application of noninvasive functional imaging tests to epilepsy localization, such as magnetoencephalography (MEG)-based source localization combined with MRI (or magnetic source imaging [MSI]), 2-[18F]fluoro-2-deoxy-D-glucose positron...
emission tomography (18FDG-PET), and ictal single-photon emission computed tomography (SPECT), has attempted to address some of the challenges of ICEEG planning and interpretation. Although the tests, where available, are readily used, no evidence exists from large, prospective studies or clinical trials to support valid and efficient utilization, either to favorably affect patient selection or ICEEG utilization. To address this issue, we designed and commenced a 5-year prospective observational study at the University of Alabama at Birmingham (UAB) Epilepsy Center in 2001 with the main goal to gain descriptive information on the predictive and prognostic value of MSI, 18FDG-PET, and ictal SPECT as compared with ICEEG in patients with nonlocalized MRI. The specific aims were: (1) to determine the relative predictive value of each of the modalities to replace or supplement information provided by ICEEG, and (2) to determine the degree of localization redundancy between tests. The primary hypothesis was that these adjunct noninvasive tests, either alone or in combination, predict localization as indicated by ICEEG in surgery candidates who have insufficiently localized surface ictal EEG studies and MRI.

Patients and Methods

Patients

Patients completing scalp video-EEG seizure monitoring at the UAB Epilepsy Center (including The Children's Hospital of Alabama) between August 2001 and March 2006 were screened. Inclusion criteria were: (1) diagnosis of medically intractable partial epilepsy based on electro-clinical-anatomic findings from seizure recordings with video and EEG, and (2) nonlocalizing MRI-normal results or ambiguous abnormalities (large, multiple, or questionable lesions of unclear epileptogenic significance). Patients with MRI indicating the pathological diagnosis of focal cortical dysplasia were included because the visualized structural abnormalities still require confirmation of the location and extent of epileptogenic tissue. Exclusion criteria were: (1) evidence of unilateral hippocampal sclerosis on MRI with concordant ictal/interictal EEG and stereotyped seizure semiology consistent with mesial temporal lobe epilepsy, and (2) MRI lesions with contrast enhancement or other features to suggest high-grade neoplasm. Of 265 patients screened, 169 met inclusion criteria and 160 were prospectively enrolled. All study patients underwent MSI. 18FDG-PET was acquired unless not clinically indicated, for example, patients with a large, destructive lesion/tissue loss or prior surgical resection. Ictal SPECT was obtained when indicated and feasible. Informed consent to participate in the study was obtained at the time of MSI.

Surgical decision making was completed at an epilepsy surgery consensus conference where the decision to place ICEEG electrodes was made. Functional imaging data could not be withheld from influencing surgical decisions; however, MSI, the least established modality with clinical validity at the time of protocol design, was excluded from generation of the initial hypothesis of seizure localization and ICEEG decisions (whether to use ICEEG and where to place electrodes). Subsequent to this initial assessment, MSI results were provided, which could then only influence ICEEG sampling by indicating supplemental coverage to that already planned based on the initial hypothesis.

Magnetoecephalography/Magnetic Source Imaging

Continuous MEG of spontaneous cerebral activity was recorded using a whole-head, 148-channel biomagnetometer system (4D Neuroimaging, San Diego, CA). EEG was recorded simultaneously using the International 10-20 system of electrode placement with FT9 and FT10 included as additional electrodes. A minimum of four 10-minute recordings was performed unless the patient had frequent spikes (more than 40 in 10 minutes). MEG signals were recorded at 508.63Hz sampling frequency and band pass was 1.0 to 100Hz; signals were then digitally filtered with a band pass of 3 to 70Hz for off-line analysis.

On first-pass review of the recordings, spikes were identified on EEG, and then MEG. Next, a second-pass review of the MEG data was performed using the waveform knowledge of the initial review to attempt identification of MEG-only epileptiform discharges. Calculation of the location, orientation, and strength of the dipole sources that best fit the measured magnetic fields just before or near the spike peak was performed with 4D Neuroimaging software. Dipole fits were accepted if the following criteria were met: (1) a correlation coefficient of 0.97 or greater, (2) no simultaneous magnetic artifact, and (3) a 95% confidence volume less than or equal to 20mm^3. A specific criterion for signal-to-noise was not required, but all accepted dipole fits were associated with events having clearly visible signal above background activity (approximately three- to four-fold baseline activity).

Additional details of image registration and classification of MSI localization is described in an earlier report.11 Distinction between mesial and lateral temporal lobe classification was an exception to simple rules of localization of five or more spikes in a defined sublobar region(s). MSI examinations were defined as localized to the “mesiobasal” temporal regions if spike dipoles were located predominantly in the anterior half of the temporal lobe and had horizontal or anterior vertical dipole orientation. Dipole sources located exclusively to the posterior half of the temporal lobe with vertical orientation were classified as localized to the lateral temporal lobe. These definitions are based on studies of both EEG and MEG dipole orientation and correlation with ICEEG and surgery outcome.12-14

2-[(18F)fluoro-2-deoxy-D-glucose Positron Emission Tomography

PET scans were obtained as outpatients after injection and uptake of 5 to 10mCi 18FDG during the interictal state, resting with eyes closed. Scans were performed on a high-resolution tomograph, either a CTI ECAT EXACT (Siemens AG, Munich, Germany) or a Discovery LS PET/CT (General Electric, Madison, WI). Scans were coregistered to the same volumetric MRI used for MSI with Automated Image Registration (AIR; http://bwh.brain.uchicago.edu/).15 Visual analysis, independent of other imaging studies (except coregistered MRI), was performed by two reviewers with expertise...
in the interpretation of $^{18}$FDG-PET scans in epilepsy, one blinded (B.O.) and one unblinded (R.C.K.). A consensus interpretation was achieved about presence and localization of relative focal hypometabolism. Both reviewers were required to make a decision about which regions of interest (defined later in Analysis and Statistics) were affected; then scans were classified as normal or abnormal. Abnormal findings were further characterized as “large/ambiguous,” “questionable,” “multifocal,” “lateralized,” or “unifocal.” Topography of metabolic abnormalities was defined by regions of interest described in Analysis and Statistics (see later).

Ictal Single-Photon Emission Computed Tomography

Ictal and interictal SPECT scans were performed with injections (mean injection time, 14 seconds) of 20 to 40mCi Tc-99m hexamethylpropyleneamine-oxime. Scans were always acquired within 1 to 3 hours of injection. Each patient was scanned on either a Picker Prism 3000XP (Picker International, Bedford, OH) triple-head gamma camera equipped with low-energy, high-resolution collimators yielding an image resolution of approximately 7mm full-width at half maximum at UAB Medical Center or a Siemens e-Cam (Siemens, Erlangen, Germany) dual-head gamma camera system at The Childrens Hospital. The matrix size was 128 × 128 for both cameras. Acquisition parameters were 120 degrees rotation, 40 stops per head at 45 sec/stop (120 total projections). Image attenuation correction was performed by the Chang method; reconstruction was performed using a Butterworth filter with frequency cutoff of 0.28 and Nyquist order of 8. Coronal, transverse, and sagittal SPECT images were generated.

Image processing was performed in the environment of a Unix-based workstation (Apple G5, Cupertino, CA) using the SISCOM module in Analyze 7.0 (Analyze Direct, Lenexa, KS; www.analyzedirect.com). Final subtraction images were interpreted by the same reviewers as PET. Each reviewer determined areas of cortical hyperperfusion or hypoperfusion, and lateralized basal ganglia and cerebellar hyperperfusion. Consensus on presence and localization of relative perfusion changes was required. Scans were classified and scored as described earlier with PET.

Intracranial Electroencephalography and Image-Guided Surgery

Subdural grid arrays and strip electrodes were placed according to the consensus hypothesis of epilepsy localization based on ictal EEG, semiology, imaging, and neuropsychology. At the time of electrode removal and surgical resection, localization of seizure-onset electrodes was determined in relation to imaging tests using frameless stereotaxy surgical navigation systems. For cases with subtemporal epidural or subdural strip electrodes, frameless stereotaxy was not used and source agreement was determined by visual confirmation of accurate electrode placement of mesial basal and lateral regions of the middle cranial fossa on skull radiographs or computed tomographic scan.

ICEEG primarily defined the location and extent of resection. If ICEEG was nonlocalizing, then imaging tests could be used to determine whether and where a resection was performed. All available tests in a given patient were taken into account for such surgical decisions without control to weigh one over another.

Analysis and Statistics

All functional imaging tests were subclassified as “localized,” “nonlocalized,” “inconclusive,” or “negative” according to the Standards for Reporting of Diagnostic Accuracy. ICEEG (the reference standard) was first classified as “localized,” “multifocal,” “no seizures,” or “nonlocalized,” then converted to Standards for Reporting of Diagnostic Accuracy definitions (eg, multifocal to “nonlocalized” and “no seizures” to “inconclusive”). For comparison of localization between each imaging test and ICEEG, all cases were classified with respect to concordance as follows: A = localized on test and ICEEG, concordant for site; B = localized on test and not ICEEG; C = localized on ICEEG and not test; D = not localized on test or ICEEG; and E = localized on test and ICEEG, discordant for site. Concordance was defined as localization to the same sublobar region(s): frontal polar, dorsal frontal (superior), frontal (inferior), mesial frontal, anterior parietal, posterior parietal (superior), posterior parietal (inferior), mesial parietal, lateral occipital, mesial occipital, lateral temporal, temporal polar, and mesial temporal. Concordance was present if the maximal test abnormality indicated the same sublobar region(s) as ICEEG; otherwise, the findings were considered discordant.

Analysis for imaging test agreement with ICEEG was assessed at the level of each of the five possible test outcomes (A through E) and for the two outcomes assessing the degree of concordance (levels A + D) and discordance (levels B + C + E). Analysis of the five-level outcome was considered as arising from a multinomial distribution, whereas that of the two-level outcome was considered as arising from a binomial distribution, allowing estimates of the proportion of patients in all of the categories together with 95% confidence limits.

Assessment of the relation between localization concordances of two imaging tests (or combination of tests) was identical to the assessment between imaging test and ICEEG localization. For MSI, separate analyses were performed on all available cases, and then with nondiagnostic cases removed (no spikes captured during test).

Results

Epilepsy Type and Magnetic Resonance Imaging Classification

Table 1 lists the number of patients by MRI classification in each of the video-EEG–defined epilepsy classes (classification based on electroclinicoanatomic impression). Sixty-one percent of cases were classified as lateral temporal or extratemporal lobe epilepsy. MRI showed no abnormality in 43% of all patients and 50% in those with mesial temporal lobe epilepsy. Only seven patients had a single localized abnormality, either transmanteal focal cortical dysplasia or a developmental tumor-like lesion.

Table 2 lists the test localization results for ICEEG, MSI, $^{18}$FDG-PET, and ictal SPECT for each of the video-EEG–defined epilepsy categories. The results are provided as “localized,” “nonlocalized,” and “negative.”
For diagnostic values, “nonlocalized” and “negative” may be combined (both considered negative).

Diagnostic Values of Magnetic Source Imaging, 2-[18F]fluoro-2-deoxy-D-glucose Positron Emission Tomography, and Ictal Single-Photon Emission Computed Tomography

Tables 3 through 7 show the sensitivities, specificities, and predictive values for each of the modalities, alone and in combination, all computed with ICEEG localization as the standard test. MSI consistently showed sensitivity and specificity values greater than PET and ictal SPECT. Most notable was the high positive predictive value (PPV) of approximately 90% seen with localized MSI in all comparison groups. Increases in sensitivity were seen with combination of either PET or ictal SPECT with MSI, but not with other combination (diagnostically positive if either of a pair or both tests are localized and concordant with ICEEG localization). Predictably, sensitivity is low when two or three tests are required to be localized and concordant, but specificity is high (approximately 90%) for all test combinations except PET and ictal SPECT (67%).

Levels of Concordance with Intracranial Electroencephalography: Magnetic Source Imaging and 2-[18F]fluoro-2-deoxy-D-glucose Positron Emission Tomography

Figure 1 shows the concordance results for the patients who had both MSI and 18FDG-PET (n = 60). The proportion of cases concordant with ICEEG was greater for MSI compared with PET. The agreement for total concordance is measured by the grouping of levels A + D versus the group of B + C + E. The κ measure for MSI agreement ranged was 0.267 or 0.374 depending on whether nondiagnostic MSI cases were

<table>
<thead>
<tr>
<th>MRI class</th>
<th>MSI, n</th>
<th>PET, n</th>
<th>Ictal SPECT, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>14 (50)</td>
<td>2 (22)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>14 (50)</td>
<td>7 (78)</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Large, ambiguous, multiple</td>
<td>7 (25)</td>
<td>3 (33)</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Questionable</td>
<td>5 (18)</td>
<td>3 (33)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Localized</td>
<td>2 (7)</td>
<td>1 (11)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>28 (39)</td>
<td>9 (12)</td>
<td>31 (43)</td>
</tr>
</tbody>
</table>

Table 2. Localization Frequencies for Intracranial Electroencephalography, Magnetic Source Imaging, 2-[18F]fluoro-2-deoxy-D-glucose Positron Emission Computed Tomography by Video-Electroencephalography–Defined Epilepsy Classification

<table>
<thead>
<tr>
<th>VEEG</th>
<th>ICEEG, n</th>
<th>MSI, n</th>
<th>PET, n</th>
<th>Ictal SPECT, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Localized</td>
<td>NL&lt;sup&gt;a&lt;/sup&gt; Negative&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Localized</td>
<td>NL&lt;sup&gt;a&lt;/sup&gt; Negative&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ExTL</td>
<td>E</td>
<td>22</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>MTLE</td>
<td>E</td>
<td>20</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>LTE</td>
<td>E</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NL</td>
<td>E</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>E</td>
<td>54</td>
<td>18</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Indicates nonlocalized seizure-onset ictal patterns (intracranial electroencephalography [ICEEG]); nonlocalized and multifocal localized spikes (MSI); or large or ambiguous, questionable, lateralized, and multifocal imaging abnormalities (positron emission tomography [PET] and ictal single-photon emission computed tomography [SPECT]).

<sup>b</sup>No seizures captured during ICEEG recording session (minimum 5 days).

<sup>c</sup>No spikes captured during magnetic source imaging (MSI) recording session.

<sup>d</sup>Normal glucose metabolism.

<sup>e</sup>No change in regional cerebral blood flow.

NL = nonlocalized ICEEG at or before ictal onset; VEEG = video-electroencephalography (suspected localization based on scalp recorded interictal and ictal electroencephalographic and seizure semiology); ExTLE = extratemporal lobe epilepsy; MTLE = mesial temporal lobe epilepsy; LTE = lateral temporal lobe epilepsy.
included. The $\kappa$ for PET agreement with ICEEG was negligible (seven cases were localized on PET and not ICEEG). The difference between MSI and PET concordance with MSI was significant when measured in the 48 cases with diagnostic MSI (McNemar’s ($S$) = 5.83; $p = 0.016$).

Figure 2 shows the concordance results for the patients who had both MSI and ictal SPECT. The proportion of cases concordant with ICEEG was greater for MSI, but not statistically significant, even when nondiagnostic MSI cases were excluded. The $\kappa$ measure for MSI agreement with ICEEG in this subset of cases was similar to that measured earlier in the larger PET subset. Also similar was the absence of any effective agreement between ictal SPECT and ICEEG (five cases were localized with ictal SPECT and not ICEEG).

Figure 3 shows the concordance results for the patients who had all three tests. As seen in the prior pairings, MSI had the largest proportion of cases concordant with ICEEG. Ictal SPECT localized the largest number of cases (n = 5) that were not localized with ICEEG. In the comparison between modalities for total concordance (levels A + D), MSI was significantly greater than PET (McNemar’s ($S$) = 5.8275; $p = 0.016$). Significant agreement was seen between PET and ictal SPECT ($\kappa = 0.452$; $p = 0.0107$). No other comparisons, either concordance with ICEEG or agreement between modalities, were found to be significant.

**Discussion**

The main findings from this study are fixed around the strength and weaknesses of ICEEG as a “gold standard.” Although 84% of cases with localized ICEEG (n = 49) may be considered true positives, either Engel I (n = 35) or II (n = 6) surgical outcomes, the concordance results do not necessarily reflect imaging test accuracy. This is particularly the case for specificity, in which positive (localized) imaging tests could be obtained in cases of nonlocalized ICEEG. In several of these cases, the imaging test was correct but was considered a false-positive relative to ICEEG.

MSI sensitivity ranged between 60 and 80% depending on whether nondiagnostic cases were included. This is highly consistent with previously reported larger series that include a wide mix of partial epilepsy cases. As per Standards for Reporting of Diagnostic Accuracy definitions, of the 58 cases comprising the MSI diagnostically conclusive cases, 33 (52%) were positive, that is, demonstrating unambiguously localized spikes (unifocal or multifocal). The remaining diagnostic cases were defined as negative; that is, spikes that were either widely scattered or could not meet source localization criteria with the single equivalent

<table>
<thead>
<tr>
<th>Diagnostic Values</th>
<th>MSI (n = 72)</th>
<th>MSI or PET* (n = 58)</th>
<th>MSI and PETb (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, % (CI)</td>
<td>62.7 (48.1–75.5)</td>
<td>80.0 (63.9–90.4)</td>
<td>15.6 (8.7–19.2)</td>
</tr>
<tr>
<td>Specificity, % (CI)</td>
<td>75.0 (47.4–91.7)</td>
<td>69.2 (38.9–89.6)</td>
<td>86.7 (66.1–97.6)</td>
</tr>
<tr>
<td>PPV, % (CI)</td>
<td>88.9 (78.0–96.4)</td>
<td>88.9 (73.0–96.4)</td>
<td>77.8 (43.6–96.0)</td>
</tr>
<tr>
<td>NPV, % (CI)</td>
<td>38.7 (22.4–57.7)</td>
<td>52.9 (28.5–76.1)</td>
<td>25.5 (19.5–28.7)</td>
</tr>
<tr>
<td>Discordant cases, n</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

aNegative “nondiagnostic” magnetic source imaging (MSI) (no spikes) cases excluded.

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

Table 4. Magnetic Source Imaging and Positron Emission Tomographic Diagnostic Measures Based on Intracranial Electroencephalography Localization (n = 60)
current dipole (ECD) model, the latter typically characterized by some combination of heterogeneous and complex spike morphology, variable field distribution, and temporal instability of magnetic flux patterns.

Measuring features of MEG spikes with relation to localization confidence (conclusive vs inconclusive) was not an aim of this study; however, this issue is a likely important confounder for MSI diagnostic utility. Others have begun to examine features of MSI spikes, and not just localization in regard to a diagnostic utility. The main features of interest appear to be degree of tightness and temporal stability of dipole parameters. Such parameters may aid in defining true negatives that can yield an important improvement in overall accuracy and may potentially highlight a valuable role for MSI as an epilepsy surgery screening tool.

The sensitivities of both PET and ictal SPECT were relatively low (40 and 48%, respectively) compared with MSI (60% and 64%). These differences, however, are complementary from a diagnostic standpoint as demonstrated by the 80% sensitivity with both the combination of PET-MSI and ictal SPECT-MSI pairs. This additive sensitivity shows a lack of large redundancy between MSI and either PET or ictal SPECT, and suggests the possibility of considering a protocol based on serial acquisition of the tests, starting with MSI.

The sensitivities of both PET and ictal SPECT were relatively low (40 and 48%, respectively) compared with MSI (60% and 64%). These differences, however, are complementary from a diagnostic standpoint as demonstrated by the 80% sensitivity with both the combination of PET-MSI and ictal SPECT-MSI pairs. This additive sensitivity shows a lack of large redundancy between MSI and either PET or ictal SPECT, and suggests the possibility of considering a protocol based on serial acquisition of the tests, starting with MSI.

Only modest additive value for either sensitivity or specificity was present when combining PET and ictal SPECT. A surprisingly high κ score further supported this finding. However, the agreement measure between PET and ictal SPECT was with respect to concordance with ICEEG. Some cases were localized with one or the other modality (two with PET, five with ictal SPECT) demonstrating a lack of redundancy that has to be considered on a case-by-case basis. As a further limitation of these data, the patients that had both PET and ictal SPECT were few and certainly reflected selection bias, that is, cases that were reasonably amenable to ictal injection for SPECT, as well as patients likely to be nonlocalized on PET (63%). Thus, no suggestion can be made for the selective use of PET versus ictal SPECT based on these data other than to note that it is possible to obtain a localized ictal SPECT when PET is negative.

The additive diagnostic value of either PET or ictal SPECT to MSI is an interesting finding regarding the role of the combined tests. But first, the implications for clinical utility of each of the tests have to be understood in the setting of epilepsy surgery as an expensive elective treatment. Although chronic and disabling, intractable epilepsy is not imminently life threatening. As a result, diagnostic tests, in this instance, those that are asked to discriminate among surgical candidates re-

<table>
<thead>
<tr>
<th>Diagnostic Values</th>
<th>MSI</th>
<th>iSPECT</th>
<th>MSI or iSPECT</th>
<th>MSI and iSPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, % (CI)</td>
<td>60.0 (48.4–63.8)</td>
<td>48.0 (36.9–59.1)</td>
<td>80 (70.0–90.2)</td>
<td>24.0 (13.1–27.8)</td>
</tr>
<tr>
<td>Specificity, % (CI)</td>
<td>87.5 (51.1–99.3)</td>
<td>50.0 (22.3–77.7)</td>
<td>40 (15.1–65.7)</td>
<td>90.0 (62.8–99.5)</td>
</tr>
<tr>
<td>PPV, % (CI)</td>
<td>93.8 (75.6–99.7)</td>
<td>70.6 (54.3–86.9)</td>
<td>76.9 (67.3–86.8)</td>
<td>85.7 (46.8–99.2)</td>
</tr>
<tr>
<td>NPV, % (CI)</td>
<td>41.2 (24.1–46.7)</td>
<td>27.8 (12.4–43.2)</td>
<td>44.4 (16.8–73.0)</td>
<td>32.1 (22.4–35.5)</td>
</tr>
</tbody>
</table>

Discordant cases, n 2 0 0 0

Magnetic source imaging (MSI) results include nondiagnostic studies. iSPECT = ictal single-photon emission computed tomography; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

<table>
<thead>
<tr>
<th>Diagnostic Values</th>
<th>MSI</th>
<th>PET</th>
<th>iSPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, % (CI)</td>
<td>57.9 (43.6–62.9)</td>
<td>22.2 (9.5–33.9)</td>
<td>38.9 (25.5–53.8)</td>
</tr>
<tr>
<td>Specificity, % (CI)</td>
<td>85.7 (47.0–99.2)</td>
<td>62.5 (33.9–88.7)</td>
<td>44.4 (17.7–74.3)</td>
</tr>
<tr>
<td>PPV, % (CI)</td>
<td>91.7 (69.1–99.6)</td>
<td>57.1 (24.5–87.1)</td>
<td>58.3 (38.3–80.7)</td>
</tr>
<tr>
<td>NPV, % (CI)</td>
<td>42.9 (23.5–49.6)</td>
<td>26.3 (14.3–37.4)</td>
<td>26.7 (10.6–44.6)</td>
</tr>
</tbody>
</table>

Discordant cases, n 1 1 0

Magnetic source imaging (MSI) results include nondiagnostic studies. PET = positron emission tomography; iSPECT = ictal single-photon emission computed tomography; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.
garding who will and will not be localized with ICEEG and benefit from surgery, should tend toward high specificity more than sensitivity. And because high prevalence of having localized epilepsy should be expected in the population of surgical candidates studied with these tests, the PPV can be used as a valid and generalizable diagnostic measure. Compared with our earlier report, MSI continued to demonstrate moderately high specificity and PPV for concordant localization with ICEEG. A high PPV may suggest use for MSI as a noninvasive tool to better select surgical candidates. Ideally, a positive (conclusively localized) MSI should indicate a candidate for whom it is worthwhile to proceed with ICEEG. In this sense, the value of an accurate patient selection test is even greater than the other often considered role of MSI: to aid in the optional placement of ICEEG electrodes. Arguably, however, the specificity from MSI, at least as it was performed in this study with the single ECD model, is still not sufficient to rule out patients for further surgical evaluation. The addition of PET or ictal SPECT may add sufficient specificity for this role. But only if potential false-positives can be detected, or at least suspected, should conclusions be made about proceeding further with surgery evaluation and testing, including where to place ICEEG electrodes.

The goal of this study was to prospectively collect observational data to assess the role of MSI, PET or iSP, MSI and PET or iSP, PET and iSP, and MSI or PET or iSP in concordant localization with ICEEG. A high PPV may suggest use for MSI as a noninvasive tool to better select surgical candidates. Ideally, a positive (conclusively localized) MSI should indicate a candidate for whom it is worthwhile to proceed with ICEEG. In this sense, the value of an accurate patient selection test is even greater than the other often considered role of MSI: to aid in the optional placement of ICEEG electrodes. Arguably, however, the specificity from MSI, at least as it was performed in this study with the single ECD model, is still not sufficient to rule out patients for further surgical evaluation. The addition of PET or ictal SPECT may add sufficient specificity for this role. But only if potential false-positives can be detected, or at least suspected, should conclusions be made about proceeding further with surgery evaluation and testing, including where to place ICEEG electrodes.

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Table 7. Magnetic Source Imaging, Positron Emission Tomography, and Ictal Single-Photon Emission Computed Tomographic Diagnostic Measures Based on Intracranial Electroencephalography Localization: Combined Imaging (n = 27)

<table>
<thead>
<tr>
<th>Diagnostic Values</th>
<th>PET or iSP</th>
<th>PET and iSP</th>
<th>MSI or PET or iSP</th>
<th>MSI and PET and iSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, % (CI)</td>
<td>44.4 (31.0–59.3)</td>
<td>22.2 (9.2–33.9)</td>
<td>72.2 (63.2–86.4)</td>
<td>5.6 (0.3–10.8)</td>
</tr>
<tr>
<td>Specificity, % (CI)</td>
<td>44.4 (17.5–74.2)</td>
<td>66.7 (40.6–90.1)</td>
<td>22.2 (4.2–50.5)</td>
<td><strong>88.9 (78.4–99.4)</strong></td>
</tr>
<tr>
<td>PPV, % (CI)</td>
<td>61.5 (42.9–82.2)</td>
<td>57.1 (23.6–87.2)</td>
<td>65.0 (56.9–77.7)</td>
<td>50.0 (2.7–97.3)</td>
</tr>
<tr>
<td>NPV, % (CI)</td>
<td>28.6 (11.2–47.7)</td>
<td>30.0 (18.3–40.5)</td>
<td>28.6 (5.3–65.0)</td>
<td>32.0 (28.2–35.8)</td>
</tr>
</tbody>
</table>

Magnetic source imaging (MSI) results include nondiagnostic studies.

PET = positron emission tomography; iSP = ictal single-photon emission tomography; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.
PET, and ictal SPECT in the evaluation of patients who typically require ICEEG for ultimate localization of their epilepsy. The patients were broadly selected and should be generalizable to a large percentage of people seen at other tertiary epilepsy surgery centers.

The methods of MSI analysis and image acquisition were standard of care. The largest limitation, apart from the small “n” for ictal SPECT and patients who had all three modalities, was the ICEEG electrode sampling. Most ICEEG recordings were performed with

Fig 2. Simple proportions of patients in each of the listed concordance categories (A–E) for magnetic source imaging (MSI; white bars) and ictal single-photon emission computed tomography (SPECT; hatched bars) (n = 35) with respect to intracranial electroencephalography (ICEEG) localization. A = localized on test and ICEEG, concordant for site; B = localized on test and not ICEEG; C = localized on ICEEG and not test; CI = confidence interval; D = not localized on test or ICEEG; and E = localized on test and ICEEG, discordant for site.

Fig 3. Simple proportions of patients in each of the listed concordance categories (A–E) for magnetic source imaging (MSI; white bars), 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography ($^{18}$FDG-PET; gray bars), and ictal single-photon emission computed tomography (SPECT; hatched bars) (n = 27) with respect to intracranial electroencephalography (ICEEG) localization. A = localized on test and ICEEG, concordant for site; B = localized on test and not ICEEG; C = localized on ICEEG and not test; CI = confidence interval; D = not localized on test or ICEEG; and E = localized on test and ICEEG, discordant for site.
subdural strip and grid electrodes, which even when overlying epileptogenic tissue may not adequately record seizure onsets localized to deep sulcal gray matter. In fact, of the 72 patients who had seizures recorded on ICEEG, 17% had nonlocalized recordings. This is a relatively high percentage for what was to be the gold standard, a problem that negatively affects diagnostic value measures for all imaging modalities, especially ictal SPECT (50% of the ictal SPECT cases had nonlocalized ICEEG). Indeed, when accuracy measures are performed against surgery outcome (see companion article), imaging specificity measures increased to that comparable in other similar series.24–32

Four of the seven patients who had surgery despite nonlocalized ICEEG had localized ictal SPECT or PET (or both), all with either Engel I (n = 3) or II (n = 1) outcome.

The problem of ICEEG regarding test accuracy in the form of a gold standard is more than a limitation of this work. Rather, the problem highlights the need for a better reference in measuring accuracy of diagnostic epilepsy imaging tests. False-negative ICEEG is not an uncommon clinical problem and should be remembered in the discussion of surgical decision making. First, nonlocalized ICEEG does not necessarily preclude successful surgery. Because many such cases have nonfocal desynchronization or apparent attenuation as the initial ictal pattern due to sources that are likely in deep sulcal gray matter, use of stereotactically placed depth electrodes may help. The availability and expertise required for high-density stereotactically placed depth electrodes, however, is highly restricted. Second, the problems of ICEEG in total, that is, risks, expense, and limited sampling, raises the often-asked question whether if it can be “skipped” in selected cases where concordant noninvasive localized data unequivocally indicate likely epilepsy localization. The seven patients in this series that proceeded to surgery based on imaging when ICEEG was nonlocalized raise this question. In fact, the first aim of this study was to determine whether any of the tests, alone or in combination, could serve as a noninvasive alternative to replace or supplement ICEEG. Taking the results as is with only modest overall concordance rates, the answer would be “no” to replace; however, the answer truly remains unclear because of ICEEG limitations in localization. As to the question to supplement ICEEG, the answer is “yes” because of the cases with nonlocalized ICEEG that had resection based on the imaging tests and became seizure free (n = 5 Engel I; n = 2 Engel II). The study does not identify the multiple potential imaging variables and criteria that best characterize potential skip cases. A clinical trial randomizing patients to ICEEG or imaging-based surgery would be scientifically ideal, but this is not ethically possible. A propensity score analysis-based observational study33 may be feasible but will require more knowledge of covariates that are associated with surgical treatment decisions.

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References