Predicting Seizure-Free Status for Temporal Lobe Epilepsy Patients Undergoing Surgery: Prognostic Value of Quantifying Maximal Metabolic Asymmetry Extending over a Specified Proportion of the Temporal Lobe

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Conventional visual analysis of brain ^{18}F-FDG PET scans is useful for predicting postsurgical improvement for temporal lobe epilepsy (TLE) patients, but prognostic value for identifying patients who will achieve seizure-free status is considerably lower. We aimed to develop an approach with which to quantitatively assess prognostically pertinent aspects of metabolic asymmetry in presurgical PET scans for forecasting postsurgical seizure-free clinical outcomes. **Methods:** Presurgical brain PET scans of 75 TLE patients were examined using a display/analysis tool that quantified maximal metabolic asymmetry in a specified proportion (x%) of the temporal lobe pixels in the most asymmetric plane, generating a temporal lobe asymmetry index (T-AI_x). Results of this analysis were compared with patients' actual postsurgical outcomes after an average of approximately 4 y of clinical follow-up. The investigation was divided into 2 main steps: The PET scans examined in the first step, selected by chronological order of scan acquisition dates, comprised just less than two thirds of the patient group studied (n = 47) and were used to look for parameters predicting seizure-free postsurgical outcome; in the second step, the predictive value of the parameters suggested by the analysis in the first step was independently examined using the set of remaining PET scans (n = 28) to check for wider applicability of the approach. **Results:** Of the 75 patients studied, 42 became seizure free after surgery, whereas 33 continued to seize beyond the immediate postoperative period, during a mean 3.8-y follow-up interval. The specified proportion of temporal pixels with which to assess maximal asymmetry that provided the highest prognostic value with respect to achieving seizure-free status was 20%. Across the study population, those patients with scans having lower T-AI_{20} values (corresponding to $<$40% difference in pixel intensities between left and right temporal lobes, among the 20% most asymmetric left–right pixel pairs measured in the most asymmetric plane) were only half as likely to continue to have seizures postsurgically as those with scans having higher T-AI_{20} values (positive likelihood ratio for achieving seizure-free outcome, 1.98; 95% confidence interval, 1.07–3.67). Overall, those patients with greater maximal asymmetry, as indexed by higher T-AI_{20} values, had a significantly decreased chance of achieving seizure-free status after surgery than those with lower degrees of asymmetry (P = 0.017), and this same tendency was observed for both the first and second series of PET scans examined. **Conclusion:** A quantifying approach to assessing maximal temporal asymmetry over a specified proportion of the temporal lobe may help to predict whether patients will likely be free of seizures during the years after neurosurgical resection of epileptogenic tissue.

Key Words: temporal lobe epilepsy; metabolic asymmetry; quantitative assessment; seizure-free status; ^{18}F-FDG; PET; presurgical evaluation

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Epilepsy affects 0.5%–1% of the general population over the course of their lifetimes (*1*). Although the majority of these patients are successfully treated with antiepileptic medications, up to 20% of seizure disorders (and >40% of complex partial-seizure cases) may be inadequately controlled by pharmacotherapy (*2–5*). Surgical intervention is an effective and widely accepted form of treatment for some forms of intractable epilepsy (*2,6*). The majority of patients undergoing surgery have temporal lobe epilepsy (TLE) (*7*). Patients randomized to surgical treatment fare better than those randomized to long-term pharmacotherapy in the treatment of intractable TLE (*8*). Successful neurosurgery has 2 important effects: (a) decreasing or eliminating seizure episodes and (b) reducing cognitive impairment due to recurrent seizures or the higher doses of anticonvulsants otherwise used in treating them (*9,10*). In an analysis of 3,579 patients who had undergone anterior temporal lobe resections for TLE, 68% were seizure free postsurgically

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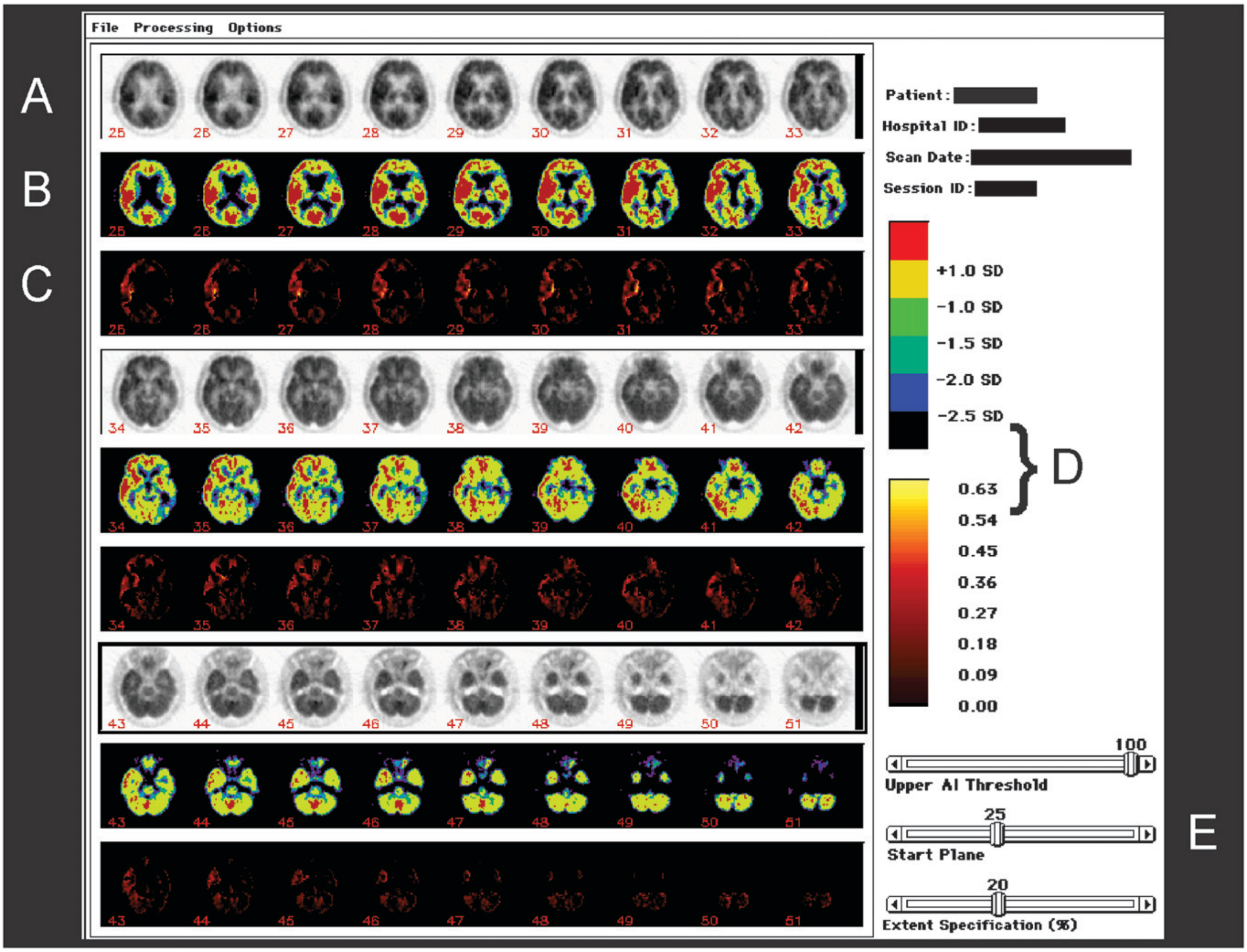

FIGURE 1. Axial tomographic brain slices were displayed in original linear (or inverse linear) gray scale (A), according to a statistically parameterized scale (B), and by an asymmetry parameterized scale (C), as described in the text. Numerically labeled color bars were displayed adjacent to the parameterized scales (D). Scan interpreter could specify the proportion of cortex (x%) for which maximal asymmetry was to be quantified as well as certain display features that would not directly affect quantification, using interactive slider controls (E).

and 92% experienced significant improvement with respect to seizure frequency (*11*). Extratemporal cortical resections performed for seizure foci in the frontal, parietal, or occipital lobes are less successful in decreasing seizure frequency, and only 40%–50% of such patients are rendered seizure free postsurgically (*12*).

Successful surgical intervention requires accurate localization of the seizure focus. Contemporary seizure-localizing techniques used in presurgical planning include ictal electroencephalography (EEG), interictal PET, interictal and ictal SPECT, MRI, and neuropsychologic testing (*13*). One study found that quadruple concordance from any of the contemporary seizure focus–localizing techniques could accurately predict postoperative seizure-free outcome in 85% of patients (*13*). Many patients with complex partial seizures, particularly those who have EEG evidence of a temporal lobe focus but inconclusive MRI findings, may be referred for functional brain imaging, generally to assess ictal perfusion by SPECT or interictal metabolism by PET (*14,15*). The clinical utility of ictal SPECT, though widely regarded as more accurate in identifying surgical candidates than interictal SPECT, is compromised by logistical difficulty in attaining properly timed radiotracer injection and acquisition of images with respect to ictal episodes (*16,17*). PET studies using ^{18}F-FDG can be performed as a straightforward outpatient procedure interictally to identify regions of cerebral hypometabolism associated with epileptogenic zones (*18,19*). ^{18}F-FDG PET as an interictal imaging technique detects unilateral temporal lobe hypometabolism near the seizure foci in 86% of intractable TLE patients (*20*).

Although clinical application of PET in this context generally involves qualitative categorization of scans as either normal, marked by unilateral hypometabolism, or demonstrating bilateral hypometabolism, there has also been substantial interest in identifying methods to quantify ^{18}F-FDG PET parameters in the localization of epileptogenic zones (*21–29*). Several investigations have examined

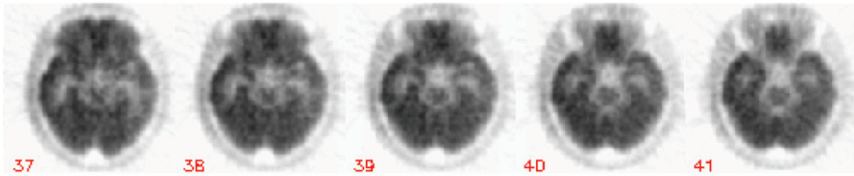

FIGURE 2. Scan interpreter selects plane(s) reflecting maximal temporal asymmetry.

quantitative features of presurgical PET with varying results. Many of these studies have used labor-intensive methods, such as hand-drawn region-of-interest (ROI) analyses (*24,26–28*). The objective of the present study was thus to develop an automated quantifying approach and to test its ability to separate presurgical patients into those who will continue to have some seizures from those who will be seizure free postsurgically.

MATERIALS AND METHODS

Patient Population

Subjects included in this study ($n = 75$) were identified as those patients (a) having been diagnosed with TLE based on clinical, EEG, and MRI findings, (b) having undergone interictal ^{18}F-FDG PET with EEG monitoring at our institution during a consecutive 10-y period, (c) having undergone subsequent attempted surgical resection of the epileptogenic focus at our institution, (d) having clinical follow-up data from their neurologists of at least 1 postsurgical year available to us, and (e) having their original PET data retrievable from digital archives. Two databases of brain scans from the subjects meeting these criteria were analyzed separately, divided according to scanner types used; the first patient series ($n = 47$) included scans performed over the first 8 y of the 10-y period, acquired on ECAT 831 or ECAT 931 scanners (Siemens Medical Solutions USA, Inc.); the second patient series ($n = 28$) included scans performed over the subsequent 2 y, acquired on HR or HR+ scanners (Siemens Medical Solutions USA, Inc.) that had been installed at our institution in the interim.

PET

Brain PET scans were obtained 40 min after the intravenous administration of ^{18}F-FDG (5.2 MBq/kg). EEG monitoring was performed throughout the ^{18}F-FDG uptake period to ensure interictal status. Images were acquired for 30 min and reconstructed with a calculated attenuation algorithm.

Postsurgical clinical outcomes were compared with imaging findings using the methods described below. Although no rigid criteria existed for the clinical interpretations rendered at our institution, PET scans were read by a physician holding certification with the American Board of Nuclear Medicine, who visually assessed whether temporal cortex appeared to be less metabolically active than would normally be expected for that part of the brain and, if so, whether one or both sides of the brain were affected. PET scans of the patients were considered to be localizing for the identification of resectable epileptogenic tissue if unilateral temporal hypometabolism was visually identified. All interpretations and quantifying analyses were made with no knowledge of clinical follow-up data.

Extent-Specified Quantified Asymmetry-of-Lobe (EQuAL) Analysis

The EQuAL approach tested in this study was implemented on a UNIX platform with a software package written in interface definition language. Axial tomographic brain slices were displayed in their original linear (or inverse linear) gray-scale formats, and also parameterized statistically, and by an asymmetry measure, as described (Fig. 1). A linear gray scale was used on the top row, showing all planes through the temporal cortex, with the intensity at each pixel reflecting the concentration of radioactivity (Fig. 1A). The statistically parameterized scale was displayed on the middle row of corresponding planes, with the intensity of each pixel coded to reflect the number of SDs by which its activity fell above or below the mean for all gray matter in the brain (Fig. 1B). The software program automatically identified the axis of bilateral symmetry in the transaxial planes, and an asymmetry-parameterized scale was displayed on the bottom row, showing images coded to reflect the degree of asymmetry of activity at each point in the brain, relative to contralateral brain tissue. This asymmetry index (AI) was represented by pixel intensity on the side of the brain possessing greater activity at that location (Fig. 1C), whereas the contralateral pixel value intensity was set to zero. The AI was defined as the ratio of the absolute value of the difference between contralateral pixels and the mean value of those pixels ($|L - R|/0.5(L + R)$).

A numerically labeled color bar was displayed adjacent to each parameterized row of images of the EQuAL software (Fig. 1D). Visually guided by the top and middle rows, a reader who was unaware of the clinical outcome identified the plane(s) reflecting the maximal temporal asymmetry (Fig. 2). The reader then specified for the corresponding plane the proportion of pixels (x%) for which asymmetry was to be quantified (with a default initially set to the most asymmetric $x = 20\%$ of pixels contained within the temporal lobe), using the bottom-most slider control (Fig. 1E). To initiate the EQuAL calculation, the reader drew a loose region around the temporal cortex in the maximally asymmetric plane, on the side of the brain visually possessing the greater activity (Fig. 3). The AI above which the most asymmetric x% of the temporal lobe pixels fell in the maximally asymmetric plane was automatically

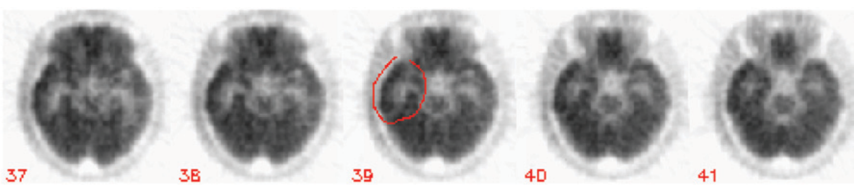

FIGURE 3. Interpreter draws loose region around temporal cortex in one of maximally asymmetric planes, on side of brain visually possessing greater activity, to initiate calculation of T-AI_x (temporal lobe asymmetry index).

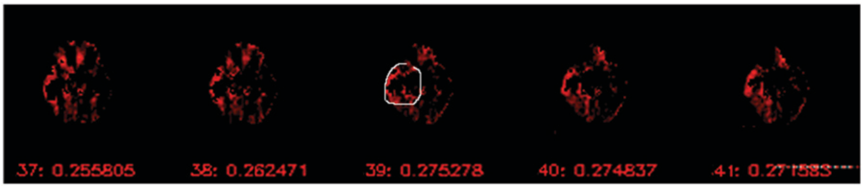

FIGURE 4. $T\text{-}AI_x$ (temporal lobe asymmetry index) values are automatically generated for 5 adjacent planes and displayed immediately below image planes (in this case, equaling 0.275, as seen below central image, plane 39).

calculated (Fig. 4). This AI value ($T\text{-}AI_x$ [temporal lobe asymmetry index]) was assigned to each scan to characterize its extent-specified maximal temporal asymmetry.

Clinical Data and Statistical Analysis

Pre- and postoperative physician evaluations were obtained. Clinical data records included—in addition to original ^{18}F-FDG PET scan results—date of any neurosurgery, age at surgery, type of surgery, details of surgical outcome, pre- and postscan seizure frequencies, and any medical therapies prescribed. Patients were classified as seizure free or not seizure free during a mean follow-up interval of 3.8 y, based on review of their medical records and written contact with their managing physicians. The significance of differences between patient groups of categorized data with respect to achieving seizure-free status was assessed by χ^2 analysis; the significance of differences between groups with respect to parametric data was assessed by a 2-tailed Student t test. Differences were considered significant at $P < 0.05$.

RESULTS

Patient Characteristics

As seen in Table 1, the first PET series of 47 subjects included 22 females and 25 males, having a mean age ± SD of 23.9 ± 15.9 y at the time of PET. There were 14 children 12 y of age or younger (including 4 patients who were <2 y old) and 33 patients older than the age of 12 y. The second PET series of 28 subjects included 15 females and 13 males, having a mean age ± SD of 22.6 ± 15.0 y at the time of PET. There were 8 children who were ≤12 y of age (including 2 patients who were <2 y old) and 20 patients older than the age of 12 y. The mean follow-up time was 3.8 y. Distributions of age and sex were similar for the 2 series, and neither the mean age nor the follow-up time significantly differed between the first and second series of patients undergoing PET.

TABLE 1
Patient Characteristics (n = 75)

Variable	First PET patient series* (n = 47)	Second PET patient series* (n = 28)
Sex		
Male	25 (53)	13 (46)
Female	22 (47)	15 (54)
Mean age ± SD at time of PET	23.9 ± 15.9	22.6 ± 15.0
<2 y	4 (9)	2 (7)
2–12 y	10 (21)	6 (21)
>12 y	33 (70)	20 (72)
Clinical follow-up time (y)	3.8	3.8

*Values in parentheses are percentages.

EQuAL Parameters

In analyzing the first PET series, the temporal AI corresponding to an extent specification of 20% ($T\text{-}AI_{20}$) range was divided into equal thirds to form low (0.26–0.40), medium (0.41–0.55), and high (0.56–0.70) $T\text{-}AI_{20}$ range groups across the full $T\text{-}AI_{20}$ range within which seizure-free status was achieved. A total of 24 patients fell in the low $T\text{-}AI_{20}$ range, 19 in the medium $T\text{-}AI_{20}$ range, and 3 in the high $T\text{-}AI_{20}$ range (In addition, 1 patient who had $T\text{-}AI_{20} < 0.26$ continued to have seizures after surgery.). In this low $T\text{-}AI_{20}$ stratum, a relatively high proportion of patients achieved seizure-free status (17/24) after temporal lobectomy compared with patients outside this stratum (11/23). Thus, moderately low $T\text{-}AI_{20}$ values were associated with an increased likelihood of achieving postsurgical seizure-free status.

Various T-AI extents and ranges were then tested to systematically identify the extent specification that would yield the highest overall accuracy in predicting seizure-free outcome. The extent specification of 20% with EQuAL was consistently found to be useful for predicting seizure-free status in the lower third $T\text{-}AI_x$ stratum (0.26–0.41 and 0.19–0.42, respectively) for both the first and the second PET series (Fig. 5). This extent specification was then applied to determine in a systematic empiric manner the optimal $T\text{-}AI_{20}$ range for predicting postsurgical seizure-free success for the patients in the second PET series (Fig. 6). The optimal range was found to be 0.19–0.40 for this series.

The pooled results of the 2 patient series revealed the low $T\text{-}AI_{20}$ stratum (characterizing 33 of the 75 patients) to be a significant predictor overall of the likelihood of achieving seizure-free status (24/33 = 73% of low $T\text{-}AI_{20}$ patients, compared with 19/42 = 45% of the remaining patients) ($\chi^2 = 5.71$, $P = 0.017$, $n = 75$) and the low $T\text{-}AI_{20}$ stratum also tended to be predictive in each of the separately studied series of patients ($\chi^2 = 2.58$, $P = 0.11$, $n = 47$ for the first patient series; $\chi^2 = 3.12$, $P = 0.08$, $n = 28$ for the second patient series). Moreover, the $T\text{-}AI_{20}$ values were significant predictors of both positive (i.e., seizure free) postsurgical outcomes (positive likelihood ratio = 1.98; 95% confidence interval [CI], 1.07–3.67), and negative postsurgical outcomes (negative likelihood ratio = 0.61; 95% CI, 0.41–0.92).

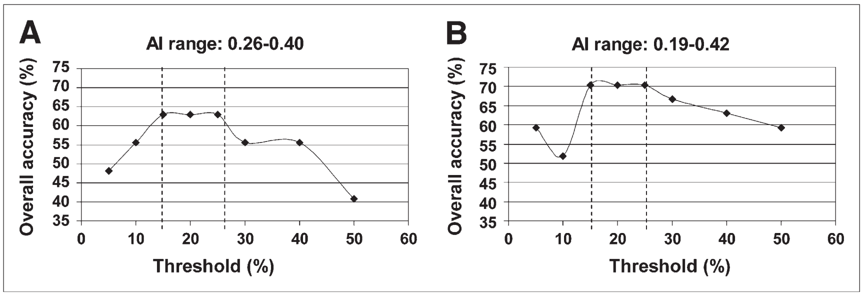

FIGURE 5. Extent specification yielding highest overall accuracy was consistently determined to be 20% by systematic tests in both first (A) and second (B) PET patient series.

Visual identification of unilateral temporal hypometabolism ($n = 70$) was a good predictor for clinical improvement postsurgically but was not specifically predictive of seizure-free status (achieved in 40 of those 70 subjects and 3 of the 5 subjects with nonlocalizing scans; $\chi^2 = 0.015$, $P > 0.90$) (Fig. 7).

DISCUSSION

The present study examined prognostic accuracy for the presurgical evaluation of TLE patients using a quantitative approach for assessing maximal temporal asymmetry over a specified proportion of tissue in brain PET scans. Whereas previous studies often used labor-intensive methods in examining quantitative features of presurgical PET, we examined an automated, analytic approach readily usable in clinical settings. The software we used displayed the PET data not only conventionally but also parameterized according to statistical and asymmetry-based representations. Before the EQuAL approach was applied, visual assessment was required to determine if the PET scan showed identifiable temporal asymmetry and, if so, on which side the brain was more metabolically active. Seizure-free outcome rates were compared with scan interpretations made with the EQuAL approach by readers who were unaware of the clinical outcome. Our results suggested that this method, used in combination with visual analysis, could successfully identify a subpopulation of TLE patients who were significantly less likely to achieve seizure-free status postsurgically—in particular, those patients with a greater maximal metabolic asymmetry across a specified proportion of the temporal region.

The clinical implication of these findings is that TLE patients with greater maximal temporal asymmetries ($\text{T-AI}_{20} \geq 0.40$ in the first and second PET patient series) who undergo surgery will less likely respond to treatment by becoming seizure free, relative to patients with a lower

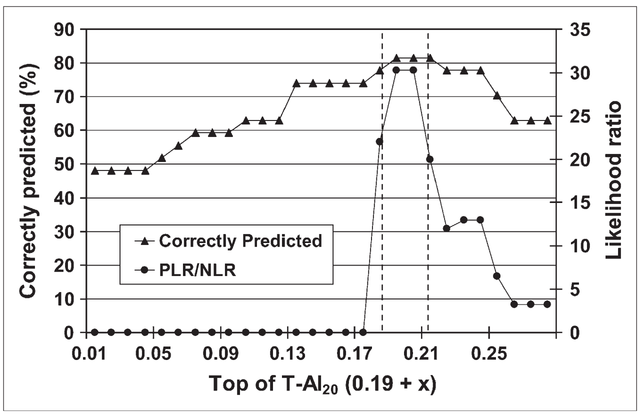

FIGURE 6. Optimal determined extent specification (20%) was applied systematically to identify optimal T-AI range for achieving seizure-free outcome in second PET patient series. By both overall accuracy and likelihood ratio measures, this optimal range extended from 0.19 to 0.40 (0.19 + 0.21). PLR = positive likelihood ratio; NLR = negative likelihood ratio; numbers on right-sided *y*-axis correspond to 10 × PLR/NLR.

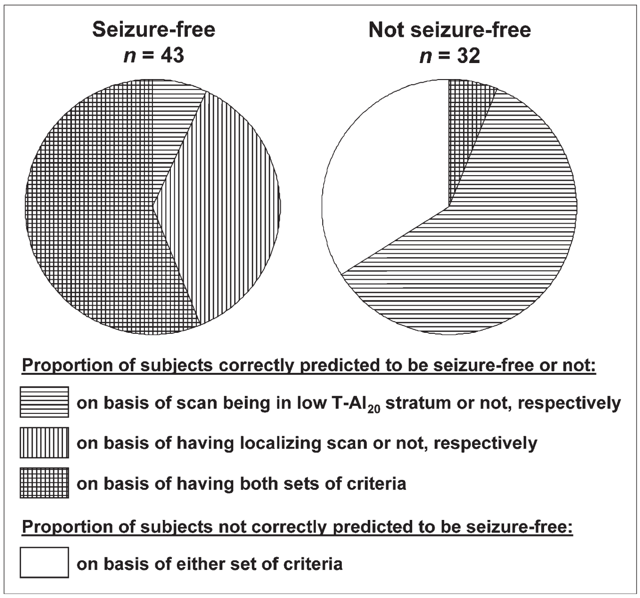

FIGURE 7. Distribution of prognoses based on visual and quantitative interpretations of PET scans, among patients who achieved seizure-free status (left, $n = 43$) and patients who continued to have seizures (right, $n = 32$) after surgical therapy. A high T-AI_{20} value (>0.40) was identified before surgery in most patients who continued to seize postsurgically, despite having unilaterally localizing patterns of hypometabolism on visual assessment of presurgical PET scans (horizontally lined segment in right pie chart), but in only a minority of patients who became seizure free (vertically lined area in left pie chart)—an indication of the added prognostic value of the T-AI_{20} index over visual assessment alone, in predicting seizure-free status.

maximal asymmetry of temporal lobes. In principle, a lower degree of maximal asymmetry could represent either less dysfunction of the epileptogenic temporal lobe or more symmetric involvement of both lobes. In the patient series in whom attempted resection had been performed, 70 of 75 patients demonstrated unilateral cortical hypometabolism by PET based on visual analysis, suggesting that lower maximal asymmetry as determined by EQuAL was generally more likely indicative of the first of these possibilities.

Although the current study focuses on cerebral metabolism assessed with ^{18}F-FDG—the radiotracer most widely used in clinical PET studies—it should be mentioned that several studies have also demonstrated the value of using other PET tracers in the evaluation of epilepsy (*20,30–35*). Additionally, although interictal SPECT is generally regarded to be the least-sensitive nuclear imaging modality of those commonly used in the evaluation of TLE patients, some clinically pertinent parameters have been found to correlate with interictal SPECT findings (*36*). Previous studies have found the noninvasive monitoring techniques to be preferable and possibly even more effective than invasive methods with regard to achieving postsurgical seizure-free status after temporal lobectomy in some patients; one study reported only 40% of temporal lobectomy patients selected by invasive methods to be rendered seizure free postsurgically as opposed to 80% of patients selected by noninvasive methods (*13*). Another recent study reported that double concordance from noninvasive or invasive presurgical localization techniques (including ictal scalp or subdural EEG, PET, and subtraction SPECT) was significantly correlated with seizure-free outcome (*37*).

CONCLUSION

The prognostic value of using a quantifying measure of maximal temporal metabolic asymmetry in evaluating presurgical PET scans was examined, and patients with greater maximal temporal asymmetries were found to be less likely to achieve seizure-free status, as demonstrated in 2 independent samples of TLE subjects. Thus, this quantitative approach could potentially be useful for helping to identify in advance those patients who would be more likely to achieve seizure-free outcome after initial surgical treatment of TLE.

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