Multimodality image-guided surgery for the treatment of medically refractory epilepsy


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Object. The aim of this study was to review seizure outcome, imaging modalities used, and complications following surgery in patients with epilepsy who had undergone multimodality image-guided surgery at our institution.

Methods. Data from patients with epilepsy who had undergone surgery between April 1999 and October 2001 were reviewed. During this time period, 116 operations were performed in 109 patients with medically refractory epilepsy. Among these patients, 22 were selected to undergo multimodality image-guided surgery primarily on the basis of whether they had no lesion visible on conventional magnetic resonance (MR) imaging sequences, multiple lesions, or one very large lesion that could not be completely resected without the risk of significant postoperative morbidity. A fourth group of patients in whom there was a single lesion in the eloquent cortex, a location associated with a significant risk of postoperative morbidity, was also included in the analysis. This latter group was assessed with the aid of intracranial grid electrodes that were coregistered to the MR image and were used intraoperatively to minimize electrode position error. Other imaging modalities used included positron emission tomography (PET), fluid-attenuated inversion recovery (FLAIR) MR imaging, and subtracted ictal–interictal single-photon positron emission computerized tomography (SPECT) coregistered with MR imaging (SISCOM). After coregistration, images were then downloaded onto an image-guided surgical system and the epileptogenic area was then resected.

The mean patient age was 33 years (range 17–46 years), and there was a mean follow-up of 27 months (range 14–41 months). Multimodality coregistrations used were as follows: nine PET scans, seven subdural electrode grids, four SISCOM studies, one FLAIR MR image, and one combined PET/subdural grid. Seizure outcome was excellent in 17 patients (77%) and not excellent in five (23%), or favorable in 19 (86%) and unfavorable in three (14%). Six patients (27%) had a transient neurological deficit, one patient (5%) a permanent major deficit, and three patients (15%) a permanent minor deficit. Five patients (24%) had a transient psychiatric problem postoperatively.

Conclusions. Multimodality image-guided surgery offers a new perspective in surgery for epilepsy. Functional imaging modalities previously lateralized and often localized a seizure focus, but did not provide enough anatomical information to resect the epileptogenic zone confidently and safely. The coregistration of these modalities to a volumetric MR image and their incorporation into an image-guided system has allowed surgeons to offer surgery to patients who may not previously have been considered eligible, with outcomes comparable to those in patients with more straightforward lesional epilepsy.

Key Words • epilepsy • image-guided surgery • outcome

It has been estimated that 4 to 10% of the population will experience at least one seizure at some point during their lifetime, with a cumulative lifetime incidence of epilepsy estimated to occur in at least 2 to 4% of the population. Although antiepileptic drugs will provide seizure control in many patients, at least 20 to 40% remain refractory to medical therapy. Epilepsy surgery offers the potential for seizure control in a subgroup of these patients. Despite the developments and advances made during recent years, surgery has been underused often due to difficulties in localizing the area of seizure onset or a lack of awareness of surgery’s potential as a treatment option. Recent developments in imaging and an increased availability of MR imaging and other functional imaging modalities combined with a wider knowledge of available surgical options has during the last decade led to a significant increase in the number of patients being offered surgery for the treatment of epilepsy.

Despite an increased awareness regarding surgical therapy and improved surgical techniques, there remains a group of patients with uncontrolled seizures whose MR imaging studies are nonlocalizing or nonlesional and thus are not considered ideal surgical candidates. These patients some-
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times have focal abnormalities on functional imaging, in particular, on PET and ictal SPECT scanning. The coregistration of these modalities to T<sub>1</sub>-weighted MR images as well as FLAIR MR images and subdural electrode grids and their incorporation into an IGSS has allowed for a number of patients who were previously considered ineligible for surgery to undergo successful resection of their epileptogenic focus. This approach has been termed “MMIGS.”

The application of image-guided surgery for the treatment of epilepsy has improved our ability to resect lesions causing epilepsy. Currently, it is based on a T<sub>1</sub>-weighted volumetric MR image with high structural resolution and anatomical detail. Note that functional imaging modalities do not have the structural resolution to be used as IGSSs on their own. Image coregistration is applied to integrate the functional imaging data with high-resolution T<sub>1</sub>-weighted images ready for use in the IGSS. The purpose of this study was to review the outcome in a consecutive series of patients who had undergone MMIGS at our institution.

Clinical Material and Methods

Between April 1999 and October 2001, 116 operations were performed for medically refractory partial epilepsy in 109 patients at St. Vincent’s Hospital. Twenty-two cases involved the use of MMIGS, which was defined as the use of two or more imaging modalities in the intraoperative stereotactic guidance system that was used to identify the surgical site (that is, the site of resection and/or intracranial electrode implantation). The imaging modalities consisted of a volumetric T<sub>1</sub>-weighted whole-brain image, which provided the anatomical template, onto which was coregistered a second data set from a functional imaging modality (that is, PET scanning, SISCOM studies, intracranial EEG data in the form of electrode positions, FLAIR MR imaging, and functional MR imaging). In all cases the second imaging modality was the primary determinant of the location of the epileptogenic zone.

Patient Selection and Examinations

A nonlocalizing or nonlesional structural MR image was the primary indication for MMIGS. This was defined as the following: 1) no lesion demonstrated on MR imaging studies; 2) more than one lesion visualized on imaging studies; or 3) a single lesion that was so large that it could not be completely resected without the risk of significant postoperative morbidity. A fourth group of patients consisted of those with a single lesion situated in eloquent cortex where it was associated with a significant risk of postoperative morbidity. In this latter group intracranial electrode grids were used and their positions were coregistered to a volumetric MR image and were used intraoperatively to minimize electrode position error.

Of 22 patients, 12 were male and 10 were female, with a mean age of 33 years (range 17–46 years). All patients underwent extensive preoperative investigations according to our program’s protocol, including MR imaging with FLAIR sequences and volumetric imaging, functional MR imaging, scalp EEG, video-EEG monitoring, ictal SPECT scanning, PET scanning, implantation of depth electrodes and subdural electrode grids/strips, Wada testing, and neuropsychological and psychiatric assessments. Not all patients had a Wada test, that is, it was performed only if indicated after a full neuropsychological assessment. After analysis of all data, localizing imaging data were coregistered for surgical planning.

Image-Guided System

The StealthStation Image-Guided System (Medtronic Sofamor Danek, Memphis TN) is a frameless stereotactic infrared-based surgical guidance system. With this system, six to 10 external fiducial markers were applied to the scalp preoperatively, after which a T<sub>1</sub>-weighted volumetric MR imaging data set was acquired. The imaging protocol used to acquire this data set was as follows: 1-mm contiguous axial slices, single-echo scan with 256 × 256 matrix. Data were then transferred onto the StealthStation Image-Guided System with which a 3D model of the patient’s head was built. Orthogonal, axial, sagittal, and coronal images of the brain as well as a 3D volume-rendered image were displayed.

After administration of an anesthetic agent, the patient’s head was placed in a Mayfield three-point head fixation system and the scalp fiducials were registered using a handheld three-emitter probe to the 3D model. This allowed the surgeon to determine the relationship between the actual position of the probe in the patient’s head and the identified targets on preoperative imaging.

Coregistration With PET Studies

The FDG-PET images were acquired on a high-resolution 3D Penn-PET 300H tomograph scanner (GE Medical Systems, Waukesha, WI). The field of view was 25 cm and a 3D whole-head acquisition was obtained. Processing and registration of the images for use in the image-guided system was performed offline using Analyze software (version 5.0; Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). Thresholding was performed to remove extracerebral activity, and then a binary image of the brain uptake was created. The FDG-PET images were then registered and transformed into the 3D space of the stereotactic MR image by matching the surfaces of the respective binary images of the brain, as previously described. The transformed FDG-PET images were imported into the StealthStation Image-Guided System as a second volume (Fig. 1). The software within the system allowed the MR images or the PET volumes to be viewed either as themselves or as an overlay with the two registered volumes and their relative intensities set by the user (Fig. 2).

Having merged the volumes, the surgical plan was determined, with the posterior extent of hypometabolism defined on the IGSS and then intraoperatively. The boundary was defined as a significant asymmetry compared with the contralateral hemisphere. The position of this boundary in stereotactic space was then registered on the system. If the abnormality was in the dominant hemisphere, then the surgery was usually performed while the patient remained awake to define the speech areas by using electrical cortical stimulation. If the region of hypometabolism was very extensive, the positions of visual field pathways were also considered prior to resection.

Coregistration With SISCOM

The SISCOM images were constructed as previously described. This method consists of five major steps. 1) The
interictal SPECT image is coregistered and transformed into the 3D space of the ictal/postictal SPECT image by using an automated, voxel-based matching technique (Automated Image Registration, version 3.0; Laboratory of Neuro Imaging, Los Angeles, CA). 2) The ictal/postictal SPECT and the transformed interictal SPECT scans are normalized to a standard mean pixel intensity. 3) The transformed and normalized interictal SPECT data are subtracted from the normalized ictal/postictal SPECT data. 4) The subtracted image is then thresholded to two standard deviations above and below zero for images of periictal hyperperfusion or hypoperfusion, respectively. 5) A $4 \times 4$ matrix describing the transformation of the ictal SPECT data into the 3D space of the stereotactic MR image is calculated using a surface matching technique. This matrix is applied to the thresholded subtraction image to create the SISCOM image.

The SISCOM image was imported into the StealthStation Image-Guided System as a second volume (Fig. 3). The merged volumes show the region of significant periictal hyper- or hypoperfusion, which was then used to guide either the placement of intracranial electrodes or the resection. Boundaries of the lesion were defined statistically, as outlined in a previous publication.

Coregistration With FLAIR MR Imaging

In selected patients the FLAIR MR images were registered to the stereotactic T$_1$-weighted volume and were imported into the StealthStation Image-Guided System as a second volume (Fig. 4). This was undertaken in patients in whom a potentially epileptogenic lesion was identified on FLAIR images, but was not obvious on the structural T$_1$-weighted volumetric images that are generally used to guide conventional stereotactic surgery. For this process the brain surface was segmented from the extracerebral tissues on the FLAIR images in Analyze by using a combination of automatic thresholding and manual editing. The segmented cerebral surface image was then converted into a binary format and was coregistered and transformed into the 3D space of the stereotactic MR image by using a surface matching technique identical to those used for other registrations. The abnormality was then identified on the stereotactic system and the surgical plan determined.

Coregistration With Intracranial Electrodes

Intracranial subdural electrodes were inserted over the
postulated epileptogenic zone, regardless of whether the case involved a lesion visible on focal MR imaging or an abnormal function study or both. Within 24 hours of implanting the intracranial electrodes, imaging was performed to determine the position of the electrodes. In patients in whom stainless steel electrodes were used, a spiral CT scan was acquired with the aid of 3-mm contiguous slices covering the entire head. In patients with platinum electrodes, an MR image was acquired using 1-mm contiguous slices. These images were then transferred offline and were processed using Analyze software. In patients with stainless steel electrodes, the electrode positions (which are of high attenuation) were segmented from the rest of the CT scans by using a threshold-based semi-automatic tracing. The brain surface was also segmented out from the original CT scan. Segmentation of the brain from the stereotactic volumetric MR images was then performed using an automated morphological segmentation tool (Object Extractor, Analyze). Binary images of the CT- and MR-derived segmented brains were created and used to register and transform the CT data to the MR data by using the surface matching technique described earlier.31 Adding the MR binary image of the brain, a segmented binary image of the lesion, and the transformed electrode images created a trilevel image. These data were imported into the StealthStation Image-Guided System as a second volume (Fig. 5). This second volume provided a 3D image of the subdural electrode positions and their relationship to the structural anatomy on MR imaging, in stereotactic space. This image can be viewed throughout the surgery, even after the electrodes have been physically removed. The accuracy of this process was validated successfully in all cases at the time of the second craniotomy, prior to removal of the subdural electrode grid. This was accomplished by visually comparing the actual electrode position on the cortex (which was indicated by the display of the infrared stereotactic probe positioned on that electrode by the surgeon) relative to the virtual electrode displayed on the surgery system 3D model. Additionally, we measured this displacement in five cases by storing the actual position of 10 electrodes (using the probe) as digital IGSS plans and archiving them. The displacement of the actual probe position to the centroid of the virtual electrode was subsequently measured. The mean error for the CT scanning–derived electrode positions was 3.4 mm (range 0.5–5.4 mm) and the mean error for the MR imaging–derived electrode positions was 2.5 mm (range 0.5–5.2 mm).40

Results
The multimodality coregistrations used included nine PET scannings, seven subdural electrode grids, four SISCOM studies, one FLAIR MR imaging, and one combined PET/subdural electrode grids. There were 10 right-sided and 12 left-sided cases of epilepsy. Three patients underwent frontal lobe surgery, two patients parietal lobe, and 17 patients temporal lobe. Another three patients did undergo insertion of a subdural electrode grid, but their functional
imaging modality (two SISCOM studies and one PET scanning) was used for coregistration and not their grid. A detailed summary of preoperative information including side, location, and MR imaging abnormality is featured in Table 1. Magnetic resonance imaging abnormalities were demonstrated in all but one patient. These abnormalities ranged from subtle signal changes, particularly in the temporal lobe, to more discrete focal lesions. In one case, a lesion was only clearly visualized on a FLAIR sequence.

Six patients had undergone previous surgery. In two of these cases (Cases 5 and 13) surgery had been performed several years previously at a pediatric hospital, whereas in the other four cases it had been performed at our institution.

A summary of postoperative information, including modality, complication, pathological features, patient outcome, and duration of follow up, is outlined in Table 2. In Case 22, the follow-up period was measured from the patient’s second operation, even though it was during the first operation that MMIGS was used, because the second resection was essentially based on the first. In all other patients who had undergone two resections, the information contained within the tables relates to the second operation. Results of histological analysis correlated well with MR imaging findings. Those patients demonstrating just minor signal change usually had nonspecific changes such as subpial gliosis and/or minor dysplastic changes as is often seen in patients with chronic epilepsy. Patients with discrete focal lesions had clearly defined pathological features such as DNET, focal cortical dysplasia, or glioma. In patients who had previously undergone surgery there was only evidence of ischemic or gliotic changes. In two patients there were dual (distinct) pathological features. For example, in one of these patients (Case 10) there was MTS as well as a DNET in the neocortex of that same lobe, which was visible on a FLAIR sequence (coregistration was used for the FLAIR sequence). Pathological examination of resected tissue revealed residual cortical dysplasia at the posterior margin, and seizure control was incomplete (Class III). The other patient (Case 11) had a schizencephalic cleft in the basal temporal lobe adjacent to the mesial temporal structures and ipsilateral MTS. Another patient (Case 20) had tuberous sclerosis and multiple cerebral tubers. A single focus associated with ha-

TABLE 1
Summary of preoperative data obtained in 22 patients who had undergone MMIGS*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Side &amp; Location of Abnormality</th>
<th>MRI Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35, M</td>
<td>rt, frontal</td>
<td>focal lesion</td>
</tr>
<tr>
<td>2</td>
<td>34, F</td>
<td>lt, temporal</td>
<td>focal lesion</td>
</tr>
<tr>
<td>3</td>
<td>35, M</td>
<td>lt, temporal</td>
<td>postop change</td>
</tr>
<tr>
<td>4</td>
<td>30, F</td>
<td>lt, temporal</td>
<td>signal change in temporal pole</td>
</tr>
<tr>
<td>5</td>
<td>21, F</td>
<td>lt, frontal</td>
<td>focal lesion</td>
</tr>
<tr>
<td>6</td>
<td>30, F</td>
<td>rt, temporal</td>
<td>signal change in temporal pole</td>
</tr>
<tr>
<td>7</td>
<td>44, F</td>
<td>lt, temporal</td>
<td>postop change</td>
</tr>
<tr>
<td>8</td>
<td>30, F</td>
<td>lt, temporal</td>
<td>signal change in temporal pole</td>
</tr>
<tr>
<td>9</td>
<td>34, M</td>
<td>rt, temporal</td>
<td>normal</td>
</tr>
<tr>
<td>10</td>
<td>24, M</td>
<td>lt, temporal</td>
<td>lesion on FLAIR imaging</td>
</tr>
<tr>
<td>11</td>
<td>43, F</td>
<td>lt, temporal</td>
<td>postop change</td>
</tr>
<tr>
<td>12</td>
<td>18, M</td>
<td>rt, parietal</td>
<td>focal lesion</td>
</tr>
<tr>
<td>13</td>
<td>45, M</td>
<td>rt, temporal</td>
<td>signal change in temporal pole</td>
</tr>
<tr>
<td>14</td>
<td>24, M</td>
<td>rt, parietal</td>
<td>lesion on FLAIR/PD imaging</td>
</tr>
<tr>
<td>15</td>
<td>23, F</td>
<td>rt, temporal</td>
<td>signal change in temporal pole</td>
</tr>
<tr>
<td>16</td>
<td>28, F</td>
<td>rt, temporal</td>
<td>signal change in temporal pole</td>
</tr>
<tr>
<td>17</td>
<td>23, M</td>
<td>rt, temporal</td>
<td>MTS &amp; signal change</td>
</tr>
<tr>
<td>18</td>
<td>23, F</td>
<td>lt, temporal</td>
<td>encephalomalacia w/ extensive atrophy in temporal pole</td>
</tr>
<tr>
<td>19</td>
<td>46, M</td>
<td>lt, temporal</td>
<td>focal lesion</td>
</tr>
<tr>
<td>20</td>
<td>18, M</td>
<td>lt, temporal</td>
<td>focal lesion, tuberous sclerosis</td>
</tr>
<tr>
<td>21</td>
<td>34, M</td>
<td>rt, temporal</td>
<td>signal change in temporal pole</td>
</tr>
<tr>
<td>22</td>
<td>41, M</td>
<td>lt, frontal</td>
<td>thickened frontal cortex</td>
</tr>
</tbody>
</table>

* PD = proton density.
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**TABLE 2**

Summary of postoperative results in 22 patients who underwent MMIGS*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Side &amp; Location of Abnormality</th>
<th>Modality</th>
<th>Complication</th>
<th>Pathological Features</th>
<th>Patient Outcome</th>
<th>Duration of Follow Up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt, frontal</td>
<td>SISCOM</td>
<td></td>
<td>SPG &amp; MDC</td>
<td>Class I</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>lt, temporal</td>
<td>grids</td>
<td>homonymous hemianopia, dysphasia</td>
<td>DNET</td>
<td>Class I</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>rt, temporal</td>
<td>SISCOM</td>
<td></td>
<td>SPG</td>
<td>Class I</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>rt, temporal</td>
<td>PET</td>
<td></td>
<td>SPG</td>
<td>Class I</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>rt, frontal</td>
<td>grids</td>
<td>monoparesis, dysphasia</td>
<td>low-grade astrocytoma w/ focal anaplastic changes</td>
<td>Class I</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>rt, temporal</td>
<td>PET</td>
<td></td>
<td>SPG</td>
<td>Class I</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>rt, temporal</td>
<td>SISCOM</td>
<td>depression†</td>
<td>scar</td>
<td>Class I</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>rt, temporal</td>
<td>PET</td>
<td></td>
<td>SPG</td>
<td>Class I</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>rt, temporal</td>
<td>SISCOM</td>
<td>osteomyelitis</td>
<td>SPG &amp; MDC</td>
<td>Class I</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>rt, temporal</td>
<td>FLAIR MRI</td>
<td>depression†</td>
<td>DNET &amp; MTS</td>
<td>Class III</td>
<td>29</td>
</tr>
<tr>
<td>11</td>
<td>rt, temporal</td>
<td>grids</td>
<td>mild dysphasia</td>
<td>SPG &amp; postop ischemic change</td>
<td>Class I</td>
<td>28</td>
</tr>
<tr>
<td>12</td>
<td>rt, parietal</td>
<td>grids</td>
<td>foot weakness</td>
<td>DNET &amp; CD</td>
<td>Class I</td>
<td>25</td>
</tr>
<tr>
<td>13</td>
<td>rt, temporal</td>
<td>PET</td>
<td>depression†</td>
<td>SPG &amp; GND</td>
<td>Class I</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>rt, parietal</td>
<td>PET</td>
<td>hemineglect</td>
<td>GND</td>
<td>Class III</td>
<td>22</td>
</tr>
<tr>
<td>15</td>
<td>rt, temporal</td>
<td>PET</td>
<td>depression†</td>
<td>SPG</td>
<td>Class I</td>
<td>19</td>
</tr>
<tr>
<td>16</td>
<td>rt, temporal</td>
<td>PET</td>
<td></td>
<td>SPG, CD, &amp; HS</td>
<td>Class I</td>
<td>18</td>
</tr>
<tr>
<td>17</td>
<td>rt, temporal</td>
<td>PET</td>
<td>mild dysphasia</td>
<td>ischemic brain injury</td>
<td>Class II</td>
<td>18</td>
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<tr>
<td>18</td>
<td>rt, temporal</td>
<td>grids</td>
<td>mild dysphasia, homonymous hemianopia</td>
<td>tubes w/ focal calcification &amp; giant cells</td>
<td>Class II</td>
<td>16</td>
</tr>
<tr>
<td>19</td>
<td>rt, temporal</td>
<td>grids</td>
<td>dysphasia</td>
<td>pilocytic astrocytoma</td>
<td>Class I</td>
<td>17</td>
</tr>
<tr>
<td>20</td>
<td>rt, temporal</td>
<td>PET/grids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>rt, temporal</td>
<td>PET</td>
<td>depression†</td>
<td>SPG</td>
<td>Class I</td>
<td>15</td>
</tr>
<tr>
<td>22</td>
<td>rt, frontal</td>
<td>PET</td>
<td>subpial gliosis</td>
<td>mild dysplasia</td>
<td>Class II</td>
<td>14</td>
</tr>
</tbody>
</table>

* CD = cortical dysplasia; CSF = cerebrospinal fluid; GND = glioneuronal dysplasia; HS = hippocampal sclerosis; MDC = minor dysplastic changes; SPG = subpial gliosis; — = no complication occurred.
† Patients were defined as having a psychiatric complication (depression) if they had experienced an exacerbation of a previous condition or developed a new condition for which treatment was instituted.
‡ Based on Engel classification.

Bitemporal seizures was identified in the temporal pole on video-EEG monitoring, an electrode grid was implanted over this area, and resection of the epileptogenic zone was undertaken (Class I outcome). A large region of encephalomalacia was found in the patient in Case 1, but SISCOM studies demonstrated activation superior to the area of macroscopic damage. Again, electrode grids were positioned to cover this region and adjacent eloquent cortex. Resection was performed based on results of the intracranial mapping, and only part of the lesion was resected given its relationship to eloquent cortex. The patient in Case 5 had a low-grade glioma in the left frontal lobe, of which 70% was resected due to overlap with eloquent cortex. A Class I outcome was achieved in this case.

Postoperative follow up ranged from 14 to 41 months. Characterization of seizure outcome was based on the Engel classification and set up as two types of dichotomous analyses: excellent (Engel Class I) compared with nonexcellent (Engel Classes II to IV) and favorable (Engel Classes I and II) compared with unfavorable (Engel Classes III and IV), as previously described. Seizure outcome was excellent in 17 patients (77%) and excellent in five (23%), and favorable in 19 patients (86%) and unfavorable in three (14%).

**Discussion**

**Epilepsy Surgery**

Epilepsy surgery offers the potential for long-term seizure control in patients with chronic partial epilepsy whose condition has not responded to medical therapy. During recent years there has been a significant increase in the number of surgical procedures being performed in such patients, which is attributable to a growing awareness of surgery as a treatment option by both the medical profession and lay groups. This is largely due to published data showing significant improvements in seizure outcome following epilepsy surgery as well as to improved education.

The advent of high-resolution MR imaging has advanced the presurgical evaluation for partial epilepsy more than any other single procedure since the introduction of EEG. Mod-
tems have advantages over conventional surgery and even framed stereotaxy, because they are minimally invasive and maximally effective with respect to localization and cost.\textsuperscript{33} These IGSSs avoid problems associated with a framed system, such as the time required for ring application and neu-

\textbf{Image Registration}

The use of newer imaging techniques, such as PET scanning, SISCOM studies, and FLAIR MR imaging, in the localization of epileptogenic foci has allowed surgery for epilepsy to be performed in patients who previously may have been considered ineligible surgical candidates. The process of formulating a plan for resection in patients with intractable partial epilepsy, who do not have a clear structural abnormality visualized on MR imaging, is difficult. Ideally, one or more noninvasive tests will provide a guide to the general region of epileptogenic focus, and noninvasive protocols have successfully been used to select patients for epilepsy surgery.\textsuperscript{44} Intracranial EEG recordings are sometimes required to define the site and extent of the resection precisely and to clarify the relationship to eloquent cortex. The clinical value of various functional imaging modalities is greatly enhanced by the process of coregistration with high-resolution MR imaging.

Image registration, or coregistration, is the alignment of two or more image volumes into the same geometric space, so that voxels in the same anatomical location can be directly compared. The process may be applied to image volumes from different modalities by using tomographic or slice-based images, including MR images and CT, PET, or SPECT scans. As a result of acquiring contiguous slices of two-dimensional image data, a 3D image volume can be constructed. To convert coordinates of one volume into the same space as another, a transformation matrix is required. Each volume is translated along the \(x\), \(y\), and \(z\) axes, with rotations around each of these axes. Various techniques of coregistration have been described\textsuperscript{39} and they differ only in the method used to determine the transformation matrix.

Techniques for the coregistration of functional and structural imaging and the accuracy of such methods have previously been described\textsuperscript{1,2,10,11,12} and include those used at our institution, that is, a Unix-based workstation and commercially available software packages (Analyze).\textsuperscript{27,28} Previous reports have not detailed all the modalities that we have incorporated, and other researchers have used visual interpretation of interictal and ictal SPECT scanning rather than the more objective SISCOM studies.

\textbf{Multimodality Image-Guided Surgery}

The incorporation of multimodal registrations into the IGSS has previously been reported in only two series on surgery for intractable epilepsy.\textsuperscript{20,26} Multimodal registration allows for the optimal evaluation of the spatial concordance of a site of seizure localization established using different modalities as well as the relationship of the structural, functional, and electrophysiological changes to the anatomical features in the area. It also permits the clinician to determine the proximity of the epileptogenic zone to eloquent cortical areas that subserve language and motor functions. The sites of eloquent cortex identified on functional MR imaging or cortical electrical stimulation (intraoperative or extraoperative) can also be coregistered to determine whether they are encroached on by the identified seizure focus.\textsuperscript{41,44,46,48}

Previously, the challenge in patients without a localizing MR image has been the difficulty in identifying a resectable epileptogenic focus and correlating it with relevant structural anatomy. The use of the modalities described here allows us to create a preoperative localizing image by coregistration with the stereotactic modality that best defines the epileptogenic zone. The value of this technique is proven by the better-than-expected postoperative outcomes in our series. The application of MMIGS, to incorporate an image of the subdural grid placement and therefore to allow anatomical definition of the location of the seizure onset zone to within millimeters, and the use of extra- and intraoperative stimulation to better define eloquent cortex permits potentially more extensive resections to be performed without compromising a patient’s health. Display of a virtual grid through MMIGS allows the surgeon to assess the anatomically correlated extraoperative localization even after the physical removal of the subdural electrodes during a second surgery.

Stereotactic guidance systems have contributed significantly to the surgical management of cerebral lesions with respect to their localization and resection as well as to a patient’s reduced length in hospital stay.\textsuperscript{6,21,22,29,43} These systems have advantages over conventional surgery and even framed stereotaxy, because they are minimally invasive and maximally effective with respect to localization and cost.\textsuperscript{33}
Multimodality image-guided surgery for the treatment of epilepsy

roimaging, system bulkiness and limitation of the operative field, potential mechanical error, and discomfort for the patient. Demarcation of the brain lesion interface may also be more difficult with a framed system because of a lack of near real-time imaging, which is available with frameless systems.

Accuracy in neuronavigation has been defined as the ability of a system to provide the exact location of a point in space and the degree of precision reflecting the variability of the system in repeatedly localizing the same point in space. The accuracy of all commercially available systems is said to be better than 2 mm. Authors recently studied the accuracy of three different IGSSs by using the same data set. Each had a different method of spatial localization, with the mechanical linkage/arm system having an accuracy of 1.67 ± 0.43 mm, the magnetic field system an accuracy of 1.9 ± 0.7 mm, and the optical system an accuracy of 2.61 ± 0.99 mm. Accuracy has been a major issue with frameless IGSSs and numerous factors affect the intraoperative accuracy of systems. Errors may occur at several different levels, including geometrical distortion with preoperative imaging, registration, data analysis, orientation of the patient’s head, and tracking of the surgical instruments. Currently, with most IGSSs, fiducials are placed on the patient’s scalp and the 3D coordinate system is established from these on the imaging study. Note that brain shift results in inaccuracy, and an error rate of 2.5 to 3 mm may be insignificant with large tumors, but may be significant in epilepsy surgery, particularly with small extratemporal lesions in an eloquent area. To date there is no known method that can eliminate brain shift, although intraoperative ultrasoundography and, more recently, intraoperative MR imaging have reduced inaccuracies associated with this phenomenon.37,8,9,25,32,49,63

Functional Imaging

In our series FDG-PET scanning was found to be the most useful functional imaging modality in patients with TLE. It has been demonstrated as being highly reliable in lateralizing TLE in patients with no discrete neocortical mass. Reported sensitivity of the FDG-PET scanning in TLE has been reported between 60 and 90%.

In our experience, a resection based on coregistration was maximal for the functional abnormality, achieved an excellent seizure-freedom rate, and had minimal permanent complications.

The SISCOM method was used to guide seizure focus localization and resection in four patients. In two of these patients SISCOM was used to guide the placement of intracranial electrode grids, whereas in the other two it was used for resection. In the case in which the frontal lobe was involved, the patient had a large area of encephalomalacia; the SISCOM study demonstrated an epileptogenic focus distinct from the lesion. This clearly allowed for the more accurate placement of the electrode grid; otherwise, the grid would have been laid over the lesion and the immediately adjacent area, which would have excluded the epileptogenic focus revealed on the SISCOM study.

Intracranial subdural grid electrodes were coregistered with MR imaging in six patients. Three grids were placed over the temporal lobe, two over the parietal lobe, and one over the frontal lobe. Two further implantations were performed using the coregistered SISCOM for guidance (one each in the frontal lobe and temporal lobe). Note, however, that it was not necessary to coregister the grids themselves in these cases, because the findings did not alter the plans for resection. In one patient, both the PET scanning and subdural electrode grids were coregistered. This patient experienced seizures originating from the left temporal lobe, as indicated on an abnormal PET scan (Case 20).

The value of chronic intracranial electrode implantations in the presurgical evaluation of nonlocalizing MR imaging has been documented, as has implantation with the aid of image-guided systems. During recent years there has been an increased emphasis on directly defining the relationship of individual electrodes to the cortical surface. Initially, CT data sets and MR imaging data were fused and 3D reconstructions were subsequently performed, but more recently MR imaging curvilinear formatting has been used. The curvilinear reformating allows for individual electrodes to be displayed in relation to an underlying lesion, epileptogenic zone, and/or eloquent cortex, and according to the authors of these papers allows for a more accurate resection. Nevertheless, it does not define cortical vessels and therefore intraoperative photography has been proposed for electrode localization relative to underlying cortex.

Coregistration of electrode grids to MR imaging data and the incorporation of this into the IGSS creates a virtual grid, which incorporates the relationship of the electrodes to the cortical surface and vessels, and hence the area of resection and its relationship to eloquent cortex. This allows the sur-
geon to remove the electrodes without fear of any loss of man-made landmarks used to define the electrodes and to perform the resection more accurately and safely.

The last modality used in this series was FLAIR MR imaging. In the sole case in which it was used it altered the surgical plan, because a second pathological feature (DNET) was demonstrated in addition to the MTS that had been visible on the T2-weighted volumetric images. It is important to include this sequence in the MR imaging protocol, particularly in patients with otherwise nonlocalizing MR images. In a number of cases such as this, however, focal lesions are associated with signal change on FLAIR images but not with anatomical distortion visible on T2-weighted volumetric images used as the basis for IGSS. The coregistration and transformation of FLAIR images into the same 3D space as the volumetric MR images and the subsequent incorporation into the IGSS as a second volume allows for both the sensitivity in lesion detection of the FLAIR images and the anatomical detail of the volumetric images to be used when performing the resection.

Neurological Complications

Neurological complications following epilepsy surgery are commonly reported in the literature, with up to a 61% rate in minor morbidity and up to a 33% rate in major morbidity. In this series, six patients (27%) experienced a transient neurological deficit, one (5%) a permanent major deficit, and three (15%) a permanent minor deficit. Five patients (24%) had a transient psychiatric problem postoperatively. The minor or transient complications in five of eight patients related to the proximity of neighboring eloquent cortex, and these complications were most likely caused by edema. The major complication occurred following a repeated operation and damage to the anterior choroidal artery, as judged based on the postoperative scan. An anterior choroidal artery looping into the choroid plexus through the choroid fissure is well acknowledged as one of the risks associated with coagulating the plexus.

Outcome With Regard to Seizures

Seventy-seven percent of patients in this series had an excellent outcome with respect to seizures. There was a follow up of at least 12 months in all patients. Furthermore, 86% had at least a favorable outcome. This outcome is comparable to that generally reported in patients with more straightforward, surgically treatable epilepsy due to a focal resectable neocortical lesion or MTS. Nonetheless, this rate is considerably better than the generally reported postoperative seizure-freedom rate of 30 to 50% in similar groups of “difficult” surgical candidates, most of whom do not have a single discrete resectable lesion demonstrated on preoperative MR imaging. Given that our data represent a retrospective report of our clinical practice results, there was not a control group that underwent surgery without the aid of MMIGS. Thus we acknowledge that we cannot definitively state that the use of MMIGS was the reason for better-than-expected outcomes in our patients.

Five patients had a nonexcellent outcome. One patient had dual pathological features, two had dysplasia, and another had hippocampal sclerosis and a recurrence of seizures 2 years later (in this latter patient, despite an initial seizure-free period following additional neocortical resec-

tion, seizures have recurred). The fifth patient experienced extensive changes consistent with an ischemic prenatal brain injury. In the patient with dual pathological characteristics, the MR image demonstrated obvious hippocampal sclerosis and a lesion seen in the neocortex on the FLAIR sequence. Both lesions were resected and postoperative MR imaging demonstrated no residual lesion, but some signal change in the neocortex adjacent to the resected area. The pathological features of the lesion in the neocortex was that of a DNET surrounded by dysplastic cerebral tissue. Dysplasias may be circumscribed lesions or part of a much more extensive disease process, even without obvious changes on MR imaging. In the three cases in which there was evidence of dysplasia, these may well have fallen into the group of widespread rather than focal dysplastic changes.

Conclusions

In this paper, we describe a series of patients who underwent MMIGS for medically refractory epilepsy and achieved seizure-free results substantially better than those previously reported in patients with nonlesional epilepsy. The high rates of excellent and favorable outcomes in this series indicate that the incorporation of additional imaging modalities, in particular functional modalities, into an IGSS may allow for improved seizure outcome and potential freedom from seizures in patients with no discrete structural pathological feature or with large, and complex lesions. The elimination of, or the reduction in, seizures offers an improved quality of life, reduced seizure-related morbidity, and potential cost benefits to both the patient and the community. Multimodality image-guided surgery provided in specialist epilepsy centers may offer therapy to an important group of patients previously believed to be ineligible for surgery on conventional grounds.

References

8. Black PMcL, Moriarty T, Alexander E III, et al: Development and implementation of an intraoperative magnetic resonance imag-
Multimodality image-guided surgery for the treatment of epilepsy.


40. Morris K: A computer generated stereotactic virtual subdural grid to guide resective epilepsy surgery. AJNR (In press)


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