Integration of functional neuronavigation and intraoperative MRI in surgery for drug-resistant extratemporal epilepsy close to eloquent brain areas

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Object. The authors performed a retrospective study to assess the impact of functional neuronavigation and intraoperative MRI (iMRI) on surgery of extratemporal epileptogenic lesions on postsurgical morbidity and seizure control.

Methods. Twenty-five patients (14 females and 11 males) underwent extratemporal resections for drug-resistant epilepsy close to speech/motor brain areas or adjacent to white matter tracts. The mean age at surgery was 34 years (range 12–67 years). The preoperative mean disease duration was 13.2 years. To avoid awake craniotomy, cortical motor-sensory representation was mapped during preoperative evaluation in 14 patients and speech representation was mapped in 15 patients using functional MRI. In addition, visualization of the pyramidal tract was performed in 11 patients, of the arcuate fascicle in 7 patients, and of the visual tract in 6 patients using diffusion tensor imaging. The mean minimum distance of tailored resection between the eloquent brain areas was 5.6 mm. During surgery, blood oxygen level–dependent imaging and diffusion tensor imaging data were integrated into neuronavigation and displayed through the operating microscope. The postoperative mean follow-up was 44.2 months.

Results. In 20% of these patients, further intraoperative resection was performed because of intraoperatively documented residual lesions according to iMRI findings. At the end of resection, the final iMRI scans confirmed achievement of total resection of the putative epileptogenic lesion in all patients. Postoperatively, transient complications and permanent complications were observed in 20% and 12% of patients, respectively. Favorable postoperative seizure control (Engel Classes I and II) was achieved in 84% and seizure freedom in 72% of these consecutive surgical patients.

Conclusions. By using functional neuronavigation and iMRI for treatment of epileptogenic brain lesions, the authors achieved a maximum extent of resection despite the lesions' proximity to eloquent brain cortex and fiber tracts in all cases. The authors' results underline possible benefits of this technique leading to a favorable seizure outcome with acceptable neurological deficit rates in difficult-to-treat extratemporal epilepsy.
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KEY WORDS • functional neuronavigation • eloquent brain area • seizure outcome • intraoperative MRI • extratemporal epilepsy • surgery

EXTRATEMPORAL epilepsy is one of the most challenging entities in the field of epilepsy surgery. Compared with temporal lobe epilepsy, where a good clinical outcome in terms of significant seizure reduction and improvement in quality of life after resection

has been reported to be between 58% and greater than 80%,^{4,11,47,50} extratemporal seizures are more difficult to treat surgically, with reported seizure freedom rates of only 10%–54%.^{9,16,24,27,52}

With the advent of iMRI, an intraoperative quality control was introduced to document whether a lesion had been resected sufficiently.^{18,38,41} Additionally, a dynamic adaption to different perioperative phenomena such as brain shift and localization of a residual lesion by updating navigation with intraoperative image data became possible. Moreover, damage of eloquent brain areas, such as motor, somatosensory, or speech cortex, can be avoided by integrating data from fMRI (BOLD imaging).

Abbreviations used in this paper: BOLD = blood oxygen level–dependent; DNT = dysembryoplastic neuroepithelial tumor; DTI = diffusion tensor imaging; ECoG = electrocorticography; EEG = electroencephalography; FCD = focal cortical dysplasia; fMRI = functional MRI; iMRI = intraoperative MRI; MEG = magnetoencephalography; MPRAGE = magnetization prepared rapid acquisition gradient echo.

Thus, resections adjacent to these important brain regions can be performed with more safety and efficiency.^{13,17,37} Additionally, white matter tracts can be detected (“fiber-tracking”) by DTI and included in the neuronavigation, which we termed “multimodal navigation,”³¹ mainly to avoid awake craniotomies, which are cumbersome for the patient and surgeon.

Still, there are few studies that have reported on the short- and long-term outcomes of extratemporal lobe epilepsy surgery after integrating these technical advances. Thus, we retrospectively reviewed the records of patients with extratemporal lesions in or adjacent to eloquent brain who suffered from intractable epilepsy and who underwent epilepsy surgery at our center with the aid of integration of multimodal functional imaging and intraoperative high-field MRI.

Methods

Examination Protocol

From a total of 329 consecutive patients with treatment-refractory seizures who underwent surgery in our department between 2002 and 2011, 25 patients with extratemporal epilepsy were identified for this analysis. Inclusion criteria were 1) drug-resistant epilepsy, 2) extratemporal lesion location determined by MRI, 3) extratemporal epileptogenic focus, and 4) distance to eloquent brain area ≤ 20 mm. Drug-resistant epilepsy had been defined according to the recent proposal by the International League Against Epilepsy.²⁵ Each patient underwent an extensive presurgical epilepsy protocol⁴⁵ that consisted of video-EEG monitoring, high-resolution (1.5- to 3-T) MRI, and neuropsychological testing. Additionally, 5 patients underwent invasive EEG monitoring with implantation of subdural and/or depth electrodes, and in 7 patients we obtained MEG recordings. Extratemporal localization of the epileptogenic zone was confirmed by these investigations at the Center of Epilepsy, University Hospital Erlangen. The results of these investigations were discussed in an interdisciplinary conference, for which a preliminary surgical treatment plan was established.

Data Acquisition and Analysis

BOLD Imaging. Functional MRI was performed using a 1.5-T MR clinical whole-body scanner with echo planar imaging (Magnetom Sonata, Siemens Medical Solutions) equipped with a standard head coil as previously described.¹⁴ A T1-weighted 3D data set (MPRAGE sequence; TE 4.38 msec, TR 2090 msec, matrix size 256 $\times$ 256, FOV 256 mm, slice thickness 1 mm) was obtained. To localize eloquent brain areas, several stimulation paradigms were developed and tested. The tasks were chosen according to the individual cognitive abilities of each patient.

For the determination of the Broca and Wernicke cortical speech areas, patients had to perform specific tasks, including 1) performing the build a sentence from a noun task, 2) conjugating verbs, 3) answering questions, and 4) performing the picture-naming task. The activation protocols were described previously by Grummich

and coworkers.¹⁴ The picture-naming task consisted of 40 animals and objects, which had to be named in random order. Furthermore, the sentence-reading task was used, where the introduction of grammatical patterns boosts language area activation in fMRI. Verbal memory performance was tested using a memorize numbers task. In this task, patients had to memorize specific words with each word standing for a character between the numbers 1 and 9. Then, the patients were tested on their ability to reproduce each number and the assigned word randomly. The arithmetic task was used both to test verbal memory and language areas, and patients were asked to either add up numbers one by one or build a sum.

DTI and Fiber Tracking. Diffusion tensor imaging makes use of the directional properties of diffusion of water molecules in brain tissue. The primary eigenvector from voxel to voxel is believed to represent the orientation of axons in white matter, which can be displayed as a neuronal fiber tract. For DTI, we applied a single-shot spin echo diffusion-weighted echo planar imaging sequence (TE 86 msec, TR 9200 msec, matrix size 128 $\times$ 128, FOV 198 mm, slice thickness 1.9 mm).

For reconstruction and visualization of the fiber tracts, we used the fiber-tracking module of the navigation planning software iPlan 2.6 (Brainlab). The process of localizing fiber bundles was described previously.^{5,30} The starting point (region of interest) for pyramidal tract reconstruction depended on the lesion site and was chosen in the primary motor cortex (hand, arm, leg, and foot area). As a starting region of interest for the language and visual tracts, relevant brain areas such as the Wernicke and Broca area or primary visual cortex were chosen. The diffusion probability density function was used to determine diffusion tensors and their preferred direction within a specific 3D brain position (voxel). The proportion of molecules in a voxel was calculated by the vector from 6 different diffusion-weighted acquisitions, each obtained with a different orientation of the diffusion-sensitizing gradients. Here, we only used diffusion tensors, whose main axis of direction had a minimum fiber length of 50 mm. After defining the mesencephalon as the target region, 3D tractography of the pyramidal tract was segmented. Tractography results were displayed in color-coded fractional anisotropy maps (Fig. 1).

Manual segmentation of the epileptogenic lesion on the preoperative MR image and coregistration with functional imaging data were performed using iPlan 2.6 neuronavigation software (Brainlab AG). This data set was then fused with the first iMRI scan as described below. For determination of the least distance between eloquent brain areas, fiber tracts, and the epileptogenic lesion, we screened the appropriate MRI slices in every axis and measured the distance manually using the ruler function of the iPlan software. The mean minimal distance was 5.6 mm.

Intraoperative MRI. All procedures were performed under general anesthesia. At the beginning of surgery, the patient's head was fixed in an MRI-compatible ceramic headholder. Then, the patient was moved from the operating position parallel to the scanner into the 1.5-T iMRI unit (Magnetom Sonata Maestro Class, Siemens Health-

Fig. 1. Case 13. Lesionectomy performed for a DNT (WHO Grade I) in a 31-year-old woman. Initial axial (**A and E**), coronal (**B**), and sagittal (**C and D**) T1-weighted MPRAGE iMRI sequences showing the pyramidal tract (purple and pink tracts) and the segmented lesion (yellow cloud). The ideal trajectory and the target point (cross) are displayed in light blue. **F:** The intraoperative microscope view with projected neuronavigation data before dura opening.

care) to acquire the imaging data set. The intraoperative imaging sequences included a T1-weighted MPRAGE sequence (TE 4.38 msec, TR 2020 msec, matrix 128×128 [interpolated to 256×256], FOV 250 mm, slice thickness 1 mm, slab 16 cm), T2-weighted coronal and transverse images (TE 98 msec, TR 6520 msec, matrix size 512×307 , FOV 250 mm, slice thickness 3 mm), and DTI sequences (TE 86 msec, TR 9200 msec, matrix size 128×128 , FOV 240 mm, slice thickness 3 mm). In cases of contrast-enhancing brain tumors, we administered Gd-diethylenetriamine pentaacetic acid during intraoperative T1-weighted axial spin echo sequences for resection control. The pre- and intraoperative MRI sequences were acquired using the same protocol. Then, the patient was shifted back into the operating position. After fusion of preoperative functional data and iMRI data, the lesion was defined and manually segmented using our neuronavigation software (iPlan 2.6, Brainlab AG). Functional data were coregistered. Finally, data were transferred to an OPMI Pentero operation microscope (Zeiss), as described previously.²⁹ The coregistration of iMRI with anatomical structures was accomplished with a mean error of 1.3 ± 0.7 mm when surgery was started.

Operative Technique

We chose the surgical approach and type of resection according to the lesion site and the findings of the presurgical epilepsy protocol. A segmental resection entails removal of the circumscribed epileptogenic tissue with the perilesional cortex based on anatomical borders. In 2 patients, a “tailoring” of the resection included an extended lesion-

ectomy with removal of the epileptogenic zone, which was defined in compliance with preoperative invasive EEG and MEG results as well as intraoperative ECoG with subdural strips and depth electrodes (Table 1). Microsurgical techniques were used for lesionectomies or tailored resections according to intraoperative functional navigation, where we kept close to the displayed boundaries of suspected pathological tissue and spared normal brain. After we had the impression of a complete resection, iMRI was performed. In cases of residual lesions, the patient was returned to the operative position, and after refreshing the neuronavigation with intraoperative data (Figs. 1 and 2), a complete resection was performed and confirmed by a second iMRI examination before the closing procedure.

Definition of Postoperative Neurological Deterioration

We documented neurological deterioration by careful clinical investigation before and immediately after surgery as well as 3 months after surgery and at the most recent follow-up visit for completing the follow-up data for this study. A severe neurological deficit included manifest hemiparesis, complete hemianopia, or hemineglect, which caused a clinically significant worsening in the patients' quality of life and led to disability and necessitated further medical care. Quadrantanopia, slight aphasia, and latent monoparesis were defined as mild deficits.

Definition of Epilepsy Outcome

We used the most recent Engel classification¹⁰ to evaluate postsurgery seizure outcome. An excellent outcome was defined as Engel Class IA, whereas a favorable outcome included Engel Classes I and II. Classes III and IV were considered poor outcome.

Fig. 2. Case 13. Intraoperative MR images. After resection, the control iMRI showed a remnant tumor mass. Neuronavigational data were updated, and the remaining lesion (orange) was manually segmented (**A–E**). The microscope view of the resection cavity and the segmented lesion are depicted in panel **F**.

TABLE 1: Characteristics of patients undergoing extratemporal epilepsy surgery*

Case No.	Age (yrs), Sex	Time Until Op (yrs, mos)	Type of Resection	fMRI Regions	DTI Tracts	Update of iMRI Navigation Performed	Distance to Eloquent Area (mm)	Op Time (mins)	FU (mos)	Seizure Outcome (Engel class)
1	39, M	34, 0	rt parietal lesionectomy	MC, WA		no	0	54	89	IIB
2	66, F	3, 5	rt frontoparietal tailored (+ECoG)	MC		no	6	349	4	IIIA
3	35, M	0, 3	rt frontal lesionectomy		PT	no	17	107	9	IA
4	12, F	2, 2	rt occipital tailored (+ECoG)		VT	no	3	352	56	IIB
5	67, F	3, 1	lt occipital lesionectomy	WA		no	7	260	73	IA
6	24, F	16, 0	lt frontoparietal lesionectomy	MC		no	0	149	9	IA
7	54, M	5, 11	lt frontal lesionectomy	BA, MC	PT	no	16	227	62	IA
8	25, F	18, 0	lt frontal segmental resection	BA, MC	PT	no	6	247	55	IA
9	25, M	0, 1	rt parietal lesionectomy	MC		no	6	120	48	IA
10	20, M	1, 1	lt frontal segmental resection	BA, WA		no	10	226	53	IC
11	36, M	2, 2	rt postcentral lesionectomy	WA, MC	PT	no	2	180	5	IA
12	54, M	0, 5	rt parietal lesionectomy	MC, BA, WA, SC	PT, LT	no	5	191	52	IA
13	31, F	22, 4	lt occipital lesionectomy	MC, SC	PT	yes	5	320	55	IA
14	33, F	31, 0	rt parietooccipital lesionectomy		VT	no	4	150	6	IIIA
15	18, M	0, 9	rt occipital lesionectomy	WA	LT, VT	no	3	180	43	IA
16	21, F	3, 0	rt occipital lesionectomy	WA	LT, VT	no	17	210	43	IA
17	37, M	30, 0	rt parietal lesionectomy	WA	LT	yes	0	199	3	IA
18	25, M	4, 10	rt frontal lobectomy	BA, WA	LT, PT	no	10	315	7	IA
19	43, F	23, 10	lt frontal lesionectomy	MC, BA	PT	no	3	254	27	IA
20	27, F	14, 0	rt parietooccipital lesionectomy	WA		no	3	176	32	IVC
21	33, F	32, 8	rt occipital lesionectomy		VT	yes	0	270	13	IA
22	14, F	13, 8	rt frontal lesionectomy	MC	PT	yes	15	268	12	IA
23	32, M	37, 9	lt frontal lesionectomy	MC, BA	PT, LT	no	0	156	6	IIIA
24	26, F	3, 11	rt frontal lesionectomy	MC	PT	no	3	101	11	IA
25	53, F	30, 9	lt occipital lesionectomy	WA	LT, VT	yes	0	253	5	IA

* BA = Broca area; FU = follow-up; LT = language tract; MC = motor cortex; PT = pyramidal tract; SC = sensory cortex; VT = visual tract; WA = Wernicke area.

Multimodal neuronavigation in extratemporal epilepsy surgery

Patients' most recent neurological and epilepsy outcome data were obtained from the follow-up examinations in the Neurological Epilepsy Center at the University Hospital Erlangen and via telephone interviews.

Results

Twenty-five patients (14 females and 11 males) with drug-resistant epilepsy underwent presurgical evaluation and epilepsy surgery between September 2002 and November 2011 at the University Hospital of Erlangen. Demographic and clinical data of the patients are presented in Table 1. Nine resections were performed in the left hemisphere. The mean preoperative duration of pharmacoresistant epilepsy was 13.2 years (range 0–34 years). Patients underwent follow-up for a mean of 44.2 ± 26.9 months after surgery.

Neuroimaging Findings

Preoperative MRI identified a structural lesion corresponding to the epileptogenic zone in all patients. The distribution of the pathological tissue was seen in the following brain regions: frontal (n = 9), frontoparietal (n = 2), parietal (n = 5), parietooccipital (n = 2), and occipital (n = 7).

Amount of Resection and Histology

In all cases, complete lesionectomy or cortical resection according to functional data was documented by iMRI. Table 1 illustrates that a complete resection of the predefined lesion was confirmed intraoperatively in 20 patients (80%). In 5 patients (Cases 13, 17, 21, 22, and 25), resection was considered as incomplete and an update of neuronavigation was performed (Fig. 2). A complete resection then was achieved by extending the surgery, as confirmed by iMRI. The mean operating time was 213.3 ± 78.7 minutes, while overall scan time for the acquisition of intraoperative MRI sequences (T1-weighted MPRAGE, T2-weighted coronal and axial, DTI) was 13.9 minutes.

Histopathological examination of resected tissue revealed FCDs in 7 patients (1 Type IIa FCD, 6 Type IIb FCDs according to the classification of Blümcke et al.³), posttraumatic glial scars in 5, cavernous hemangiomas in 5, DNTs in 2, anaplastic astrocytomas in 2, gangliogliomas in 2, neocortex with reactive gliosis in 1, and vascular hamartoma in 1 patient.

Neurological Outcome

Mild neurological deterioration was seen in 2 patients: the patient in Case 4 who had previously undergone surgery for meningioma and who underwent resection of postsurgical occipital lobe gliosis, and the patient in Case 16 who underwent a hemangioma resection. These patients suffered from a quadrantanopia despite intraoperative integration of functional (visual tract) neuronavigation. Overall, 4 patients experienced a transient dysphasia: in 1 patient (Case 5, left occipital lobe gliosis), the preexisting Wernicke aphasia was aggravated for the duration of 6 postoperative days, the patient in Case 7 experienced a transient Broca aphasia for 3 days after resection of a left frontal anaplastic astrocytoma, and the

patient in Case 23 with a left frontal Type IIb FCD reported amnesic aphasia lasting 5 days. In 1 patient (Case 13, who had a left occipital DNT), transient amnesic aphasia lasted as long as 6 months. In 3 of those 4 patients, language mapping had been used except for the patient in Case 13, in whom the lesion was located far away from speech areas (Table 1).

Another patient (Case 22 with a right frontal Type IIb FCD), in whom we preoperatively segmented the motor cortex and the pyramidal tract, experienced a transient paresis of the left arm lasting the duration of the 1st postoperative day (Fig. 3). Severe surgical deficits occurred in 1 patient (Case 6), in whom the lesion was located within the motor cortex and who experienced a permanent hemiparesis postoperatively, from which the patient fortunately recovered almost completely after 9 months. Overall, 20% of all patients in this study had a transient, 8% a permanent minor, and 4% a severe permanent neurological deficit (Table 2).

Seizure Outcome

Of all patients, 18 (72%) of 25 had an excellent outcome and were completely seizure free. Favorable seizure outcome was achieved in 21 (84%) of 25 patients (Fig. 4). In 16%, we found a poor outcome with 1 patient (Case 20) who had an aggravation of seizure frequency and intensity (Engel Class IVC).

Four-year follow-up data were available in 13 patients, of whom 11 (85%) had Engel Class I or II seizure outcome. Of all patients who had either transient (4 patients, Engel Classes IA, IA, IA, and IIIA) or permanent (3 patients, Engel Classes IA, IA, and IIB) neurological deficits, 71% were seizure free.

Postsurgical Complications

Among the 25 neurosurgical interventions, there was

FIG. 3. Case 22. Example of a patient with transient monoparesis of the left arm after resection of a Type IIb FCD. Preoperative 3D view of functional data (A) and iMRI (B) before resection showing the localization of the lesion (yellow) in relation to the motor cortex (light green) and pyramidal tract (purple). Note the resegmentation of the remnant lesion (light green) and its vicinity to the pyramidal tract (purple) on the iMRI control scan (C) and the corresponding microscope view (D) including projected navigation data. 'fid' denotes the position of the scalp fiducial for additional registration accuracy control.

TABLE 2: Properties of fMRI and DTI

Imaging Modality	No. of Patients	Neurological Deficit After Epilepsy Surgery	
		Transient	Permanent
functional imaging			
MC	13	1/13	1/13
SC	2	0	0
BA	7	2/7	0
WA	11	2/11	0
language (BA+WA)	3	0	0
DTI			
PT	11	1/11	0
LT	7	0	0
VT	6	0	2/6

1 wound infection (4%), which led to a local wound revision. No severe surgical complications such as intracranial hemorrhage, meningitis, or death occurred.

Discussion

Our retrospective analysis demonstrates that in patients with lesional extratemporal epilepsy, multimodal navigation assists in the decision making of whether resection is justified, can offer patients with pharmacoresistant epilepsy a good chance to gain seizure control with acceptable risks, can reduce the rate of incomplete resections when used in combination with iMRI, and can be implemented in daily routine surgery at epilepsy centers.

Lesional Extratemporal Epilepsy Surgery

There are different reasons why extratemporal lesionectomies only represent a small percentage of about 9%–18% of all epilepsy surgeries.^{2,4} First, extratemporal lobe lesions present with a variety of histopathological findings,¹² which are unsteady and diffuse and not that well defined as, for example, hippocampal sclerosis. Some of them, such as cortical dysplasia, turn out to have a more favorable course and chance of surgical success.^{9,40} However, even with additional diagnostic tools such as MEG,

FIG. 4. Pie chart showing the seizure outcome at last follow-up according to Engel classification. Seventy-two percent of all patients (18 of 25) had excellent (Engel IA); 84% (21) had favorable; and 16% (4) had poor seizure control.

intraoperative electrocorticography, or invasive electrode grid implantation, the exact anatomical localization of the epileptogenic zone often remains inaccurate. Finally, the localization of extratemporal lesions in the vicinity of functional cortex or fiber tracts make them difficult to resect without harming susceptible brain tissue and causing severe permanent neurological deficits. Our patients had mainly well-defined epileptogenic lesions, such as FCDs, intrinsic WHO Grade I tumors, or vascular lesions. However, 24% of our patients suffered from ill-defined epileptic foci, where histological investigation displayed gliotic tissue and another 8% had diffuse gliomas. In a subgroup analysis of patients (Cases 1, 4, 6, 11, 14, 15, 17, 19–21, and 23–25) in whom the minimum distance between the lesion and eloquent brain structures lay between 0 and 4 mm (Table 1), we noticed only 2 patients with a permanent neurological deficit (quadrantanopia in Case 4 and hemiparesis in Case 6). It becomes apparent that in epileptogenic foci within or very close to eloquent brain areas, epilepsy surgery is still possible with the aid of multimodal navigation and intraoperative imaging.

Functional MRI, Tractography (DTI), Neuronavigation, and iMRI

Extratemporal surgery of lesions close to eloquent brain areas needs sophisticated processing of image data compared with standard temporal lobe surgery. BOLD MRI and DTI tractography are noninvasive, useful tools to detect eloquent gray matter and white matter tracts. Their accuracy and specificity were discussed in recent studies.^{1,28,36,37} Eloquent cortex that can be mapped using fMRI includes the primary motor and somatosensory regions, and Broca and Wernicke areas along with hemispheric language lateralization and their connectivity within the CNS by using DTI for displaying pyramidal, language, and visual tracts.^{32,51}

Intraoperative high-field (≥ 1.5 -T) MRI systems are well established in operating rooms and were used in glioma surgery or frameless stereotaxy.^{23,41} To our knowledge, only a few studies on epilepsy surgery performed with the aid of 1.5-T iMRI systems exist.^{5,21,22,26,46} Neuronavigation became popular recently for lesionectomy of temporal and extratemporal regions,⁶ lesions of the insular region,⁴⁹ and callosotomy.²⁰ With more than 15 years of experience with neuronavigation and intraoperative imaging, our department successfully developed and integrated multimodal imaging techniques in daily neurosurgery.

In our retrospective investigation of patients with lesional extratemporal epilepsy, fMRI and DTI tractography, as well as their combination with iMRI, were successfully implemented in routine resective epilepsy procedures. This multimodal approach led to a complete resection of the lesion in all 25 of our patients, which seems an exceptional result, compared with the published incomplete extratemporal lesionectomy resection rates ranging from 71% to 85% (Table 3). The observation that the neurological outcome is significantly improved when compared with previously published studies^{2,4,40} stresses the application of functional navigation and iMRI as an advantageous technique.

TABLE 3: Literature review of patients with extratemporal drug-resistant epilepsy*

Authors & Year	No. of Patients	Structural Lesion as Determined by Preop MRI	Location/Type of Op	Complete Resection as Defined by Surgeon or Postop MRI	Mean FU in Mos (range)	Seizure Free After Surgery†	Transient Neurological Deficit Postop	Permanent Neurological Deficit Postop	Surgical Morbidity
Binder et al., 2009	40	38/40	parietal (100%)	NA	45 (5–32)	23/40 (57.5%)‡	12/40 (30%)	3 (7.5%)	2/40 (5%)
Chaudhry et al., 2010	61	61/61	frontal (36%), parietal (12%), occipital (21%), multilobar (31%)	51/61	60 (24–120)	37/59 (63%), 2 patients lost to FU	9/61 (14.8%)	11/61 (18%)	2/62 (3.2%)
Cho et al., 2005	23	23/23	NA	NS	54 (34.8–73.2)	18/23 (78.3%)§	NS	NS	NS
Cohen-Gadol et al., 2006	27	27/27	NA	NA	NS (12–120)	9/27 (33.3%)	NS	NS	NS
Cukiert et al., 2001	16	0/16	NA	NA	20.6 (12–48)	13/16 (81%)	6/16 (37.5%)	3/16 (18.8%)	NA
Elsharkawy et al., 2008	218	160/218	frontal (44%), central (16%), parietal (5%), occipital (3%), multilobar (9%), "posterior cortical" (23%)	NA	60 (NS)	53/160 (33%)	9/218 (4.2%)¶	8/218 (3.7%)¶	4/218 (1.8%)¶¶
Holmes et al., 2000	126	76/126	frontal (53%), frontotemporal (12%), parietal (8%), frontoparietal (7%), parietotemporal (6%), temporooccipital (9%), occipital (2%), hemispherectomy (3%)	NA	36 (24–72)	33/76 (43%)	NA	NA	NA
Pondal-Sordo et al., 2006	52	52/52	central (100%)**	30/52	50.4 (7.8–93.6)	13/52 (25%)	26/52 (50%)††	26/52 (50%)††	NA
Shukla et al., 2003	25	25/25	NA	NA	16.8 (3–78)	9/24 (37.5%), 1 patient lost to FU	8/25 (32%)	none	3/25 (12%)
Siegel et al., 2001	11	9/11	frontal (46%), frontoparietal (27%), parietal (9%), parietooccipital (18%)	NS	52.8 (12–120)	5/11 (45.5%)	NA	NA	NA
von Lehe et al., 2009	24	24/24	insular (100%)**	17/24	37.5 (12–168)	13/24 (54%)	2/24 (8.3%)	4/24 (16.7%)	none
Zentner et al., 1996	60	49/60	frontal (67%), parietal (11%), occipital (22%)	34/60	48 (20–85)	30/60 (54%)‡	2/60 (3.3%)	1/60 (1.7%)	3/60 (5%)

* NA = not available; NS = not specified.

† Engel Class IA.

‡ Only Engel Class I mentioned.

§ "Seizure-free except aura."

¶ Article gives no exact definition of distribution; overall transient morbidity is 5%, and overall permanent morbidity is 4.6%.

** Simplified localization groups.

†† Not further specified.

Awake craniotomy with intraoperative cortical brain mapping is considered to be the primary method to monitor eloquent brain areas during surgery.⁴² However, the superiority of this technique regarding efficiency and safety is still a matter of debate, lacking randomized controlled trials with larger patient cohorts.^{15,33} Inadequate pain control, airway obstruction leading to intubation, vomiting, brain swelling, and intraoperative seizures are among the common objectionable events during awake surgery. The risk of new appearance or worsening of permanent neurological deficits using this technique has been reported to be between 0% and 29%, with surgical complication rates between 0% and 14.8%.^{15,33,42} Regarding intraoperative electrophysiological monitoring, we based our strategy on previously published results in 230 patients from our department in which we compared cortical brain mapping and functional neuronavigation to identify the sensorimotor cortex.³⁹

Considering the aforementioned obstacles of awake craniotomy from our own experience, as well as the accompanying promising results,^{5,29,30} we preferred a non-invasive preoperative localization of eloquent brain areas by fMRI and DTI with general anesthesia over awake craniotomy and found no inferiority regarding neurological outcome and surgical complication rates.

Neurological and Seizure Outcome

There is evidence that in the presence of brain lesions, patients undergoing extratemporal surgery have better epilepsy control than those without lesions.^{19,24,40} In terms of neurological outcome, our results are even more favorable than those in other studies, where permanent deficits occurred in up to 18% of all lesional extratemporal epilepsy operations (Table 3). One patient (4%) suffered from a hemiparesis after resection of an FCD that was located immediate to the primary motor cortex. Fortunately, the patient recovered almost completely after 9 months. Two more patients with a postsurgical occipital gliosis and a cavernoma near the visual field tracts had quadrantanopia, which is below the reported incidence of visual field defects after anterior temporal lobe resections.³⁵

In our study, favorable seizure outcome in lesional extratemporal lobe epilepsy (Engel Classes I and II) was achieved in 84% of all patients, of whom 72% are completely seizure free after resection of an epileptogenic lesion near eloquent cortex (Engel Class IA). The proximity to eloquent brain areas with a mean minimum distance to the lesion of 5.6 mm and the long follow-up period of nearly 4 years on average highlight the favorable results of our study, which were achieved using advanced multimodal neuronavigation procedures. However, we cannot give a reliable safety margin in terms of absolute values to avoid damage to eloquent structures. The errors that occur during calculation of functional data, target registration of the navigation system, coregistration while fusing the pre- and intraoperative MR images, and the observer error in the manual segmentation procedure are cumulative and leave no room for an exact threshold determination in our series.

Studies on extratemporal lesionectomy reported seizure-free (Engel Class I) rates ranging between 25% and

57.5% (Table 3). A meta-analysis by Téllez-Zenteno and colleagues⁴⁸ identified 6 studies regarding extratemporal epilepsy (4 in children and 2 in adults) between 1995 and 2007, which showed a seizure-free outcome of 53% (lesional, 95% CI 28%–68%) and 26% (nonlesional, 95% CI 13%–38%) for all patients. Thus, our results are remarkable compared with recent literature and previously published series of extratemporal epilepsy surgery.

Limitations of This Retrospective Investigation

Important limitations of our study are the lack of prospective, randomized controlled data that compare surgery of extratemporal lesions close to eloquent cortical structures with and without using multimodal neuronavigation. Another drawback of this study is the small sample size. Further improvement concerning the identification of eloquent brain areas and possible postsurgical deficits could have been made performing awake craniotomies and using intraoperative electrophysiological and neurological monitoring. Compared with other observations and their pre-surgical diagnostic workup, we demonstrate a consequent integration of functional data and iMRI in all investigated patients. The acquisition of iMRI sequences only minimally increases the operating time. This is tolerated in favor of a remarkable outcome in our series, and no complications occurred due to a longer operating time. In 5 of 25 patients, the course of surgery was corrected according to iMRI results, which led to complete lesionectomy or cortical resection. Additionally, questions arose concerning the usefulness of surgical planning and accuracy of the non-invasive fMRI method. For example, the relatively gross spatial solution of fMRI studies and the threshold rate of fMRI data can lead to inaccuracy in localization and interpretation of BOLD signal intensity and activation patterns. Another problem concerning the use of preoperative functional data during surgery is volumetric brain deformation and intraoperative loss of cerebrospinal fluid (“brain shift”), which is known to diminish the accuracy of the depicted eloquent brain areas and fiber tracts. In our study, we took into account the brain structure translocation and performed an intraoperative MRI update in 5 patients with new acquisition of navigation data and reassignment of residual pathological tissue using the navigation planning software. In all of those patients, remnant tissue could be removed completely, and fortunately, all were seizure free and only 1 patient suffered from discrete amnesic aphasia.

Conclusions

In extratemporal pharmacoresistant lesional epilepsy, functional neuronavigation and iMRI are useful tools for performing resections close to eloquent brain areas. Our study supports the estimation of maximum resection extent independently of the distance to important functional brain areas and guides through the operation. These favorable results demonstrate that intraoperative functional neuronavigation is a major contribution to the prevention of functional deficits in presumably unresectable lesions, where in the past the risk-benefit ratio was more unfavorable for the patient. Considering possible brain shift

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during the surgery, iMRI can adjust inaccuracy of coregistration and improve the accuracy of functional mapping and fiber tracking. This method may lead to avoidance or marked reduction of postoperative neurological deficits.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sommer, Buchfelder, Roessler. Acquisition of data: Sommer, Grummich, Coras, Kasper. Analysis and interpretation of data: Sommer, Grummich, Kasper, Roessler. Drafting the article: Sommer, Roessler. Critically revising the article: Grummich, Coras, Kasper, Blumcke, Hamer, Stefan, Buchfelder, Roessler. Reviewed submitted version of manuscript: Sommer, Roessler. Approved the final version of the manuscript on behalf of all authors: Sommer. Study supervision: Roessler.

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