Frameless Stereotactic Functional Neuronavigation Combined with Intraoperative Magnetic Resonance Imaging as a Strategy in Highly Eloquent Located Tumors Causing Epilepsy

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Key Words

Intraoperative high-field MRI · Surgery · Tumor-related epilepsy · Eloquent brain area · Seizure control

Abstract

Background: Intractable epilepsy due to tumors located in highly eloquent brain regions is often considered surgically inaccessible because of a high risk of postoperative neurological deterioration. Intraoperative MRI and functional navigation contribute to overcome this problem. **Objectives:** To retrospectively investigate the long-term results and impact of functional neuronavigation and 1.5-tesla intraoperative MRI on patients who underwent surgery of tumors associated with epilepsy located close to or within eloquent brain areas. **Methods:** Nineteen patients (9 female, 10 male, mean age 41.4 ± 13.4 years, 11 low-grade and 8 high-grade glial tumors) were evaluated preoperatively using BOLD imaging, diffusion-tensor imaging tractography and magnetoencephalography. Functional data were implemented into neuronavigation in this multimodal approach. **Results:** In 14 of 19 patients (74%), complete resection was achieved, and in 5 patients significant tumor volume reduction was accomplished. Eight of 14 (57%) complete resections were achieved only by performing an intraoperative image update. Neuro-

logical deterioration was found permanently in 2 patients. After a mean follow-up of 43.8 ± 23.8 months, 15 patients (79%) became seizure free (Engel class Ia). **Conclusions:** Despite the highly eloquent location of tumors causing intractable epilepsy, our multimodal approach led to complete resection in more than two-thirds of patients with an acceptable neurological morbidity and excellent long-term seizure control.

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Introduction

One of the most frequent symptoms leading to the diagnosis of a brain tumor is the occurrence of epileptic convulsions. Approximately 30–50% of all patients with brain tumors present with first-time seizures, leading to further diagnostic procedures [1]. Especially low-grade tumors such as gangliogliomas, dysembryoplastic neuroepithelial tumors or astrocytomas are often associated with epilepsy [2–5]. Nevertheless, if cerebral tumors are located in or close to functional cortex or fiber tracts that connect primary eloquent areas with each other, complete lesionectomy without causing severe neurological deficits remains challenging and is often impossible [6, 7].

Visualization of these areas using functional magnetic resonance imaging (fMRI) and embedding them into the neuronavigation maps used for operative resection may be of major advantage in such cases. It may allow targeting of the lesion and preservation of the adjacent eloquent brain during resection. Especially an early intraoperative image update using MRI (iopMRI) may permit the detection and resegmentation of residual tumor and allow immediate revision of the operative situation resulting in complete resection and positive effect on seizure outcome [8]. Thus, the aim of this retrospective study was to investigate the effect of frameless stereotactic neuronavigation combined with functional imaging and intraoperative high-field MRI and its effect on seizure outcome.

Patients and Methods

Examination Protocol

Between December 2002 and October 2011, we selected 19 patients suffering from tumor-associated epilepsy (TAE) for this investigation (table 1). Inclusion criteria were (a) application of intraoperative 1.5-tesla MRI and functional neuronavigation; (b) resection, not only biopsy; (c) distance to eloquent brain area ≤ 10 mm, and (d) minimum follow-up of 18 months. The 1.5-tesla MRI revealed tumors in the following regions: frontal ($n = 7$, adjacent to the central sulcus), parietal ($n = 2$, adjacent to speech areas), and temporal ($n = 10$, adjacent to speech areas and visual tracts). In 14 of 19 patients, drug-resistant epilepsy had been defined according to the recent proposal by the International League against Epilepsy [9]. All these patients underwent an extensive presurgical epilepsy protocol [10] at the Epilepsy Center, University Hospital Erlangen, which included video-EEG monitoring, neuropsychological testing and high-resolution 1.5–3.0-tesla MRI scanning. The remaining 5 patients presented with first-time sporadic seizures and received scalp EEG and high-resolution 1.5-tesla MRI (for seizure characteristics, see table 2). Mean seizure duration prior to surgery was 10.9 years (range: 1 month to 50 years) and seizure frequency ranged from 3/day to 1/year.

Data Acquisition and Analysis

Functional MRI

The displayed eloquent brain regions involved Broca's and Wernicke's areas as well as motor cortex (hand and foot areas), which were outlined by stimulation paradigms using functional MR technique as described in detail elsewhere [11]. Additionally, we calculated fiber tract bundles (visual, pyramid, language tracts) by using diffusion-tensor imaging (DTI). In 3 patients, speech magnetoencephalography (MEG) was used for confirmation of language areas (table 1). The data set for fMRI was generated using a 1.5-tesla MR clinical whole-body scanner with echo planar imaging (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany). In detail, T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequences were used with

the following settings: echo time (TE) of 4.38 ms, repetition time (TR) of 2,090 ms, matrix size of 256×256 , field of view (FOV) of 256 mm, slice thickness of 1 mm, scanning time 4 min 44 s.

Speech Magnetoencephalography

In 3 individuals, MEG was used instead of fMRI to detect language areas. The MEG processes magnetic signals which are generated by intracellular current flow in brain cells. The neurons activated by external stimuli create electrical currents and magnetic fields. These activity sources are co-registered with high-resolution (1.5 T) MRI to determine activated brain regions. We used a dual-sensor 74-channel biomagnetometer whole head system (Magnes II, 4-D Neuroimaging, San Diego, Calif., USA). For detailed explanation of the stimulation paradigm and source localization used during MEG measurements, we refer to the work of Grummich et al. [11].

DTI and Fiber Tracking

For calculation and localization of fiber bundles with DTI, we applied the navigation planning software iPlan 2.6 (Brainlab AG, Feldkirchen, Germany) as described previously [12]. The fiber tracking included representation of the optic radiation, pyramidal tract and the arcuate fascicle. The same MRI scanner as for fMRI was used. However, for this purpose we applied a single-shot spin-echo diffusion-weighted echo planar imaging sequence (TE 86 ms, TR 9,200 ms, matrix size 128×128 , FOV 198 mm, slice thickness 1.9 mm, scanning time 5 min 31 s).

Manual segmentation of the tumor in the preoperative MRI 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 iopMRI scan as described below. For determination of the least distance between eloquent brain areas, fiber tracts and the tumor margin, we screened the appropriate MRI slices in every axis and measured the distance manually using the 'ruler' function of the iPlan software.

Surgical Workflow

The surgical workflow is described in detail elsewhere [13]. Briefly, after the patient was put under general anesthesia, we performed our first iopMRI scan (1.5 Tesla MRI, Magnetom Sonata Maestro Class, Siemens Healthcare, Erlangen, Germany). The scan sequences included a T1-weighted MPRAGE (TE 4.38 ms, TR 2020 ms, matrix size of 128×128 (interpolated to 256×256), FOV 250 mm, slice thickness 1 mm, slab 16 cm), T2-weighted coronal and transversal (TE 98 ms, TR 6520 ms, matrix size 512×307 , FOV 250 mm, slice thickness 3 mm) and DTI sequences (TE 86 ms, TR 9,200 ms, matrix size 128×128 , FOV 240 mm, slice thickness 3 mm). Overall, intraoperative scanning time was 13.9 min. The data set was fused with preoperative functional MRI data using neuronavigation software (iPlan 2.6; Brainlab AG). After segmentation of the lesion and coregistration of functional data (fig. 1), the navigation map was transferred into the OPMI Pentero operation microscope (Zeiss, Oberkochen, Germany). The co-registration of in vivo MRI with anatomical structures was accomplished with a mean error of 1.6 ± 0.8 mm.

Surgical Technique

The skin flap and optimal surgical trajectory was planned before skin incision using neuronavigation. A microsurgical technique was used for lesionectomy (WHO grade I and II lesions), subtotal (90–

Table 1. Characteristics of patients undergoing tumor surgery

Patient No.	Sex	Age, years	Type of resection	Histopathological result	fMRI regions	Fiber tracts	Update of fMRI navigation?	2nd resection?	Distance to eloquent area, mm	Follow-up, months	Duration of epilepsy prior to surgery, years, months	Preoperative seizure frequency	Seizure outcome, Engel	Tumor relapse?
1	F	31	Lt lesionectomy	ganglioglioma WHO I		V			10	22	3.0	2–3/day	Ia [#]	
2	M	41	Lt lesionectomy	PXA WHO II	W	LT			0	21	0.3	2/day	Ia [#]	
3	M	34	Rf subtotal	anaplastic oligoastrocytoma WHO III	MC, B	P	yes	yes	10	23	4.0	4/year	Ia	
4	F	43	Lt-o lesionectomy	ganglioglioma WHO I	W	V	yes	yes	0	24	41.0	10/month	Ia [#]	
5	F	28	Rt extended lesionectomy	ganglioglioma WHO I		V	yes	yes (2×)	5	20	10.0	2/day	Ia [#]	
6	F	43	Rf subtotal	anaplastic oligoastrocytoma WHO III	MC	P			0	41 [§]	0.1	1/month	IIa	yes
7	F	36	Lf subtotal	anaplastic oligoastrocytoma WHO III	Speech-MEG (Broca)				2	77 [§]	10.0	4/month	IIb [#]	yes
8	M	32	Rt extended lesionectomy	papillary glioneuronal tumor WHO I		V	yes	yes	0	36	8.0	5/day	Ia [#]	
9	F	25	Lf medial lobectomy	DNT WHO I	B	LT	yes	yes	1	75	16.0	3/day	Ia [#]	
10	M	65	Lt lesionectomy	ganglioglioma WHO I	W	LT			2	85	50.0	6/month	Ia [#]	
11	F	54	Lt lesionectomy	ganglioglioma WHO I	W	LT, V			0	58	17.0	4/month	Ia [#]	
12	M	34	Lp subtotal	anaplastic astrocytoma WHO III	Speech-MEG (Wernicke)				3	54	1.0	10/year	IIa [#]	yes
13	F	69	Lt subtotal	anaplastic oligodendroglioma WHO III	Speech-MEG (Wernicke)				0	47 [§]	10.0	1/year	Ia [#]	
14	M	54	Lf gross-total	anaplastic astrocytoma WHO III	W, MC	P, LT	yes	yes	9	85	5.11	4/month	Ia [#]	
15	M	54	Lf gross-total	anaplastic oligoastrocytoma WHO III	W, B	LT	yes	yes	0	60	0.1	8/month	Ia	
16	M	34	Lf gross-total	anaplastic astrocytoma WHO III	B	P, LT	yes	yes	0	44	0.1	2/month	Ia	
17	F	55	Rt lesionectomy	ganglioglioma WHO I		V			0	25	23.0	2/year	IIb [#]	
18	M	31	Lp lesionectomy	diffuse astrocytoma WHO II	W, B	LT, P	yes	yes	0	18	0.11	1/month	Ia	
19	M	24	Lt lesionectomy	ganglioglioma WHO I	W, B	V, LT			8	18	7.0	4/month	Ia [#]	

R = Right; L = left; f = frontal; t = temporal; p = parietal; o = occipital; t-o = temporo-occipital; PXA = pleomorphic xanthoastrocytoma; DNT = dysembryoplastic neuroepithelial tumor; W = Wernicke region; B = Broca region; MC = motor cortex; P = pyramidal tract; LT = language tract; V = visual tract. [§] Indicates the patient passed away. [#] Indicates drug-resistant epilepsy.

Table 2. Summary of seizure and follow-up characteristics

Characteristics		Frequency per month
Age at surgery ¹	41.4 ± 13.4	
Seizure duration prior to surgery ¹	10.9 ± 13.9	
Seizure type, n		
Simple partial (sp)	2 (10.5)	4–15
Complex partial (cp)	3 (15.8)	0.16–0.33
Secondary generalized (sg)	3 (15.8)	0.16–8
sp + cp	3 (15.8)	0.16–60
sp + sg	2 (10.5)	2–60
cp + sg	2 (10.5)	0.25–4
sp + cp + sg	4 (21.1)	1–90

¹ Years ± SD. Figures in parentheses are percentages.

Table 3. Histopathological results as confirmed by intraoperative MRI

	n
Complete resection	14 (74%)
Ganglioglioma WHO I	7
Anaplastic astrocytoma WHO III	2
Anaplastic oligoastrocytoma WHO III	1
Pleomorphic xanthoastrocytoma WHO II	1
Papillary glioneuronal tumor WHO I	1
Diffuse astrocytoma WHO II	1
DNT WHO I	1
Subtotal resection	5 (26%)
Anaplastic oligoastrocytoma WHO III	3
Anaplastic astrocytoma WHO III	1
Anaplastic oligodendroglioma WHO III	1
Total	19 (100%)

Table 4. Overview of performed functional imaging of eloquent brain areas and fiber tracts in relation to postoperative neurological deficits

	n	Transient neurological deficit	Permanent neurological deficit
Functional imaging			
Motor cortex	3	0	0
Broca region (speech MEG)	3 (1)	0	0
Wernicke region (speech MEG)	4 (2)	0	0
Wernicke + Broca regions	3	0	0
DTI mapping			
Pyramidal tract	5	0	0
Language tract	9	0	0
Visual tract	7	0	1/7

99% of tumor mass) or gross total (complete removal of contrast-enhanced pathological tissue, both in WHO grade III and IV tumors) resection according to intraoperative neuronavigation, where we kept close to the displayed navigation boundaries of suspected pathological tissue. In 2 cases, we performed an 'extended' lesionectomy with resection of an extended epileptogenic zone with perilesional cortex, which was defined in compliance with the results of the presurgical epilepsy work-up (table 1). When we had the impression of a complete resection, an iopMRI scan was performed. In cases of residual lesion, the patient was brought back in the operating position and after refreshing the neuronavigation with intraoperative MR imaging data, the resection was completed, respecting functional areas. After complete resection has been confirmed or further resection estimated as impossible by a second iopMRI scan, the operation was finished by standard closing procedure.

Definition of Postoperative Neurological Deficits

Clinical investigation of neurological deficits was performed before and immediately after surgery as well as three months after surgery and most recently, for completing the follow-up data for this study. If patients suffered from postoperative complications that had only minor effect on quality of life such as upper visual field deficits, discrete aphasia or latent monoparesis, we defined it as a 'mild neurological deficit'. Manifest hemiparesis, complete hemianopia or global aphasia leading to a dependency on further care or immobility was referred to as 'severe neurological deficit'.

Definition of Seizure Outcome

The most recent Engel classification system [14] was applied to evaluate post-surgery seizure outcome. Engel's grades Ia, I and II, III and IV were defined as the categories excellent, favorable and poor outcome, respectively. Patients' neurological and seizure outcome data were obtained by follow-up examinations in the Neurological Epilepsy Center at the University Hospital Erlangen, in our outpatients department and via telephone interviews.

Results

Nineteen patients (9 female, 10 male) with brain tumors near or within eloquent cortex and epilepsy who underwent surgery using frameless functional neuronavigation and intraoperative MRI were analyzed. Fourteen resections (74%) were performed on the dominant hemisphere. The mean age at the time of surgery was 41.4 ± 13.4 years. The mean distance between eloquent brain areas, fiber tracts and the segmented epileptogenic lesion was 2.6 mm. Eloquent cortical areas and fiber bundles were successfully activated and mapped in all patients.

Amount of Resection and Histology

Gross total resection was confirmed and documented by intraoperative MRI in 74% (14/19) of all patients. Due to expected severe neurological deficits or diffuse tumor invasion, only subtotal resection was achieved in 5 pa-

Fig. 1. Intraoperative MRI (iopMRI) scans directly before beginning of surgery of patient 4 with a ganglioglioma WHO I. Axial (a) and sagittal (b) T1-weighted MPRAGE sequences are fused with Wernicke's area (green) and visual fiber tracts (purple and pink). The segmented lesion is displayed in light blue along with the ideal trajectory and target point (blue cross). The corresponding intraoperative microscope view with projected neuronavigation data (Wernicke's area in light green) and the left vein of Labbé after dura opening can be seen (c). First iopMRI control scans showed remnant tumor mass (e, red arrows) in the axial T2-weighted sequences. After resegmentation of the residual tumor and update of the navigation system, surgery was continued. d The target point (light blue cross), the extent of remnant pathological tissue (dotted yellow line) and its boundaries within the focus level (straight yellow line) of the operating microscope. Complete resection is documented by final intraoperative T2-weighted sequences (f).

tients, all of them suffering from malignant tumors. For detailed histopathological description, see table 3.

Intraoperative MRI and Neuroimaging Follow-Up

A complete or subtotal resection of the predefined lesion was confirmed by intraoperative MRI in every case by 3-month follow-up MRI. In subjects 3, 4, 5, 8, 9, 14, 15, 16 and 18, resection was quoted as incomplete (47%) by iopMRI, which led to an enlargement of the resection after resegmentation of remnant tumor mass within the same procedure (fig. 1). Patient 5 even required a second intraoperative update of neuronavigation and further resection before complete tumor removal was confirmed by iopMRI. Altogether, repeated iopMRI scans led to a complete resection in further 8 patients, who were quoted as incomplete resections by the first intraoperative MRI. Thus, iopMRI increased the extent of resection by 42.1% (from 31.6 to 73.7%).

Neurological Outcome

Mild permanent neurological deficit occurred in 5.3% (1/19) of all cases: patient 13, who reported dyscalculia and slight cognitive (mnestic) impairment. However, the tumor in this case was not located in the hippocampal region, and therefore memory fMRI had not been performed preoperatively. A severe neurological deficit (5.3%, 1/19) occurred in patient 5 suffering from a pleomorphic xanthoastrocytoma close to the visual tract, who had an incomplete severe hemianopsia despite seizure freedom under antiepileptic medication (table 4).

Seizure Outcome

After a mean follow-up period of 43.8 ± 23.8 months, 79% (15/19) of all patients had an excellent seizure control (Engel Ia) under antiepileptic medication. Notable, of those subjects there were 11 patients (11/14, 79%) who suffered from drug-resistant epilepsy before surgery. Of

the remaining 3 patients, 1 patient had infrequent simple partial seizures (Engel Ib) and 2 more had few disabling seizures and were assigned to Engel class IIa and IIb. In 4 of the 5 patients with sporadic seizure activity, Engel's class Ia was achieved, while 1 patient reached Engel's class IIa. Altogether, favorable seizure outcome was achieved in 100% of all subjects. Patient 14 had a general tonic-clonic seizure with postictal sensorimotor aphasia, which vanished within 2 days.

Three years after surgery, 11/19 (58%) patients were investigated and 8/11 (72%) patients still had an excellent seizure outcome. The remaining 3 patients were assigned to Engel class IIa (2 patients) or IIb (1 patient).

Surgical Complications

Immediate reoperations had not been performed on any patient and no severe surgical complications such as intracranial hemorrhage, meningitis or death occurred in this series. Among the 19 patients, 2 (10.5%) suffered from delayed postoperative surgical complications. A postoperative hygroma had to be treated surgically (patient 13) and delayed left hemispheric brain edema occurred in another patient, which was treated effectively by oral application of dexamethasone (patient 18).

Postsurgical Follow-Up

Three patients (15.8%) suffering from malignant gliomas died during the observation period (table 1) due to tumor progression despite combined radiochemotherapy.

Discussion

Summary of Findings

In our retrospective study of selected highly eloquent located epileptogenic tumors, we found a significant effect of frameless stereotactic functional neuronavigation and intraoperative MR imaging on resection amount and epilepsy outcome. Intraoperative MR imaging increased the extent of resection from 31.6% after the first intraoperative MR to 73.7% after the final intraoperative imaging, which was confirmed by delayed extraoperative MRI. This means an increase in resection rate of 42.1%. Inclusion of functional imaging into frameless stereotaxy led to avoidance of permanent aphasia or hemiparesis. A favorable epilepsy outcome with 79% of patients becoming seizure free (15/19 patients Engel class Ia) after a mean follow-up of 43.8 ± 23.8 months was documented.

Functional Neuronavigation and Intraoperative Imaging

Functional MRI and tractography are noninvasive diagnostic procedures to detect eloquent gray and white matter. The reliability, accuracy and specificity of these methods are discussed in recent studies [7, 15, 16]. Functional brain areas such as primary motor and somatosensory region, Broca's and Wernicke's language areas and their connecting fiber tracts within the CNS are amongst eloquent cortex that can be mapped by functional MRI and DTI [17]. Additionally, MEG is a valid and useful alternative technique for detection of functional brain regions and epileptogenic brain tissue [18–20].

Enhanced Resection by Functional Neuronavigation and Intraoperative MRI

In our retrospectively investigated 19 patients suffering from highly epileptogenic tumors in or adjacent to eloquent areas leading to intractable epilepsy, the application of preoperative functional imaging, intraoperative neuronavigation and MRI update ('multimodal neuronavigation') led to complete resection in 74% of the investigated cases. Compared to the literature, this seems a worth mentioning high percentage, considering risky areas for brain surgery [21–23]. This is even more important not only from a neuro-oncological but also from an epileptological point of view, since about 30% of patients with medically refractory epilepsy have an underlying neoplastic lesion [24] and 65–90% of all patients with low-grade gliomas experience symptomatic seizures [25]. The histopathological diagnosis of a brain tumor predicts seizure control when a TAE is evident. In lesions that belong to the spectrum of long-term epilepsy-associated tumors, surgery can lead to very low tumor recurrence rates with exceptional high seizure-freedom in the long run [2]. In our series, over half of the lesions (11/19) were classified as long-term epilepsy-associated tumors, which may be a reason for our encouraging results. Of the remaining 8 patients with WHO grade III tumors, 6 achieved an excellent seizure control, and in 3 of those, medication with antiepileptic drugs was tapered. However, in 3 of the 8 patients with subtotal resection of high-grade astrocytomas, tumor relapse occurred despite adjuvant radio- and/or chemotherapy, and 2 of them continued to have seizures (table 1). This illustrates that gross total tumor resection is one of the key procedures not only in disease but also in seizure control, and that patients with lesions located in crucial brain areas potentially have a worse neurological and seizure outcome because of incomplete resection rates due to inaccessibility of the lesion.

The reported high percentage of complete resections in such surgical risky areas may be achieved through intraoperative MRI followed by extended resection, which has been proved in several studies for non-eloquent located lesions [26, 27]. A recent prospective, randomized trial by Senft et al. [28] showed that intraoperative MRI in 33% of the glioma patients led to an extended resection, leading to a higher rate of overall complete tumor resection compared to the control group. In our series, 32% of all patients (6/19) had a complete resection documented by the first iopMRI. After continuation of surgery complete removal was achieved in 8 of 9 more patients, increasing overall total resection rate to 74%. These results underscore the benefits of intraoperative imaging and neuronavigation, leading to a better prerequisite for postoperative adjuvant treatment in malignant disease and are even better than previous investigators found for non-eloquent located tumors [27, 29].

Multimodal Neuronavigation and Seizure Control

This retrospective study further demonstrated that 79% of the investigated patients (15/19) were seizure-free as a direct consequence of the resection (Engel class Ia). This excellent result was found after a mean follow-up period of 43.8 ± 23.8 months. Considering other reports, in summary, seizure freedom was reported in 79–87% of patients with low-grade temporal gliomas [25, 30, 31]. However, it is well known that a more favorable result of seizure freedom is achieved when the tumor is located within the temporal lobe and not extratemporal. Herein, seizure-free rates drop to 62.5–77% [32, 33]. Our patient population included 10 temporal and 9 extratemporal tumor resections, showing no difference regarding epilepsy outcome between these two groups (table 1). Among those patients, complete seizure freedom in 8 out of 10 patients (80%) with temporal and 7 of 9 patients (78%) with extratemporal lesions was found.

Without performing an intraoperative MR imaging in our patients, the resection extent would have been incomplete in 8 more patients (57%) of a total of 14 complete resections. Interestingly, all of those patients who had a resegmentation and complete removal of remnant tumor mass after the iopMR imaging were free of seizures, suggesting a success rate of our protocol of 100%.

Neurological Outcome

There is very little literature concerning neurological outcome when using multimodal imaging, intraoperative neuronavigation and iopMR imaging for surgery of TAE. The series of Ruban et al. [31], who investigated chronic

epilepsy associated with low-grade temporal tumors (WHO I–II), described 18.4% of patients suffering from a transient and 2.6% from a permanent deficit due to operative complications. In a study by Von Lehe et al. [32], there was a permanent morbidity regarding neurological deficits of 16.7% in 25 patients undergoing insular lesionectomy for drug-resistant epilepsy. With a permanent neurological deficit rate of 5.3%, we are in the lower range of the reported values. Keeping in mind that the mean minimum distance between eloquent cortex regions and the segmented tumor was only 2.6 mm, our complication rate seems low, especially concerning severe neurological complications of 5.3% (incomplete hemianopsia). Noteworthy, there were no severe postoperative neurological deficits like aphasia or hemiparesis and no severe medical complications including meningitis, bone flap infection or brain abscess.

Limitations

We present a retrospective investigation of a small series of patients with tumor-associated epilepsy. The highly selective inclusion criteria due to our refined pre-surgical protocols may create a selection bias of the presented results. Another major drawback is the lack of a prospective, randomized trial comparing tumor surgery close to eloquent areas in this patient group with and without the application of multimodal neuronavigation and intraoperative MRI. Additionally, the integration of this sophisticated method requires more resources and extra time for processing, testing and image editing compared to conventional surgery.

Even in experienced hands, neuronavigation potentially may contain many inaccuracies, including brain shift [34]. Therefore, intraoperative imaging in our opinion leads to a compensation of these sources of error. Thus, in our protocol, we performed a complete update of the neuronavigation data and resegmentation of remnant tumor mass in 10 patients to compensate brain structure translocation. The impact of brain shift on pre- and intraoperative functional imaging data was investigated previously [35, 36]. Herein, evidence was found that thorough updating of intraoperative functional and anatomical imaging data, depending on individual size of the resection cavity and tumor location, may enable safe surgery despite shifting of eloquent brain structures.

Nevertheless, BOLD imaging for definition of functional areas and also DTI for mapping of fiber tracts was not evaluated intraoperatively in this patient series by awake craniotomies. However, our technique of ‘multimodal functional neuronavigation’ has already been

evaluated by extensive pre- and postoperative neurological and neuropsychological correlative investigations [11].

Conclusion

This is the first report on application of functional neuronavigation in combination with intraoperative high-field MRI in patients with tumor-associated epilepsy located in eloquent brain areas. Our results demonstrate a high rate of complete tumor resections with low neurological complications despite the delicate location of the lesions. Additionally, this resulted in an exceptionally high rate of seizure freedom in the investigated patients underscoring the possible benefit of these tech-

niques. In our opinion, this represents a highly valuable surgical protocol for this patient group feasible in specialized centers.

Disclosure Statement

Hajo Hamer has served on the scientific advisory board of Eisai, Pfizer and UCB Pharma. He served on the speakers' bureau of Desitin, Eisai, GlaxoSmithKline and UCB Pharma and received research funding from Desitin, Janssen-Cilag GlaxoSmithKline and UCB Pharma. Dr. Blümcke has received financial support from the EuroCore EpiGENet consortium (DFG Bl 421/3-1), and received speaker's fee from UCB and Desitin Pharma during the last 24 months. The remaining authors have no conflicts of interest to disclose. The authors do not have any personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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