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THE VALUE OF PRE- AND INTRA-OPERATIVE ADJUNCTS ON THE EXTENT OF RESECTION OF HEMISPHERIC LOW GRADE GLIOMAS; A RETROSPECTIVE ANALYSIS

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Abstract

Background—To achieve maximal resection with minimal risk of postoperative neurological morbidity, different neurosurgical adjuncts are being used during low grade glioma (LGG) surgery.

Objectives—The goal of this study was to investigate the effect of pre- and intra-operative adjuncts on the extent of resection (EOR) of hemispheric LGGs.

Methods—Medical records were reviewed to identify patients of any sex, 18 years or older, who underwent LGG surgery at 'X' Hospital between January 2005 and July 2013. Patients were divided in 8 subgroups based on the use of neuronavigation system alone (NN), functional MRI-diffusion tensor imaging (fMRI-DTI) guided neuronavigation (FD), intra-operative MRI (MR) and direct electrical stimulation (DES). Initial and residual tumors were measured and mean EOR was compared between groups.

Results—Of all 128 patients, gross total resection was achieved in 23.4%. Overall mean EOR was $81.3\% \pm 20.5\%$.

Using DES in combination with fMRI-DTI (mean EOR $86.7\% \pm 12.4\%$) on eloquent tumors improved mean EOR significantly after adjustment for potential confounders, when compared with neuronavigation alone (mean EOR $76.4\% \pm 25.5\%$, $p = 0.001$).

Conclusions—Using DES in combination with fMRI and DTI significantly improves EOR when LGGs are located in eloquent areas, compared with craniotomies where only neuronavigation was used.

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Disclosure

Author contributions to the study and manuscript preparation include the following. Conception and design: X. Acquisition of data: X. Analysis and interpretation of data: X. Drafting the article: X. Critically revising the article: all authors. Approved the final version of the paper on behalf of all authors: X. Administrative/technical/ material support: X. Study supervision: X

Conflict of Interest – None

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

Keywords

low-grade glioma; extent of resection; direct electrical stimulation; intra-operative MRI; functional MRI-DTI

Introduction

Diffuse hemispheric infiltrative low grade gliomas (WHO classification grade I and II) account for 30% of all gliomas and are characterized by continuous growth and progression to anaplastic transformation¹. Because these tumors are hard to differentiate from brain at surgery and because they can infiltrate eloquent tissue, low grade glioma (LGG) surgery remains a challenge for neurosurgeons. To achieve maximal resection with minimal risk of postoperative neurological morbidity, neurosurgical adjuncts including functional magnetic resonance and diffusion tensor imaging guided (fMRI-DTI) neuronavigation (NN), intra-operative magnetic resonance imaging (i-MRI), intra operative ultrasound and direct electrical stimulation (DES) have been developed and are increasingly widely used²⁻⁴.

The benefit of improving the extent of resection (EOR) during LGG surgery remains somewhat controversial^{5,6}. Greater extent of resection has been associated with a significant improvement in five-year overall survival and in progression-free survival^{3,7-9}. Despite the increasing support for maximizing extent of resection, there remains some controversy with several other studies not finding a significant benefit from increased EOR^{10, 11}. However, these studies are more than 15 years old and as Pouratian et al⁵ has suggested, inconsistent results may be partially explained by the fact that pre- and intra-operative neurosurgical techniques and adjuvant glioma therapy developed rapidly, rendering earlier studies less comparable with recent studies. These pre- and intra-operative neurosurgical adjuncts have to be used safely to improve the extent of resection without increasing the risk of new post-operative neurological deficits.

The role of several intra-operative techniques such as DES^{1,12,13}, i-MRI¹⁴⁻¹⁶ and fMRI-DTI¹³ guided neuronavigation on the EOR of low grade gliomas has previously been studied. However, to the best of our knowledge the extent of resection has not been directly related to the differential effects of these pre- and intra-operative techniques together. Our aim in this retrospective analysis is to compare the effect of different pre- and intra-operative adjuncts on the extent of resection of hemispheric low grade gliomas.

Materials and methods

Patient population

Electronic medical records were reviewed retrospectively to include patients of both sexes, 18 years and older, who underwent craniotomy for resection of histopathologically confirmed astrocytoma, mixed oligoastrocytoma and oligodendroglioma (all World Health Organization Grade 1 and/or 2) at 'X' Hospital between January 2005 and July 2013. Pilocytic astrocytomas, gemistocytic astrocytomas and gangliogliomas were excluded. We further excluded infratentorial gliomas, patients with intractable epilepsy and patients with

insufficient preoperative and/or postoperative MRI studies. The Institutional Review Board (IRB) from 'X' approved this study.

Operative reports of all patients were reviewed to identify which pre- and intra-operative tools were used during the procedures. All patients were categorized in 8 groups based on the (combinational) use of neuronavigation system alone (NN), fMRI-DTI guided neuronavigation system (FD), intra-operative MRI (MR) (Siemens Verio 3.0 T, Open Bore (70 cm), Siemens Healthcare, Erlangen, Germany) and direct electrical stimulation (DES) (see table 1a and 1b). Stereotactic frameless neuronavigation was used intra-operatively in all cases as a standard.

Tumor Volume Measurements

Tumor volumes were assessed by manually outlining the tumor areas across all axial MRI slices on pre and post operative studies using 'brush and/or auto brush function' on the Brainlab software, iPlan Net 3.0.0 (Munich Germany). Published literature supports accurate tumor border identification on T2-weighted images¹⁷. Therefore, we used pre and post operative T2-weighted images during segmentation with the assumption that all of the abnormal T2 hyperintensity should be included within the tumor borders (figure 1). Brainlab gave an automatic calculation of the tumor volume in cubic centimeters. In 95% of cases, postoperative MRI studies were obtained within 48 hours of surgery.

Manual segmentation was done by FI (final year medical student with experience in volumetric measurements) and AO (neurosurgeon) and reviewed by TL (neuroradiologist). All three raters were blinded to any patient information during manual segmentation of the tumors to avoid bias. After measuring initial tumor volumes (cm^3) on pre operative MRI and residual tumor volumes (cm^3) on post operative MRI we calculated the extent of resection (%) with the formula: $(\text{initial tumor volume} - \text{residual tumor volume}) / \text{initial tumor volume} \times 100$ ⁷. Gross total resection (GTR) was defined 100% tumor resection as seen on T2-weighted images. We defined eloquent tumors as based on fMRI data and/or anatomical tumor involvement one or more of the following structures precentral gyrus, postcentral gyrus, Broca's and/or Wernicke's area, visual cortex, hypothalamus, thalamus, internal capsule, and/or basal ganglia.

Pre- and intra-operative neurosurgical adjuncts

Gliomas involving eloquent brain area had an indication to receive an awake craniotomy with DES, which provided the neurosurgeon to preserve neurological function with maximal possible tumor resection. Absolute contraindications for this procedure were confusion and communication difficulties (e.g. severe dysphasia or language barrier) of patients. An alternative method was to use fMRI-DTI enriched neuronavigation during surgery to determine the anatomical and functional language and motor areas. Reasons why patients could not receive fMRI-DTI was the inability of patients to perform tasks in the MRI scanner due to severe aphasia, motor disability, language barrier, claustrophobia and technical or logistical hindrances.

Patients with contraindications for DES and on patients who we had difficulties obtaining qualitative fMRI-DTI data, were alternatively operated with neuronavigation only or in more

complex cases, i-MRI only. DES in combination with i-MRI was used when the neurosurgeon needed a better intra-operative evaluation of tumor and eloquent area relationship due to a more complex localization of the tumor.

Statistical Analysis

The mean extent of resection (EOR) was calculated for each group and subgroup, and this is reported with the 95% confidence interval. Overall group comparison of Mean EOR was done using one-way ANOVA test of three or more groups with Bonferroni test (for a one to one group comparison), and a multiple regression method was used to adjust for prospective confounders. Only two-sided p-values were reported, with the significant (α) level set at 0.05. All analysis was done using STATA 11.

Results

Patient characteristics and data on tumor resection are presented in Table 1a, 1b and 2. Of 128 included patients, 75 (58.6%) patients had a tumor involving eloquent brain areas, on these patients DES was used most often (34.7%), followed by neuronavigation alone (30.7%), DES in combination with io-MRI (26.7%) and io-MRI alone (8%). fMRI-DTI enriched neuronavigation was available in 45.3% of all cases. GTR was achieved on 23.4% of all patients, 5% of patients with eloquent brain area involving tumors, and 47% of eloquent sparing tumors. The overall mean EOR was $81.3\% \pm 20.5\%$, with Mean EOR of eloquent tumors = $72.8\% \pm 22.0\%$, and mean EOR of non-eloquent tumors = $93.3\% \pm 9.5\%$. Thirty-nine percent of all patients had record of fMRI-DTI available.

Of all lesions, 29 (22.7%) were astrocytomas WHO grade 1 and 2, 59 (46.1%) were oligodendrogliomas WHO grade 1 and 2 and 40 (31.3%) were mixed oligoastrocytoma WHO grade 1 and 2. Of all 128 subjects, 7 patients died and 14 were lost to follow up. The mean follow-up time was $3.5 \text{ years} \pm 2.5 \text{ years}$ and the overall mortality rate for all the patients was 15.6 per 1000 person-years. The EOR was depended of eloquence ($p < 0.001$), operating neurosurgeon ($p = 0.01$) and the initial tumor volume ($p = 0.021$) and independent of all other confounders.

Patients with LGGs that involved eloquent brain area had significantly higher EOR when an intra-operative adjunct was used, compared with NN alone (mean EOR $54.4\% \pm 27.0\%$), with the highest EOR when intra-operative MRI ($90.7\% \pm 7.0\%$) or DES ($84.6 \pm 12.4\%$) was combined with fMRI-DTI ($p = 0.001$) (table 1a). This significance remained, even after adjusting for potential confounders such as patients' sex and age, eloquent involvement of tumor, tumor location, operating neurosurgeon, histological subtype of the tumor, and initial tumor volume on pre-operative T2 weighted MRI).

Figure 3 shows that tumors in eloquent regions had significantly lower EOR compared with tumors located in non-eloquent regions for both the NN ($p < 0.001$) and MR ($p = 0.001$) groups and non-significantly less EOR for patient in the DES group ($p = 0.1025$). All tumors within the DES-MR group were eloquent tumors.

The mean EOR differed significantly between small ($<10\text{ cm}^3$), medium ($10\text{--}50\text{ cm}^3$) and large ($> 50\text{ cm}^3$) gliomas ($p < 0.001$) (figure 4). Small gliomas had a significant higher EOR (mean $91.9\% \pm 10.4\%$) when compared with medium gliomas ($79.0\% \pm 21.7\%$, $p = 0.002$) and medium gliomas had a significant higher EOR when compared with large gliomas ($67.4\% \pm 22.3\%$, $p = 0.029$). Large gliomas had the least complete resections and differed significantly from small gliomas in EOR ($p < 0.001$). Thus, with increasing glioma sizes, the EOR decreased significantly.

Discussion

In this retrospective single institution analysis with 128 patients, we observed a significant improvement of the mean EOR of tumors located in eloquent brain areas, when intra operative MRI or direct electrical stimulation was combined with fMRI-DTI, compared with the use of neuronavigation alone ($p = 0.001$), even after adjusting for potential confounders. Adding fMRI-DTI on the use of NN, MR and DES all improved the EOR of tumors involving eloquent brain area.

As expected, the addition of fMRI-DTI on eloquent brain area sparing gliomas did not improved EOR. However, using intra-operative MRI on these 'non-eloquent' tumors did non-significantly ($p > 0,05$) increased the mean EOR to a sub-total resection of 97%, when compared with a partial resection of 90% with the use of neuronavigation only.

After many years of debate on the impact of EOR improvement on the patients, increasing numbers of studies have suggested that a more complete resection has a significant effect on the OS and malignant progression-free survival^{3,7–9}. Although Class I evidence is still missing, because of this increasing evidence supporting clinical benefits of improving EOR on LGG patients, maximal safe resection preserving functional brain is recommended by guidelines as the optimal first treatment modality¹⁸.

In this study, we mainly focused on which intra-operative adjunct had a significant role in improving the EOR of tumors involving both eloquent or non-eloquent brain areas. Previous reports have suggested the significant benefits of intra-operative adjuncts on the EOR. A recent meta-analysis including 90 publications, showed that using DES was associated with a better extent of resection of LGG and fewer late severe neurologic deficits¹⁹. Furthermore, Yordanova et al.¹ and De Benedictis et al.¹² showed that awake LGG surgery with DES significantly improved EOR for eloquently located gliomas. In addition, Ius et al.¹³ showed that adding fMRI-DTI based neuronavigation to DES further increased the EOR. Recently, Liang et al.¹⁴ reviewed several studies that investigated the role of i-MRI on EOR of patients who underwent LGG surgery. Both retrospective^{16,20–22} and prospective studies^{15,23} showed a benefit in increasing the EOR when i-MRI was used during LGG resection.

Our findings regarding to the benefits of DES, i-MRI and fMRI-DTI guided neuronavigation on improving the EOR support the observations of earlier studies^{1,12,13, 15,23}. However, 74% and 85% of the gliomas, in respectively, Senft et al. and Hatiboglu et al.^{15,23} consisted of high grade (WHO grade 3 and 4) gliomas. Since all subjects in our analysis had LGGs,

comparing our results with these studies will not be reliable. It is known that the growth and tumor border delineation is different between low and high grade gliomas.

To the best of our knowledge, the value of combining i-MRI and DES for resection of gliomas has not previously been examined in a volumetric study. Four studies have mentioned the safety and the possibility of combining these two techniques in respectively a case report²⁴, a case series with 12 patients²⁵, a technical note with 10 cases²⁶ and a study with 34 patients who underwent both i-MRI and awake craniotomy²⁷.

In this present study the EOR was measured in 20 patients in which DES was used in combination with i-MRI. The combinational use of these intra-operative adjuncts did not show any significant improvement in the EOR when compared with any other group, even after adjusting for potential confounders. However, this finding should be interpreted with caution, because of the small sample size, the retrospective character of this study which could have caused selection bias due to higher resection complexity in this group, when compared with other groups. Prospective large numbered studies are needed to have a better overview on the effect of combining i-MRI with DES during awake LGG surgery.

Timing the management of hemispheric low grade gliomas has always been controversial within neuro-oncology⁶. Our results showed a significant better resection of small gliomas, when compared with medium and large gliomas. This result supports that early surgical resection of suspected small hemispheric LGGs could be favorable over a watchful-waiting strategy, by preventing the small glioma to grow larger and have a worse EOR. A recent review showed that patients who had early LGG surgery had a benefit in overall survival when compared with patients who had a conservative management²⁸.

This study has some limitations, which are discussed below. First, like most of the available studies of surgical resection of low grade gliomas, this study has been done retrospectively. Our main outcome, which is the extent of resection, is therefore sensitive to selection bias for each “treatment arm”.

Second, achieving GTR on LGGs depends on several factors including resection complexity, which partly depends on the pathological character of gliomas. On well circumscribed gliomas, GTR can be achieved less difficult when compared with diffuse gliomas, because of their well-defined tumor borders. In our study, we did not have enough pathological data to clearly stratify between diffuse versus circumscribed gliomas, which could have been one of the important factors on achieving GTR, in addition to tumor localization, eloquence, tumor grade, tumor size and intra-operative tool.

Moreover, DLGG segmentation on both pre and post operative MRI studies is indeed a challenge even for trained neuroradiologists, because of their ill defined diffuse infiltrative tumor borders, especially when compared with circumscribed gliomas. However, even if the borders are well defined, tumor cells can significantly infiltrate normal brain tissue 20 mm beyond the abnormalities visible on conventional MR images, causing an underestimation of the tumor volumes^{1,29}. There is still a lack of consensus on how the tumor volumes can be measured at best. We tried to manage the intra-observer disagreement by making an

assumption on how to delineate initial and residual tumor volumes on respectively pre and post T2 MRI studies, as described in the method section.

Additionally, we tried to minimize the subjective bias by blinding the reviewers to the data of patients including age, sex, operating neurosurgeon, intra-operative adjunct used during surgery and histopathological subtype.

In the past several decades, increasing knowledge about the natural history of gliomas and developing new intra operative neurosurgical and functional neuroimaging techniques gave new insights within the field of LGG-surgery. Randomization of glioma patients to treatment arms with different intra operative adjuncts is a challenge, so well designed large scaled prospective studies with long follow up are needed.

In earlier published literature it is often noted whether tumors were located in eloquent areas or not. However, these studies defined eloquence based on standard anatomical areas such as internal capsule, basal ganglia, language cortex, sensory cortex, motor cortex, thalamus, and hypothalamus without individualized pre operative determination of eloquence based on functional MRI⁷. We know that inter-individual variability of eloquent areas exist and shifting of eloquent areas can occur due to slow diffuse growth of DLGGs³⁰.

Therefore, an individualized onco-functional map of both anatomical and functional brain could acquire a more accurate determination of the relationship between eloquent areas and the tumor in the future^{30–32}, instead of a standard anatomical determination of eloquent areas as we did in the past several decades.

Earlier published literature has suggested that DES should be universal implemented as standard care for glioma surgery¹⁹. The addition of fMRI and DTI to DES is still in its infancy. Neurosurgeons that do not use DES routinely, could use additional fMRI and DTI to understand white matter and functional anatomy prior to encountering it. Till the present date, there are just a few clinical studies investigating the improvement of EOR and quality of life by adding fMRI and DTI on DES as discussed before. Randomized studies with bigger population sizes are needed in the future to state the real impact of fMRI and DTI on improving the quality of life of patients after LGG surgery.

Conclusion

Using intra-operative MRI or direct electrical stimulation in combination with fMRI and DTI significantly improves EOR when LGGs are located in eloquent areas, compared with craniotomies in which only neuronavigation was used. Tumors involving eloquent brain areas had less complete resections compared with non-eloquent tumors within the same pre- and intra-operative group. Additionally, small gliomas had a significant higher EOR when compared with medium and large gliomas.

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Figure 1.

(A, B) Oligodendroglioma involving the left frontal lobe seen on axial T2 MRI sequence (A) Pre operative delineation of initial tumor volume (red) (B) Post operative delineation of residual tumor volume (green) (C, D) Astrocytoma involving the right occipital lobe seen on axial T2 MRI sequence (C) Pre operative delineation of initial tumor volume (red) (D) Post operative delineation of residual tumor volume (green)

Figure 2.

Box plot showing the differences in mean EOR, of tumors located in eloquent brain areas, between subgroups.

Abbreviations NN: neuronavigation MR: intra-operative magnetic resonance imaging DES: direct electrical stimulation FD: functional magnetic resonance imaging – diffusion tensor imaging guided neuronavigation

Figure 3.

Box plot showing the differences in mean EOR, of eloquent and non-eloquent tumors, within and between subgroups.

Abbreviations NN: neuronavigation DES: direct electrical stimulation MR: intra-operative MRI el-: tumors not involving eloquent brain areas el+: tumors involving eloquent brain areas

Figure 4.
Box plot showing the differences in mean EOR between glioma sizes.

Table 1a

Abbreviations of all groups. Extent of resection (%) based on which adjunct was used on eloquent brain area involving glioma.

Group		No. of total patients (%)	EOR % Mean $\pm$ SD	No. of E ⁺ patients in group* (%)	EOR % of E ⁺ patients* Mean $\pm$ SD	P value
Pre- and/or intra operative adjunct**						0.005
NN	Neuronavigation	55 (43.0)	78.7 $\pm$ 23.4	23 (41.8)	61.6 $\pm$ 25.6	
MR	Intra- operative MRI	24 (18.8)	93.1 $\pm$ 10.2	6 (25.0)	82.3 $\pm$ 12.0	
DES	Direct electrical stimulation	29 (22.7)	78.3 $\pm$ 22.2	26 (90.0)	76.0 $\pm$ 22.4	
DES-MR	Combinational direct electrical stimulation and intra- operative MRI	20 (15.6)	78.5 $\pm$ 14.1	20 (100.0)	78.5 $\pm$ 14.1	
	p-value***				0.031	
Subgroup						<0.001
Pre- and/or intra operative adjunct**						
NN	Neuronavigation	42 (32.8)	76.4 $\pm$ 25.5	16 (38.1)	54.4 $\pm$ 27.0	
NN-FD	fMRI-DTI guided neuronavigation	13 (10.2)	85.9 $\pm$ 12.3	7 (53.9)	78.3 $\pm$ 11.3	
MR	Intra- operative MRI	15 (11.7)	92.4 $\pm$ 11.9	3 (20.0)	73.8 $\pm$ 10.0	
MR-FD	Intra- operative MRI with fMRI-DTI guided neuronavigation	9 (7.0)	94.2 $\pm$ 6.8	3 (33.3)	90.7 $\pm$ 7.0	
DES	Direct electrical stimulation	10 (7.8)	62.2 $\pm$ 28.2	10 (100.0)	62.2 $\pm$ 28.2	
DES-FD	Direct electrical stimulation with fMRI-DTI guided neuronavigation	19 (14.8)	86.7 $\pm$ 12.4	16 (84.2)	84.6 $\pm$ 12.4	
DES-MR	Combinational direct electrical stimulation and intra- operative MRI	11 (8.6)	77.9 $\pm$ 12.9	11 (100.0)	77.9 $\pm$ 12.9	
DES-MR-FD	Combinational direct electrical stimulation and intra- operative MRI with fMRI-DTI guided neuronavigation	9 (7.0)	79.2 $\pm$ 16.1	9 (100.0)	79.2 $\pm$ 16.1	
	p-value***				0.007	

*E⁺ Patients with glioma involving eloquent brain area

**In 100% of the patients stereotactic frameless neuronavigation was used as a standard.

***Stratified comparison between the various surgical groups within each stratum of eloquent brain area (E+)

fMRI-DTI: functional magnetic resonance imaging – diffusion tensor imaging

Table 1b

Abbreviations of all groups. Extent of resection (%) based on which adjunct was used on eloquent brain area sparing glioma.

Group		No. of total patients (%)	EOR % Mean $\pm$ SD	No. of E- patients in group ** (%)	EOR % of E- patients Mean $\pm$ SD	P value
Pre- and/or intra operative adjunct **						0.005
NN	Neuronavigation	55 (43.0)	78.7 $\pm$ 23.4	32 (58.2)	90.1 $\pm$ 10.7	
MR	Intra- operative MRI	24 (18.8)	93.1 $\pm$ 10.2	18 (75.0)	96.7 $\pm$ 6.6	
DES	Direct electrical stimulation	29 (22.7)	78.3 $\pm$ 22.2	3 (10.0)	98.2 $\pm$ 1.9	
DES-MR	Combinational direct electrical stimulation and intra- operative MRI	20 (15.6)	78.5 $\pm$ 14.1	0 (0.0)	–	
	p-value ***				0.016	
Subgroup						<0.001
Pre- and/or intra operative adjunct **						
NN	Neuronavigation	42 (32.8)	76.4 $\pm$ 25.5	26 (61.9)	90.0 $\pm$ 11.4	
NN-FD	fMRI-DTI guided neuronavigation	13 (10.2)	85.9 $\pm$ 12.3	6 (46.1)	94.8 $\pm$ 5.8	
MR	Intra- operative MRI	15 (11.7)	92.4 $\pm$ 11.9	12 (80.0)	97.1 $\pm$ 6.8	
MR-FD	Intra- operative MRI with fMRI-DTI guided neuronavigation	9 (7.0)	94.2 $\pm$ 6.8	6 (66.7)	96.0 $\pm$ 6.5	
DES	Direct electrical stimulation	10 (7.8)	62.2 $\pm$ 28.2	0 (0.0)	–	
DES-FD	Direct electrical stimulation with fMRI-DTI guided neuronavigation	19 (14.8)	86.7 $\pm$ 12.4	3 (15.8)	98.2 $\pm$ 4.9	
DES-MR	Combinational direct electrical stimulation and intra- operative MRI	11 (8.6)	77.9 $\pm$ 12.9	0 (0.0)	–	
DES-MR-FD	Combinational direct electrical stimulation and intra- operative MRI with fMRI-DTI guided neuronavigation	9 (7.0)	79.2 $\pm$ 16.1	0 (0.0)	–	
	p-value ***				0.035	

*E- Patients with glioma sparing eloquent brain area

**In 100% of the patients stereotactic frameless neuronavigation was used as a standard.

***Stratified comparison between the various surgical groups within each stratum of eloquent sparing brain area (E-)

fMRI-DTI: functional magnetic resonance imaging – diffusion tensor imaging

Table 2

Characteristics of all patients and their mean extent of resection.

Parameter	No. of patients (%)	Extent of resection (%)	
		Mean $\pm$ SD	P value *
Sex			0.059
male	65 (50.8)	79.4 $\pm$ 22.1	
female	63 (49.2)	83.2 $\pm$ 18.8	
age at diagnosis (yr)			0.256
<30	27 (21.1)	85.1 $\pm$ 19.9	
30–50	76 (59.4)	80.2 $\pm$ 20.4	
>50	25 (19.5)	80.3 $\pm$ 21.9	
Tumor location			0.953
Left frontal	40 (31.3)	79.8 $\pm$ 23.1	
Right frontal	35 (27.3)	89.3 $\pm$ 11.0	
Right temporal	20 (15.6)	75.4 $\pm$ 20.9	
Left temporal	14 (10.9)	73.8 $\pm$ 29.9	
Left parietal/occipital	7 (5.5)	82.6 $\pm$ 7.3	
Right parietal/occipital	12 (9.4)	80.1 $\pm$ 20.2	
Eloquent **			< 0.001
No	53 (41.4)	93.3 $\pm$ 9.5	
Yes	75 (58.6)	72.8 $\pm$ 22.0	
Operating neurosurgeon			0.01
1	26 (20.3)	88.8 $\pm$ 10.5	
2	12 (9.4)	83.3 $\pm$ 15.4	
3	53 (41.4)	81.1 $\pm$ 18.5	
4	11 (8.6)	69.8 $\pm$ 35.1	
5	26 (20.3)	77.89 $\pm$ 24.4	
Histological subtype			0.276
Astrocytoma grade 1–2	29 (22.7)	78.6 $\pm$ 26.5	
Oligoastrocytoma grade 1–2	40 (31.3)	78.5 $\pm$ 21.9	
Oligodendroglioma grade 1–2	59 (46.1)	84.4 $\pm$ 15.6	
Initial tumor volume on pre operative T2-weighted MRI (cm3)			0.021
<10	46 (35.9)	91.9 $\pm$ 10.4	
10–50	56 (43.8)	79.0 $\pm$ 21.7	
>50	26 (20.3)	67.4 $\pm$ 22.3	
Gross total resection	30 (23.4)	100 $\pm$ 0	
Mean extent of resection		81.3 $\pm$ 20.5	

*Overall comparison adjusting for all other co-variables

**Based on fMRI data and/or anatomical involvement one or more of the following: precentral gyrus, postcentral gyrus, Broca's and/or Wernicke's area, visual cortex, hypothalamus, thalamus, internal capsule, and/or basal ganglia