Correlation of the extent of tumor volume resection and patient survival in surgery of glioblastoma multiforme with high-field intraoperative MRI guidance

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Extent of resection (EOR) still remains controversial in therapy of glioblastoma multiforme (GBM). However, an increasing number of studies favor maximum EOR as being associated with longer patient survival. One hundred thirty-five GBM patients underwent tumor resection aided by 1.5T intraoperative MRI (iMRI) and integrated multimodal navigation. Tumor volume was quantified by manual segmentation. The influences of EOR, patient age, recurrent tumor, tumor localization, and gender on survival time were examined. Intraoperative MRI detected residual tumor volume in 88 patients. In 19 patients surgery was continued; further resection resulted in final gross total resection (GTR) for 9 patients (GTR increased from 47 [34.80%] to 56 [41.49%] patients). Tumor volumes were significantly reduced from $34.25 \pm 23.68\%$ (first iMRI) to $1.22 \pm 16.24\%$ (final iMRI). According to Kaplan–Meier estimates, median survival was 14 months (95% confidence interval [CI]: 11.7–16.2) for EOR $\geq$98% and 9 months (95% CI: 7.4–10.5) for EOR <98% ($P < .0001$); it was 9 months (95% CI: 7.3–10.7) for patients $\geq$65 years and 12 months (95% CI: 8.4–15.6) for patients <65 years ($P < .05$). Multivariate analysis showed a hazard ratio of 0.39 (95% CI: 0.24–0.63; $P = .001$) for EOR $\geq$98% and 0.61 (95% CI: 0.38–0.97; $P < .05$) for patient age <65 years. To our knowledge, this is the largest study including correlation of iMRI, tumor volumetry, and survival time. We demonstrate that navigation guidance and iMRI significantly contribute to optimal EOR with low postoperative morbidity, where EOR $\geq$98% and patient age <65 years are associated with significant survival advantages. Thus, maximum EOR should be the surgical goal in GBM surgery while preserving neurological function.

Keywords: extent of resection (EOR), glioblastoma multiforme (GBM), intraoperative MRI (iMRI), patient survival, tumor volumetry.

W ith a frequency of approximately 38%, gliomas are the most common primary brain tumors,[1] most of them being glioblastoma multiforme (GBM) grade IV, as classified by the World Health Organization (WHO). GBM is one of the most malignant human neoplasms, with a mean patient survival of still only $\sim$14 months,[2] despite recent advances in surgery and radiochemotherapy.[2] The mean life expectancy for patients with anaplastic astrocytoma (WHO grade III) is slightly longer, at 41 months.[3] A complete surgical excision of high-grade gliomas (WHO grades III and IV) without tumor recurrence is impossible, due to their biological behavior. Thus, the interdisciplinary therapeutic concept today combines microsurgery followed by fractionated external beam radiation and chemotherapy. Despite better life expectancy and 5-year survival rates of 42%–92%,[4] astrocytomas (WHO grade II) tend to develop into high-grade gliomas.

In the current literature there is no general consensus regarding the role of surgical extent of resection (EOR) as a predictive parameter for longer patient survival.[3,5] Up to now, patient age, tumor histopathology, and Karnofsky Performance Scale (KPS) have proven to be dependable predictors of patient outcome. Although there remains a lack of supporting class I evidence, to date most authors favor a maximum safe EOR as being

associated with a better patient outcome in low- and high-grade gliomas. To optimize EOR, intraoperative imaging methods such as CT, ultrasound,[6] 5-aminolevulinic acid (5-ALA),[7] and MRI have been established in neurosurgical operating theaters, serving as immediate resection control. Of these, high-field intraoperative MRI (iMRI) scanners, with the major drawback of high cost, provide highest resolution for detection of even small tumor remnants and have thus proven to be a sufficient tool providing extended tumor volume resections and higher percentages of gross total resections (GTRs) in glioma surgery.[8–12] As a major addition to iMRI, integrated navigation delivers anatomical image data and information on the localization of eloquent cortical sites (functional MRI),[13] fiber bundles (diffusion tensor imaging [DTI]),[14–16] and metabolic function (single photon emission CT, positron emission tomography [PET], MR spectroscopy [MRS]).[17] Registration of iMRI to update navigation compensates for intraoperative brain deformations known as brain shift, caused by tumor mass resection itself, loss of cerebrospinal fluid, brain swelling, or the use of retractors.[18–21] The combination of multimodal navigation and iMRI contributes to higher percentages of EOR in glioma surgery with minimum postoperative morbidity.

In the present study, we evaluated the prospectively collected data of 135 GBM patients, who were operated on with high-field (1.5T) iMRI and multimodal navigation guidance (functional MRI, DTI-tractography, MRS, PET). EOR data were calculated after manual tumor segmentation of the tumor outlines in the intraoperative scans before and after tumor resection according to iMRI results. The interdependence of EOR, patient age, recurrent tumor, tumor localization, and gender for patient survival was examined in univariate and multivariate analyses.

To our knowledge, this study is the largest to assess the correlation of EOR and patient survival, involving high-field iMRI guidance and volumetric assessment of tumor volume by manual segmentation.

Patients and Methods

Patients

A cohort of 135 patients with supratentorial GBM underwent elective surgery with high-field iMRI resection control in the Department of Neurosurgery at the University of Erlangen-Nuremberg from April 2002 to October 2008. The group consisted of 78 men and 57 women, with a mean age of 59.3 years (SD: 13.3; range: 11–81 y). The cohort included 27 recurrent lesions.

The patients' postoperative survival times (in months) were retrospectively obtained according to the Erlangen tumor register database. Of the 135 patients in the study, 117 were included in the follow-up; 18 have been unavailable for follow-up.

Ethics committee approval and written informed consent of all patients or adequate family members

were obtained preoperatively. Collected prospectively was the postoperative course, including complications and morbidity, histopathological analysis, operative and discharge reports, and imaging data. Adjuvant therapy was either fractionated external beam radiation with a maximum of 54 Gy or combined radiochemotherapy with one or a combination of the following chemotherapeutics: temozolomide; procarbazine/lomustine (CCNU)/vincristine; and/or nimustine (ACNU)/teniposide (VM-26), depending on the patient's KPS or previous therapy.

Multimodal Navigation

Microscope-based neuronavigation (BrainLAB) was performed in all cases with an NC4 or Pentero multivision navigation microscope (Carl Zeiss) combined with a VectorVisionSky navigation system (BrainLAB).

Functional data sets, which were acquired 1 to 2 days prior to surgical intervention, were rigidly registered to a 1.0-mm isotropic 3D data set in magnetization prepared rapid acquisition gradient echo (MPRAGE), with the following sequence parameters: field of view (FOV), 250 mm; repetition time (TR), 2020 ms; echo time (TE), 4.38 ms; matrix, 256 × 256; voxel size, 1.0 × 1.0 × 1.0 mm). Functional MRI was obtained in 20 cases, magnetoencephalography in 1 case, DTI in 14 cases, MRS in 4 cases, and PET in 1 case. These data sets were used either separately or in combination. The 3D data set with the integrated functional data was finally registered to the navigational data set used for automatic patient registration (obtained after induction of anesthesia and head fixation and prior to skin incision, with an MPRAGE sequence with identical scanning parameters as described above) with Image Fusion Software (VectorVision Planning 1.3, BrainLAB) by a semiautomatic rigid registration algorithm.

Intraoperative Imaging Protocol

The imaging protocol on the 1.5T MR scanner (Siemens Sonata, Siemens AG) included T2-weighted turbo spin echo (slice thickness, 4 mm; FOV, 230 mm; TR, 6490 ms; TE, 98 ms), fluid attenuated inversion recovery (slice thickness, 4 mm; FOV, 230 mm; TR, 10 000 ms; TE, 103 ms), T1-weighted spin echo (slice thickness, 4 mm; FOV, 230 mm; TR, 525 ms; TE, 17 ms), echo planar imaging dark fluid (slice thickness, 5 mm; FOV, 230 mm; TR, 9000 ms; TE, 85 ms), and 1.0-mm isotropic 3D MPRAGE (described above).

An MRI after induction of anesthesia was obtained directly prior to skin incision for automatic patient registration. The first iMRI for resection control was obtained after the surgeon's estimation of best possible tumor resection. To avoid misinterpretation between residual tumor and small bleeding or contusion by accumulation of gadolinium, the pre−skin incision scan was performed without contrast agent. Application of 0.2 mL/kg gadolinium−
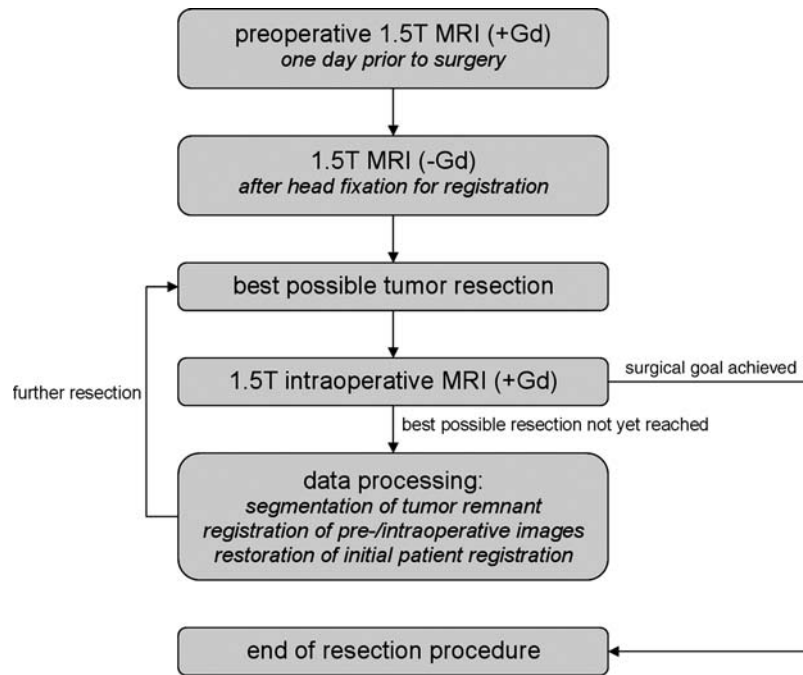
Fig. 1. Workflow figure illustrating the surgical procedure in the setting of iMRI. (Gd: gadolinium).

diethylenetriamine pentaacetic acid was used for the intraoperative scans after the intraoperative T1-weighted spin echo sequence before the 3D MPRAGE sequence. The first iMRI resection scan was performed after best possible tumor resection. For facilitating image interpretation, identical pre- and intraoperative sequences (with identical slice positions) were displayed in a side-by-side display fashion. For further detailed analysis, the images were also rigidly registered in the navigation planning software. Tumor segmentation was performed on MRI scans (obtained at least 1 day prior to surgery, contrast enhanced) on the identical scanner. Figure 1 illustrates the surgical workflow in the iMRI setting.

If iMRI revealed residual tumor, it was followed by data processing: segmentation of tumor remnant, registration of pre- and intraoperative image data sets (with the Image Fusion Software), and restoration of the initial patient registration.[22]

Tumor Volumetry

Tumor segmentation and postoperative volumetric analysis were performed with the VectorVision planning software on an offline workstation, and 1.0-mm isotropic 3D MPRAGE and T1-weighted images ($\pm$ gadolinium) were transferred with the help of PatXfer data transfer software (BrainLAB). The tumor was segmented manually across all slices, lasting approximately 5–30 min. Contrast enhancement on T1-weighted images displayed the outline of segmentation. All tumors showed a defined border with annular contrast enhancement. Metabolically active areas displayed by PET or MRS images were not taken into account due to their low resolution. T2-weighted enhancement was considered tumor-infiltrated edema but not chosen to outline the resection boundaries. After completing the segmentation, the volume was calculated in milliliters or cubic centimeters.

Statistics

All results are presented as mean $\pm$ SD.

The Wilcoxon–Mann–Whitney (Mann–Whitney U) test and Student's t-test were used for statistical analysis in Predictive Analytics SoftWare Statistics 18 for Mac (SPSS) to obtain the EOR values. For comparison of postoperative morbidity in several groups, a chi-squared test was used. Univariate analysis was performed using Kaplan–Meier estimates[23] (comparing the subgroups with the log-rank test), and a multivariate analysis was performed using a Cox proportional hazards model.[24] Hazard ratios (HRs) and their adjusted 95% confidence intervals (CIs) were calculated. Significance was at $P < .05$.

Results

Tumor Volumetry and Postoperative Morbidity

The patient cohort consisted of 135 GBM patients who were operated on with iMRI-guidance. There were no ferromagnetic accidents or difficulties during the intraoperative imaging or update procedure. The mean target registration error, documenting the localization of a separate skin fiducial placed on the patient's forehead,

Table 1. Tumor volumes for different patient cohorts

No. of Patients	Initial Tumor Volume (cm^3)	Residual Tumor Volume in First iMRI		Final Tumor Volume after iMRI Once or Twice		No. (%) of Patients with Final Gross Total Resection
		(cm^3)	(%)	(cm^3)	(%)	
Patients with intended subtotal tumor resection						
79	49.10 ± 46.41	31.20 ± 21.27	36.84 ± 19.56	10.70 ± 24.27	23.16 ± 24.67	0
Patients with intended gross total resection						
56	27.82 ± 25.65	2.32 ± 13.93	15.92 ± 27.64	0	0	56 (100%)
Patients without further removal after iMRI						
116	33.94 ± 39.67	2.29 ± 21.70	8.19 ± 25.40	2.29 ± 21.70	8.19 ± 25.40	47 (40.51%)
Patients with further tumor removal after iMRI						
19	52.65 ± 49.72	9.92 ± 20.90	34.25 ± 23.68	0.3 ± 15.88	1.22 ± 16.24	9 (47.37%)

which was not used for registration, was 2.0 mm (± 1.2 mm).

Residual tumor was seen in 88 patients in the first iMRI resection control. In 19 cases, resection was enlarged after iMRI, resulting in a significant increase of EOR from a mean tumor volume of 34.25 ± 23.68 cm^3 in the first intraoperative scans to finally 1.22 ± 16.24 cm^3 ($P < .01$). Furthermore, GTR rate was increased from 47 (34.80%) to 56 patients (41.49%). Surgery was terminated after the first iMRI in 116 cases (85.9%). Of these, in addition to the initial GTR tumors, there was subtotal resection (STR) in 51.1% of patients, further resection being impossible due to the residual tumor's close relation to eloquent areas. In these 116 patients, the initial tumor volume was 33.94 ± 39.67 cm^3. Mean final tumor volume counted 8.19 ± 25.4 cm^3.

GTR was intended in 56 cases, so that this goal was initially achieved in 83.9%, and finally in all cases. Of these 56 patients, the initial tumor volume was 27.82 ± 25.65 cm^3. STR was considered as the goal in 79 patients prior to surgery (Table 1).

For the recurrent lesions, initial tumor volume was 34.35 ± 31.02 cm^3, tumor volume in the first iMRI resection control was 10.23 ± 22.33 cm^3, and final tumor volume was 9.02 ± 15.74 cm^3.

For all cases in which the surgical procedure was supported by iMRI, subgroups were evaluated for percentage of resected tumor volume: 99.9%–98.0% = 0 patients; 97.9%–95.0% = 3 patients; 94.9%–90.0% = 1 patient, and <90% =15 patients. Further resection led to GTR in 9 patients, with resected tumor volumes of 99.9%–98.0% in 1 patient, 97.9%–95.0% in 0 patients, 94.9%–90% in 1 patient, and <90% in 8 patients. Thus, as opposed to 0 patients in the cohort of ≥98% EOR in the first intraoperative scans, after continued surgery the cohort contained 10 patients (Table 2).

Illustrative Case

A 60-year-old male patient presented with intermittent aphasia. A left parieto-occipital lesion had had GTR performed. Histopathological analysis revealed GBM, so

Table 2. Influence of iMRI on EOR

Resected Tumor Volume (%)	First iMRI, No. of Patients	Final iMRI, No. of Patients
100%	0	9
99.9%–98.0%	0	1
97.9%–95.0%	3	0
94.9%–90.0%	1	1
<90.0%	15	8

that the patient underwent adjuvant radiochemotherapy (54 Gy, temozolomide). A routine MRI after 6 months revealed a recurrent left parietal tumor. The clinical examination showed a slight right-sided hemiparesis and a sensomotor aphasia. Surgery of the recurrent lesion (initial tumor volume: 57.3 mL) was performed under high-field MRI guidance. The first iMRI revealed a residual tumor (2.32 mL) that was completely removed, as confirmed in a second iMRI (Fig. 2). Postoperatively the patient's neurological status remained at baseline function and the patient was discharged for chemotherapy with ACNU-VM26.

Further tumor volume reduction was not associated with a higher long-term morbidity evaluated for language deficits and motor deficits, the overall long-term neurological worsening among patients being 1/19 (5.26%) and 6/116 (5.17%, $P > .05$), respectively. For those 19 patients with further tumor volume resection after iMRI, there were no motor deficits. Language deterioration occurred in 2 patients (10.5%) 3 days postoperation. At discharge there was a residual aphasia in only 1 case (5.3%). This is in contrast to the group of 116 patients who did not undergo further tumor resection after iMRI. Three days postsurgery, deficits in motor and in language capacity were found in 12 and 5 patients (10.3% and 4.3%), respectively, compared with 10 and 4 patients (8.6% and 3.4%) at discharge. Long-term follow-up examination was performed after 4 months. Six patients (4.4%) had residual motor deficits, all of them included in the *no further resection* cohort. Language deficits were still apparent in only 1 patient (0.7%). This particular patient underwent further tumor resection after iMRI (Table 3).
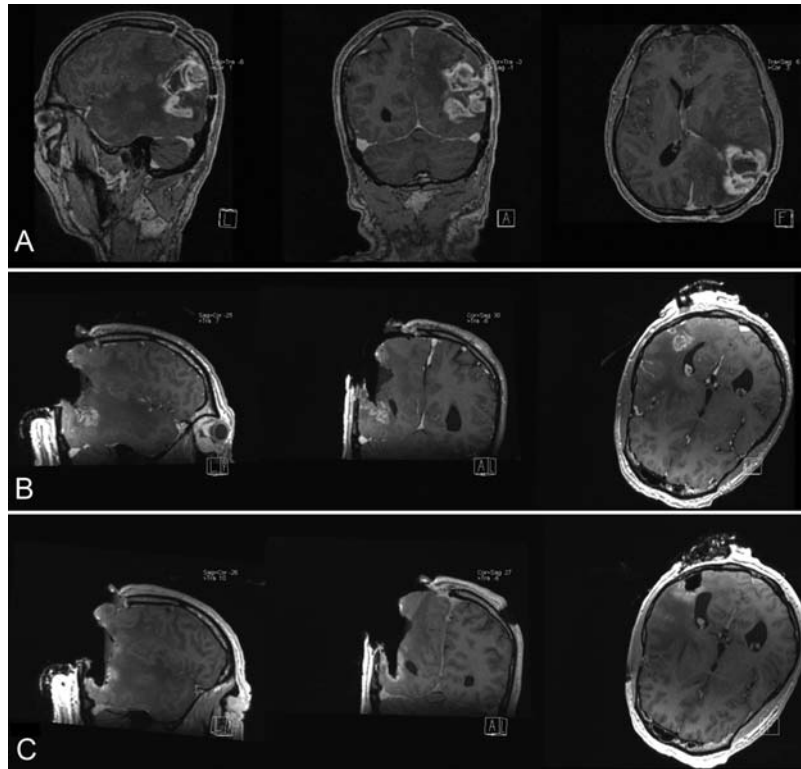
Fig. 2. Illustrative Case: MRI scans of a 60-year-old male patient with recurrent left parietal GBM during the surgical procedure. (A) Preoperative MRI, head already fixed, immediately before surgery (tumor volume: 57.3 mL). (B) First iMRI after estimated best possible tumor resection with a residual tumor mass of 2.32 mL. (C) Second iMRI after further tumor resection due to the first intraoperative scans, now showing gross total resection.

Table 3. Postoperative morbidity

Postop		At Discharge		After 4 Months	
fr	*nfr*	*fr*	*nfr*	*fr*	*nfr*
Motor deficits					
0 (0.0%)	12 (10.3%)	0 (0.0%)	10 (8.6%)	0 (0.0%)	6 (5.2%)
total: 12 (8.9%)		total: 10 (7.4%)		total: 6 (4.4%)	
Language deficits					
2 (10.5%)	5 (4.3%)	1 (5.3%)	4 (3.4%)	1 (5.3%)	0 (0.0%)
total: 7 (5.2%)		total: 5 (3.7%)		total: 1 (0.7%)	

Abbreviations: fr, further tumor removal after iMRI; nfr, no further tumor removal after iMRI.

For the recurrent tumors, morbidity was assessed separately. Postoperatively, we found new or aggravated motor deficits in 1 case (3.7%) and language deficits in 2 cases (7.4%). Long-term motor deficits were still apparent in 1 patient. Language deficits had completely resolved. Furthermore, morbidity at time of discharge (for motor and language) was evaluated for the EOR ≥98% group versus the EOR <98% group. Motor deficits were found in 4 patients in the former and in 6 patients in the latter (P = .76). Language deficits were still apparent in 2 patients in the EOR ≥98% group and in 3 patients in the EOR <98% group (P = .421). Comparing the STR and GTR groups at discharge, we found that 4/56 (7.14%) and 6/79 (7.59%), respectively, had motor deficits, while 2/56 (3.57%) and 3/79 (3.8%) had language deficits.

Length of Survival and Predictors of Survival

For 117 patients, median survival times (in months) were obtained. The remaining 18 patients were classified as censored cases in the statistical analysis, as they had been unavailable for follow-up examinations. The following variables were examined: EOR, age (<65 y and ≥65 y), gender, and recurrent tumor and its localization (frontal, temporal, parietal, or occipital).
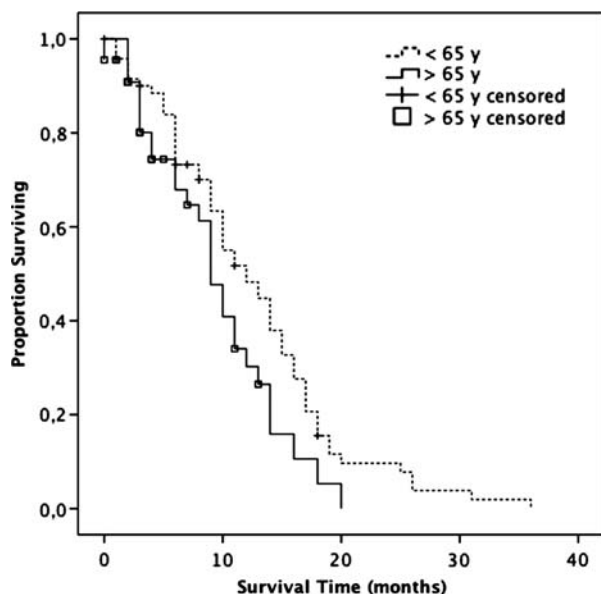
Fig. 3. Kaplan–Meier estimates of survival in univariate analysis with respect to patient age (≥65 years/<65 years). Median survival: 9 months (95% CI: 7.3–10.7) for patients ≥65 years, 12 months (95% CI: 8.4–15.6) for patients <65 years ($P < .04$).

Fig. 4. Kaplan–Meier estimates of survival in univariate analysis with respect to EOR (≥98%/<98%). Median survival: 14 months (95% CI: 11.7–16.2) for EOR ≥98%, 9 months (95% CI: 7.4–10.5) for EOR <98% ($P < .001$).

Univariate Analysis Using Kaplan–Meier Estimates

A univariate analysis was performed for each of the variables mentioned above.

Median survival in male patients was 12 months (95% CI: 9.3–14.7); in female patients, 9 months (95% CI: 7.9–10.1; $P = .323$). Median survival for primary GBM was 12 months (95% CI: 9.7–14.2) versus 10 months (95% CI: 8.0–12.0) for recurrent lesions ($P = .165$). As for the parameters gender and recurrent lesion: the different tumor localizations were not associated with a statistically significant survival advantage (each $P > .05$).

Regarding patient age, median survival was 9 months (95% CI: 7.3–10.7) for patients ≥65 years and 12 months (95% CI: 8.4–15.6) for patients <65 years ($P < .04$) (Fig. 3).

Examining the influence of EOR on the patient cohort ≥98%, median survival was 14 months (95% CI: 11.7–16.2), as opposed to 9 months (95% CI: 7.4–10.5) in the cohort of EOR <98% ($P < .001$) (Fig. 4). Identical analyses were performed for the following EOR groups: 97.9%–96.0%, 95.9%–94.0%, 93.9%–92.0%, and so on to 85.9%–84.0% (comparing ≥96% EOR with <96% EOR, ≥94% EOR with <94% EOR, etc.; each $P > .05$).

Multivariate Analysis Using a Cox Proportional Hazards Model

A Cox proportional hazards assessment was performed to estimate the relative risk for death considering the influence of our variables. For EOR ≥98%, an HR of 0.39 (95% CI: 0.24–0.63; $P = .001$) was found. For patient age <65 years, the HR was 0.61 (95% CI: 0.38–0.97;

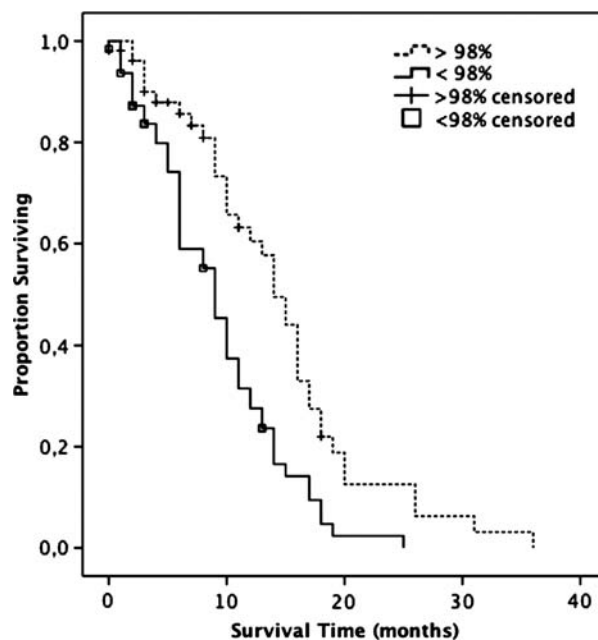$P < .05$). The HR of 0.39 corresponds to a reduced hazard for death of 61% if EOR is ≥98% (Fig. 5). For patient age <65 years, it is close to 39%. Also at the multivariate level, there was no significant influence on relative risk for death found for the variables of recurrent tumor, tumor localization, and gender (Table 4).

Discussion

We demonstrate that high-field iMRI and multimodal navigation contribute to a significantly improved EOR (34.25 ± 23.68 cm^3 to 1.22 ± 16.24 cm^3; $P < .001$) in GBM surgery with a preservation of neurological-function (long-term morbidity for motor and language deficits counting only 4.4% and 0.7%, respectively). An EOR ≥98% and a patient age <65 years are associated with a significant survival advantage in GBM surgery at both the univariate and multivariate levels, whereby further tumor resection after iMRI or tumor volume of EOR ≥98% are not associated with higher postoperative morbidity ($P > .05$). The variables of tumor localization and gender are not suitable as statistically significant prognostic factors on extended survival in our univariate and multivariate analyses. Surprisingly, we also found no significant influence on postoperative survival time for the variable of primary versus recurrent lesion. However, this might be due to bias, with a low number of recurrent tumor cases in the cohort ($n = 27$). Furthermore, it has to be noted that the further resection due to iMRI led to a significantly higher EOR in the total collective (34.25 ± 23.68 cm^3 to 1.22 ± 16.24 cm^3), but only from 10.23 ± 22.33 cm^3 to 9.02 ± 15.74 cm^3 for recurrent lesions.
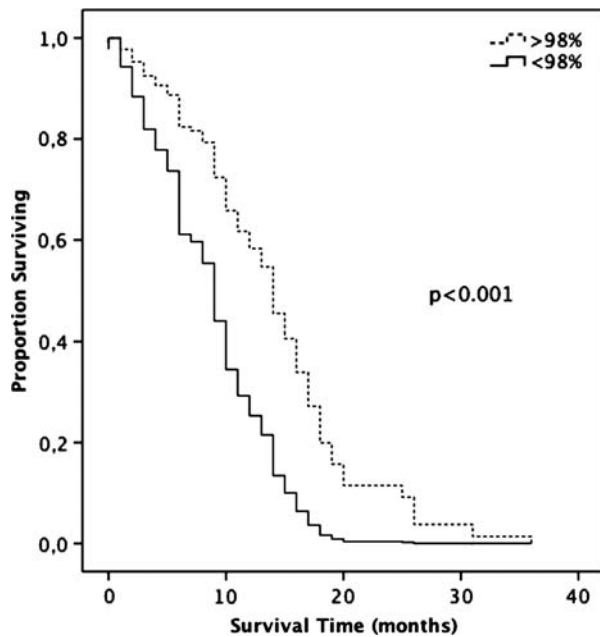
Fig. 5. Cox proportional hazards model with respect to EOR (≥98%/<98%), (P < .0001).

Table 4. Predictors of survival in multivariate analysis

Variable	HR	95% CI	P-value
EOR ≥98%	0.39	0.24–0.63	.000
Age <65 y	0.61	0.38–0.97	<.03
Localization			
Frontal	0.74	0.41–1.34	.32
Temporal	0.60	0.34–1.09	.94
Parietal	1.07	0.49–2.37	.86
Occipital	1.26	0.41–3.84	.69
Gender	0.74	0.47–1.18	.21
Recurrent	0.80	0.48–1.32	.37

Abbreviations: HR, hazard ratio; CI, confidence interval.

In this respect, our study supports iMRI as an essential tool in the surgical management of GBM. An EOR of ≥98%, which practically means tumor GTR combined with a preservation of neurological function, should be considered the surgical goal. This finding is in conjunction with the results of other large cohort studies involving quantification of tumor volumes supporting maximum EOR in glioma surgery.

Comparison with other Studies Evaluating the Postoperative Volumetric Assessment of GBM Tumor Volume and Associated Outcomes

In the current literature, there is still no general consensus regarding the role of surgical EOR as a predictive parameter for longer patient survival.[3,5] For low-grade gliomas, *all* studies published in the literature support maximum EOR.[25–27] For high-grade gliomas, *the majority* of studies using volumetric assessment consider extensive surgical resection to be associated with longer

survival rates.[28,29] An overview of the common literature by Sanai and Berger (2008) reviewing studies with and without assessment of tumor volume (high- and low-grade gliomas) found 25 studies supporting maximum EOR, as opposed to 13 studies in which statistics did not favor any resection group.[30]

In agreement with a large study reporting on volumetric tumor assessment of 416 GBM patients by Lacroix et al. at MD Anderson Cancer Center in 2001,[29] we found that an EOR of ≥98% is associated with a significantly improved outcome regarding patient survival. Keles et al.[28] studied a group of 92 GBM patients and the effect of EOR on survival. They analyzed 5 "percent of resection" subgroups: 100% EOR was associated with a mean survival of 93 weeks, whereas in the 75%–99% EOR group, the mean survival was 88.5 weeks. A mean survival of only 62.9 weeks was calculated for an EOR of 50%–74%. McGirt et al.[31] published a retrospective study on a large patient cohort of 1215 malignant glioma patients. In this study, resection was classified according to the early postoperative MRIs in near-total resection (NTR), STR, and GTR. They found that GTR versus NTR as well as NTR versus STR were independently associated with improved survival after resection of GBM (mean survival = 11 mo for GTR, 9 mo for NTR, and 5 mo for STR for primary tumors).

Comparison with other Studies Evaluating the Prognostic Factor of Glioma EOR on Survival in Association with Intraoperative Imaging Methods

5-ALA–guided resection. The largest prospective, controlled, randomized study combining patient survival with intraoperative visualization is by Stummer et al.[7] In this study, surgery guided by 5-ALA was compared with surgery without 5-ALA resection control. A significantly smaller tumor volume appeared in the 5-ALA group compared with the "white-light" control group (P < .0001). Furthermore, the median progression-free survival was 5.1 months (95% CI: 3.4–6.0) in the 5-ALA "fluorescence" group and 3.6 months (95% CI: 3.2–4.4) in the white-light group. Another recent study by Stummer et al.[32] compared the groups "residual tumor on postoperative MRI" and "no residual tumor on postoperative MRI" per the protocol of the earlier 5-ALA study, in 2006.[7] Complete resection was here identified as an independent and prognostic factor of survival (P < .0004), now providing level 2b evidence that survival depends on complete resection of contrast-enhancing tumor in GBM. Median survival was 11.8 months for patients with residual tumors and 16.9 months for patients without tumor remnant (P < .0001). Tumor volume was approximated by fitting a rotational ellipsoid defined by the maximum tumor diameters in the three dimensions.

Intraoperative MRI–guided resection. To date, there are few studies assessing glioma EOR in iMRI-guided surgery and the associated patient outcome.

Wirtz et al.[33] compared GTR and STR cases and their association with survival in a retrospective study of 62 patients. Surgery was continued due to 0.2T iMRI in 67%. The authors found that GTR was a statistically significant prognostic factor for extended survival compared with STR (13.3 mo vs 9.2 mo, $P = .0035$). Schneider et al.[12] found a significantly prolonged median survival comparing GTR and STR in their study of 31 GBM patients. In 2010, Senft et al.[34] published a study examining iMRI resection control by applying a 0.15T MR scanner compared with a control group operated on with conventional neuronavigation in a collective of 41 GBM patients. GTR was achieved in 100% of the iMRI group and 9/31 in the neuronavigation group. Median survival was 74 weeks in the GTR group and 46 weeks in the STR group ($P < .001$). Median survival in the iMRI group showed no statistically significant survival advantage compared with the neuronavigation group ($P = .07$).

Hirschberg et al.[35] found no statistically significant difference for survival time comparing an iMRI group and a control group (14.5 vs 12.1 mo, $P = .14$) in a retrospective study of 32 GBM patients.

Maximizing EOR in GBM Surgery due to iMRI and Associated Postoperative Morbidity—Comparison with Previous Studies

A few studies have shown to date that iMRI contributes to maximize EOR in glioma surgery. Among these studies, that by Hatiboglu et al.[10] evaluated prospectively 27 GBM patients who were operated on with 1.5T iMRI guidance and found after iMRI that 48% required extended tumor resection. The final GTR rate was increased from 44% to 89%. Schneider et al.[12] reported a larger GTR rate from 2 to 11 patients in a cohort of 31 GBM patients due to 0.5T iMRI. Tumor volume was reduced from 21% to 12% after iMRI and continued surgery. In a study by Bohinski et al.[9] applying 0.3T iMRI for surgery on 30 high-grade glioma patients, surgery was continued after iMRI in 60% of patients. Busse et al.[8] reported GTR in 17% of participants due to 0.5T iMRI in a study of 24 GBM patients. Our study evaluated a cohort of 22 GBM patients operated on with 1.5T iMRI guidance in 2004.[11] We showed a final GTR rate of 31.8%, whereby complete resection in the first iMRI was 13.7%. Furthermore, EOR was significantly improved by the use of iMRI (21.3% ± 13.1% [tumor volume in first iMRI] vs 5.1% ± 11.9% [tumor volume in final iMRI]). In the present study, we show a significantly enlarged EOR, with tumor volumes dropping from $34.25 ± 23.68 \text{ cm}^3$ to $1.22 ± 16.24 \text{ cm}^3$, thus the final tumor volume is extremely low compared with those in the other studies we have mentioned. The GTR rate remained slightly lower than in previous studies but was increased from 34.8% to 41.49%. We assume that this is due to the preservation of neurological function. Long-term morbidity of 0.9% and 4.4% regarding language and motor deficits after GBM surgery are comparatively low percentages. Hatiboglu et al.[10] found a long-term morbidity of 9% for his whole cohort of 46 glioma patients. Bohinski et al.[9] and Schneider et al.[12] reported a perioperative morbidity of 12.5% and 12.9%, respectively, in their studies regarding the whole patient cohort. Compared with studies omitting iMRI guidance (ie, by using alternative methods for resection control), the morbidity also remains low.[7,36–38]

Limitations of this Study

As limitations of the study we consider that tumor volume data were obtained and analyzed retrospectively, so a control group with patients operated on without iMRI guidance was not available. Furthermore, there was no standardized protocol for adjuvant therapy, so that patients were treated with different combinations of chemotherapeutics. Patients with a low KPS did not receive radiotherapy or chemotherapy.

So far, to our knowledge, the literature does not provide a prospective, controlled, randomized study including volumetric assessment of EOR and patient outcome in the setting of high-field iMRI. Although a control group could not be obtained in our study, we consider iMRI as a feasible method for extended tumor volume resection. The surgeon tried to achieve best possible tumor resection before the first iMRI resection control was performed. Of course, he might have been influenced by the certainty that iMRI would be obtained. However, his estimation was correct in the high majority (85.9%) of cases, in which surgery was terminated after iMRI (initial GTR was 34.8% of cases, and STR was terminated after iMRI in 51.1% of cases). Only in 19 cases was the surgeon mistaken. In this way, we can see that the surgeon was not really tempted toward earlier termination of surgery.

KPS was not obtained. However, we evaluated the neurological deficits for motor and language quantitatively and qualitatively pre- and postoperatively, estimating the patients' general conditions. Here, our results show no significant difference of neurological deficits, comparing the *further tumor resection after iMRI* group versus *no further tumor resection after iMRI* and *EOR ≥98%* versus *EOR <98%*.

All lesions were included in the study, including those in the vicinity of eloquent brain areas. A separate statistical analysis for lesions in non-eloquent areas versus lesions near eloquent areas could not be performed, as the distance considered to be close to an eloquent area was not explicitly defined preoperatively. However, final STR in iMRI was the case only if further resection was not to be performed. Therefore, the 79 STR lesions can be assumed to be located close to eloquent regions, while all 56 GTR lesions are located in non-eloquent areas. Percentages were comparatively low for both groups. We can therefore hypothesize that our results for the influence of EOR on outcome can also be applied to lesions near eloquent brain areas.

Conclusions

GTR with a focus on preservation of neurological function should be the major goal in surgical treatment of GBM, as an EOR $\geq 98\%$ was shown to significantly improve patient survival. This goal can be achieved with iMRI and an intraoperative update of navigation data, thus compensating for the general problem of brain deformations during surgery, known as brain-shift. In addition to EOR $\geq 98\%$, patient age <65 years significantly improves survival, whereas parameters such as gender, localization, and whether primary or recurring lesion cannot be considered as prognostic factors for a significant survival advantage.

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