

Risk of ischemia in glioma surgery: comparison of first and repeat procedures

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Abstract The role of repeat resection in the multimodal treatment of gliomas is unclear. Repeat surgery theoretically carries a higher risk of inducing neurological deficits, which might even out any advantage of cytoreduction. We sought to determine whether the occurrence of perioperative infarction is higher for repeat surgery than for first surgery, and sought to identify factors associated with the occurrence of postoperative infarction. Therefore, we searched our database to identify patients who were operated for primary or recurrent glial tumors between October 2007 and October 2010. We analyzed 177 procedures, of which 130 (73.4%) were first surgeries and 47 (26.5%) were repeat. Initial WHO grades, KPS scores, and age were evenly distributed between the groups. Forty-six (26.0%) patients had new DWI lesions on their postoperative MRI scan. Eighteen (10.2%) patients had new lesions greater than 4 cm³. Among these were 11 (6.2%) patients, for whom the new lesion caused neurologic deficit. There was no difference between first and repeat surgery with regard to the occurrence of new DWI lesions (27.7 vs. 21.3%, $P = 0.77$) or neurological deficits (10.0 vs. 10.6%, $P = 1.0$). Tumor location in the insula, operculum, and temporal lobe was found to be significantly associated with the occurrence of new DWI lesions. We conclude that repeat surgery should

not be withheld as a treatment option for patients with recurrent gliomas for fear of a higher risk of postoperative infarction or new neurologic deficit than the first surgery.

Keywords Glioma · Infarction · Repeat surgery · DWI lesion · Retrospective analysis

Introduction

Therapeutic options for recurrent malignant gliomas are diverse. Solely chemotherapeutic [1], combined surgical and chemotherapeutic [2], and radiotherapeutic approaches [3] have been advocated [4, 5]. The role of repeat resection, when feasible, has also been discussed, but EBM-based guidelines are missing [6].

A surgical approach reduces tumor cell burden immediately when the tumor is resistant to standard radio-chemotherapy. Surgery can confirm recurrence if distinction from radiation-necrosis cannot be achieved radiologically. Nevertheless, repeat surgery is traditionally regarded as carrying a higher risk than conservative therapy, which might even out its advantages [7].

In addition to extracranial and extradural complications, for example wound-healing disorders, infections, and cerebrospinal fluid leaks, intraparenchymal surgery itself might be more dangerous. Surgery in a previously irradiated area, where a scar has formed, might lead to more perioperative complications. The glial scar alters the normal intraparenchymal architecture [8–10] and small vessels that can normally be saved may be injured and sacrificed. These vascular complications might lead to greater incidence of perioperative infarction, with potentially devastating effects.

We therefore sought to determine whether the incidence of perioperative infarction is higher in repeat surgery than

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in first surgery. We further determined factors associated with the occurrence of postoperative infarction.

Methods

Patient population

We retrospectively searched our glioma-patient database in which data are prospectively entered, and selected patients who were operated at our institution between October 2007 (introduction of a DWI procedure to standard postoperative imaging) and October 2010 for primary or relapsing glial tumors.

The medical records of 200 consecutive patients were reviewed and clinical and associated operative data were collected. After surgery, we routinely followed all glioma patients with clinical and MRI examinations every 3 months. We performed adjuvant treatment according to histopathology and prior treatment.

Patient selection for first or repeat surgery

At our institution, the decision to resect a primary or recurrent tumor is based on an interdisciplinary tumor board decision taking into account the patient's clinical status, past therapeutic regimens, possible future therapeutic regimens, and resectability of the tumor. Patients with lesions suspicious of tumor recurrence usually undergo perfusion-weighted imaging or MR spectroscopy, in addition to conventional neuroimaging, to support diagnosis of tumor versus pseudoprogression.

Surgical technique

All patients underwent microsurgical tumor resection. Tumor resection was performed by use of regular microsurgical instruments, including an ultrasonic aspiration system (Stryker, Freiburg). Subpial dissection was the technique of choice for tumor dissection along the vasculature. Hemostasis was achieved by cauterization and placement of oxidized cellulose strips in the resection cavity. Patients received postoperative steroids for 5 days and mannitol for 3 days, to treat cerebral edema, and were monitored in our neurosurgical ICU for at least 12–24 h. When necessary, intraoperative neurophysiological monitoring techniques were used to enhance resection safety.

MRI modalities

All patients underwent postoperative high-field MRI within 72 h after tumor resection to determine the extent of resection and to rule out complications. MRI, including spin-echo DWI, was performed on a 1.5 T system (Intera; Philips

Medical Systems, Best, The Netherlands) and, starting January 2009, on a 3.0 T system (Siemens Verio, Siemens, Erlangen, Germany). The protocol was identical for all patients, including transversal T2-weighted images (TR/TE 4,000/99 ms) and fluid attenuated inversion recovery (FLAIR, TR/TI/TE 10,000/2,000/120 ms). For detection of contrast enhancement, T1-weighted images (TR/TE 650/15 ms) were acquired before and after intravenous application of 0.1 mmol/kg gadolinium-DTPA. A diffusion-weighted single-shot EPI sequence with two b values ($b = 0$ and $1,000 \text{ mm}^2/\text{s}$) was used. Both DWI and ADC maps were co-registered with T2-weighted and contrast-enhanced T1-weighted images and ADC maps were analyzed to exclude “shine through” effects.

Data analysis

We screened all postoperative MRI data to identify patients with lesions in the DWI scans not explained by hemostatic agents or fluid in the resection cavity.

We compared patients undergoing first or repeat resection with regard to occurrence and size of new post-operative lesions on DWI scans, new neurologic deficits, age, preoperative Karnofsky performance scale (KPS) score, and location of the tumor. Neurologic deficits with other causes, for example deliberate tissue removal, hemorrhage, or edema, were not considered.

We calculated DWI lesion-volumes and searched for clinical correlates in the patient files. Further, we classified patients with new DWI lesions into two groups:

- 1 those with small lesions, where micro-vessel injuries must be suspected; and
- 2 those with lesions $>4 \text{ cm}^3$, where bigger perforating vessels must have been injured (Fig. 1).

We defined tumor location according to preoperative MRI as (1) precentral, (2) postcentral, (3) opercular, (4) parafalcine (relation to anterior cerebral artery), (5) occipito-temporal, (6) occipito-parietal, and (7) insular (Fig. 2).

We also assessed survival after second surgery in the group of patients operated upon for recurrent tumors.

Statistics

Statistical analysis was performed by use of commercially available software (SPSS Statistics 19; IBM, Chicago, IL, USA). Binomial dichotomized data were compared by use of Fisher's exact test, and categorical data were compared by use of the χ^2 test. Median or mean values were compared by use of Student's *t* test when appropriate. Survival times were analyzed by the Kaplan–Meier method. *P* values <0.05 were considered statistically significant.

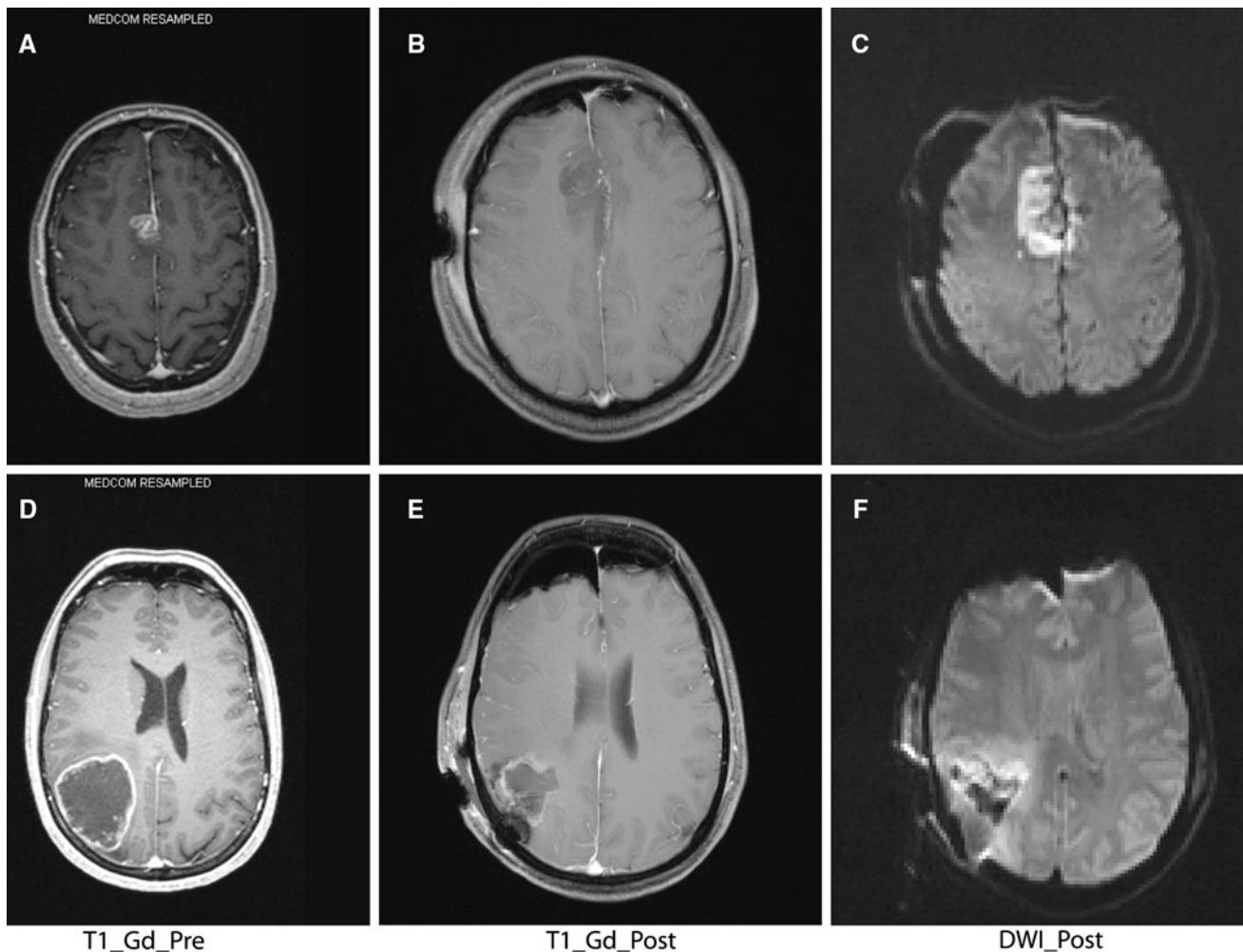


Fig. 1 Exemplary cases of two different types of DWI lesion: **a–c**: Preoperative **a** and postoperative **b**, **c** scans of a patient with new DWI lesions classified as $>4 \text{ cm}^3$; **d–f**: Preoperative **d** and postoperative **e**,

f scans of a patient with new DWI lesions classified as small new lesions not explainable by hemostatic agents

All patients gave written informed consent before the surgical procedure. The local ethics committee at the Johann Wolfgang Goethe-University approved this study (approval no. 4/09, project SNO_NCH_02_11).

Results

Two-hundred procedures were performed on 179 patients with gliomas of WHO grades II–IV. Mean age was 57 years (range: 23–84 years). Eight patients (4.5%) had initially WHO grade II tumors, nine patients (5.0%) were initially WHO grade III, and 162 patients (90.5%) had WHO grade IV tumors. Median KPS was 80. Postoperative DWI scans were not available after 23 procedures, which were excluded from the analysis. Thus, we analyzed 177 procedures, of which 47 (26.6%) were repeat surgeries for recurrent tumors. Initial WHO grades, KPS, and age were

evenly distributed between groups (Table 1). All recurrent tumors were classified as glioblastomas, corresponding to WHO grade IV. Two of these were secondary glioblastomas and the others were recurrent glioblastomas.

Forty-six (26.0%) patients had new DWI lesions on their postoperative MRI scan. All of the lesions were directly adjacent or in close vicinity to the resection cavity and the lesions were not evident on preoperative T2-weighted images. For 25 (14.1%) patients, the new lesion was clinically silent. Eighteen (10.2%) patients had new lesions $>4 \text{ cm}^3$ (Fig. 3). Among these were 11 (6.2%) patients in which the new infarction led to a new neurologic deficit (Fig. 3). In 28 (15.8%) patients the postoperative DWI scan showed solely small new lesions. In 10 (5.6%) of these patients, these lesions led to an unspecific clinical status change, i.e. new delirium, confusion, or disorientation, which required a prolonged stay in the intensive care unit. Thus, 21 (11.9%) patients in total suffered a clinical status change.

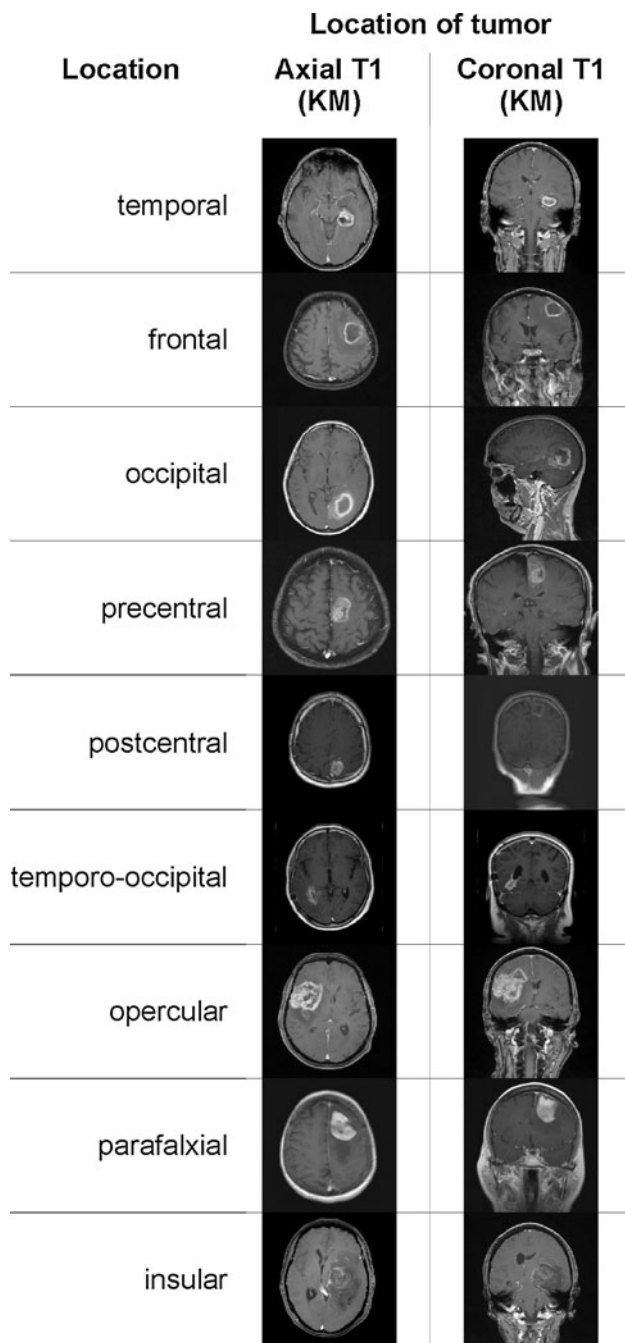


Fig. 2 Exemplary cases illustrating assessment of location of the tumor

The occurrence of new DWI lesions on postoperative MRI scans did not differ significantly between first and repeat surgery ($P = 0.44$, Fisher's exact test, odds ratio (OR) 0.7, 95% confidence interval (CI) 0.3–1.6, Table 2). Furthermore, the proportion of patients suffering a neurologic worsening did not differ between first and repeat surgery (13 (10.0%) vs. 5 (10.6%), $P = 1.0$ Fisher's exact test, (OR) 0.9, 95%-CI 0.3–2.28, Table 2). Lesion size

(small vs. large) ($P = 1.0$, Fisher's exact test, OR 0.9, 95% CI 0.3–2.9; Table 2) and “clinical status change” (6 (4.6%) vs. 4 (8.5%), $P = 0.45$, Fisher's exact test, OR 1.9, 95% CI 0.5–7.2) also did not differ significantly between first and repeat surgery.

In multivariate logistic regression analysis (forward stepwise regression) with “occurrence of new DWI lesions” as the dependent variable, the factors “repeat operation”, “age > 65”, “KPS > 70”, and “initial WHO Grade” were not associated with new DWI lesions on a statistically significant level. However, we found “location” in the insular, opercular, or temporal region to be significantly associated with occurrence of new DWI lesions (Table 3; OR 7.9, 95% CI 3.8–16.5).

To rule out a selection bias in patients undergoing repeat craniotomy, we defined tumor location around the middle cerebral artery and its major branches as “risky” and all other locations as “non-risky”. According to this stratification, 59 of 130 procedures for primary tumors (45.4%) and 17 of 47 procedures for recurrent tumors (36.2%) were for tumors in “risky” location. This difference in proportion was not statistically significant ($P = 0.30$, Fisher's exact test, OR 0.7, 95% CI 0.4–1.4).

Of the 47 patients operated for tumor recurrence, one patient was lost to follow-up. At the time of analysis (Nov 15, 2011) 10 patients were alive; according to Kaplan–Meier analysis median survival since repeat surgery was 63.7 weeks.

Discussion

Repeat surgery for glioblastoma is still controversially debated [6, 11]. In general, it is thought to carry a higher risk of causing new neurological deficits [12], which in GBM patients has a proven effect on long-term survival [13]. Some authors advocate re-resection only for patients with severe symptoms [4], and perhaps only a subgroup of patients may profit from repeat surgery. Tumor volume reduction by means of surgery can facilitate re-irradiation [14–16], and repeat resection provides new tissue for molecular profiling, which may show changes in molecular characteristics, especially MGMT methylation status [17, 18]. Thus, repeat surgery might facilitate tailoring chemotherapeutic treatment.

There is little substantial evidence about the risks or benefits of repeat resection of a malignant glioma. While there are reports of benefits in terms of improved overall survival of patients undergoing repeat tumor resection [19], this has not been validated in larger studies [20]. Therefore, weighing risks and benefits of a second or even third surgical procedure requires facts for substantive discussion by tumor boards and with patients. Recently, Park et al. [21]

Table 1 Baseline characteristics of patient groups

	Primary surgery	Repeat surgery	<i>P</i>
Initial WHO Grade IV	119	43	
Initial WHO Grade III	5	2	
Initial WHO Grade II	6	2	0.988
Mean Age (years)	56 (±10)	56 (±12)	0.977
KPS > 70	110	37	0.356

There were no significant differences regarding WHO Grade (χ^2 test for $2 \times k$ tables), age (Student's *t* test), and KPS > 70 (χ^2 test)





































Patient-No.	Age	Karnofsky Performance Scale	Initial Histologic Grading	Recurrence	Tumor-resection grade	Neurologic Worsening	Deficit	T1 pre-op.	DWI post-op.
1	72	80	GBM	No	STR	Yes	Aphasia		
2	41	80	GBM	No	GTR	Yes	Hemiparesis		
3	53	60	GBM	Yes	GTR	Yes	Hemiparesis		
4	71	60	GBM	No	STR	Yes	Hemineglect		
5	52	80	GBM	Yes	GTR	Yes	Hemiparesis		
6	45	80	GBM	No	GTR	Yes	Visual field deficit		
7	53	50	GBM	No	STR	Yes	Hemiparesis		
8	61	80	GBM	No	GTR	Yes	Armparesis		
9	47	50	GBM	No	STR	Yes	Seizures		
10	71	70	GBM	No	GTR	Yes	Altered Mental status		
11	74	60	GBM	Yes	GTR	Yes	Aphasia		
12	37	80	GBM	No	STR	No	n. a.		
13	49	80	GBM	Yes	GTR	No	n. a.		
14	25	80	GBM	No	GTR	No	n. a.		
15	64	70	GBM	No	GTR	No	n. a.		
16	69	70	GBM	No	GTR	No	n. a.		
17	52	90	GBM	Yes	GTR	No	n. a.		
18	59	80	GBM	No	GTR	No	n. a.		

Fig. 3 Overview of 18 patients with DWI lesions >4 cm³

Table 2 Comparison of patients undergoing first and repeat surgery with regard to DWI lesions

	Primary surgery	Repeat surgery	Total
No. of patients with new DWI lesions (%)	36 (27.7)	10 (21.3)	46 (26.0)
Of which large (%)	13 (10.0)	5 (10.6)	18 (10.2)
Of which symptomatic (%)	8 (6.1)	3 (6.4)	11 (6.2)
No. of patients without new DWI lesions (%)	94 (72.3)	37 (78.7)	131 (74.0)
Total	130	47	177

There were no statistically significant differences between the occurrence of any, large, or symptomatic lesions in the groups

Table 3 Occurrence of new DWI lesions with regard to location

	New DWI lesion		Total no. of patients	Monivariate <i>P</i>	Multivariate <i>P</i>
	No	Yes			
Location					
Frontal	20	3	23	0.201	0.419
Insular	0	2	2	0.069	0.006 ^a
Occipital	11	2	13	0.519	0.454
Opercular	2	4	6	0.040 ^a	0.009 ^a
Temporal	39	30	69	<0.001 ^a	0.013 ^a
Parafalxial	11	1	12	0.190	0.576
Postcentral	18	4	22	0.447	0.210
Precentral	13	1	14	0.115	0.888
Temporo-occipital	15	1	16	0.074	0.958
Total	131	46	177		

In multivariate logistic regression analysis with “occurrence of new DWI lesions” as the dependent variable, the factors “repeat operation”, “age > 65”, “KPS > 70”, “initial WHO Grade” and “location” were included

^a The occurrence of new DWI lesions is significantly higher for insular, opercular, and temporal tumors

introduced a clinical scale for prediction of survival of patients undergoing surgery for recurrent GBM, thus facilitating patient selection.

Most previous studies have focused on non-ischemic complications, e.g. wound-healing disturbances or cerebrospinal fluid leaks. They are known to occur more frequently after repeat surgery than after first surgery [12], but deficits explicitly attributable to perioperative ischemia are most often unreported. Our findings, together with the existing literature, can help clinicians to guide and advise patients in the event of tumor recurrence.

DWI sequences are widely used to detect acute ischemic brain injury [19]. We report here that the occurrence of new DWI lesions on postoperative MRI scans does not differ significantly between first and repeat surgery. Furthermore, the proportion of patients suffering neurologic worsening also did not differ between first and repeat surgery.

Estimating the general risk of developing postoperative infarction after neurosurgical procedures remains controversial. In our series, the incidence of perioperative infarction was 25%, which is rather low compared with previous studies: reportedly, as many as 60–70% [22–24]

of patients show areas of reduced diffusion. New neurologic deficits, if they had been reported, were attributable to new DWI lesions in up to 20% [22]. More generally, encompassing any reason for neurologic deterioration, reported incidence of complications ranges between 42.5 and 4.2% [4, 12, 25–28].

In one of the largest series published on complications in glioma surgery, Chang et al. [12] reported significantly different neurological worsening between first and repeat surgery (18 vs. 8%). Their results, based on 499 patients undergoing first or repeat surgery, and data from Barker et al. [25] with a 25% incidence of neurological worsening after repeat surgery, seem to contradict our findings. However, we do not report the incidence of neurologic worsening attributable to any cause except new DWI lesions. We left out cases in which worsening was attributable to the surgery itself, e.g. in a patient with a temporal or parietal tumor experiencing a new visual field deficit explained by deliberate surgical disruption of the optic radiation after tumor removal in the temporal or parietal lobe.

Our results are comparable with those of Khan et al. [29] who, in a heterogeneous series including metastases and

gliomas, saw only 19% new DWI-positive lesions with 11% of patients having new neurologic deficits. Our observed frequency of DWI lesions is not explained by lower sensitivity for detecting DWI-signal alterations, because MRI scanning modalities of the former studies were comparable with ours, and lesions as small as 0.3 cm³ were recorded [24].

In our study the site of the tumor, but not repeat resection, was the only risk factor in the development of new DWI lesions according to multivariate analysis. This strengthens the idea that location should be a major factor in risk assessment for postoperative ischemic injury. Park et al. [21] have already included and validated brain areas directly adjacent to the M1 and/or M2 segments of the MCA in their scale for prediction of survival after recurrent GBM operations, but they did not address postoperative patient status. On this basis, we stratified tumor location into “risky” and “non-risky” areas in our series; there was no statistically significant difference between patients undergoing first and repeat surgery, which makes a selection bias unlikely and strengthens our conclusion that repeat surgery alone does not impose greater risks in terms of ischemic deficits.

Kumabe et al. [30] investigated ischemic complications associated with resection of opercular gliomas and found infarction in 100% of the patients studied, possibly related to disruption of arteries from the insula to the corona radiata. Incidence of new DWI lesions in insular gliomas has, unfortunately, not been reported in the largest series published so far [31, 32] but this location per se carries a higher risk of ischemic injury [33]. Our findings seemingly support the aforementioned studies, but the small number of insular and opercular tumors in our series is a limitation.

Different mechanisms can lead to ischemic injury and DWI lesions [32]. Because all lesions in this study occurred around the resection cavity and because T2-shine-through effects were excluded, vessel injury—arterial or venous—is the most likely cause of the DWI lesions. We did not differentiate between arterial infarction, venous stasis, and other possible mechanisms, which eventually does not matter for the individual patient suffering a new deficit. Avoiding vessel injury during resection is the best way of preventing ischemia and applies to both arterial and venous vessels.

Most of our patients are referred to our service from many different institutions; all patients had undergone pre and postcontrast T1 and T2-weighted imaging outside our institution. Although DWI scans were not routinely available preoperatively, it is unlikely they were present preoperatively, because the lesions were all located around the resection cavity and these lesions were not evident on preoperative T2-weighted images, indicating that the lesions occurred in the perioperative phase [34].

Retraction of brain tissue during surgery is sometimes made responsible for the smaller areas of restricted diffusion around the resection cavity [22]. This might explain some of the small DWI lesions around the resection cavity. Because less brain retraction is required in surgery for recurrent gliomas, and because we did not see a difference in occurrence between newly diagnosed and recurrent gliomas, this mechanism becomes less likely.

Rather, our small number of patients with large DWI lesions and symptomatic ischemic areas supports our surgical strategy to avoid vascular injury. With subpial dissection techniques, we avoid vessels coming from the subarachnoid space to nourish the deep white matter, which may cross the resection area and lead to infarction of more deeply seated structures [35]. IOM techniques can help to stop resection in critical subcortical areas [36, 37], but there is no reliable warning sign when vasculature is disrupted.

In an attempt to provide a rationale to support repeat surgery, Xu et al. [13] reported the survival of 21 patients undergoing re-craniotomy to be better than that of a control group, although groups may not have been truly balanced for prognostic factors such as patient age, WHO grade, or KPS score in their study. The median survival of our patients was ~15 months after repeat surgery and thus longer than for their series and for another recent report [13, 19]. However, all patients in our series received adjuvant therapy after repeat resection, which is known to be more effective than repeat surgery alone [4, 7]. It is a limitation of our study that we did not compare survival and quality of life after repeat surgery with a control group of patients not undergoing repeat surgery in the event of tumor regrowth. Thus, we cannot prove that repeat resection is beneficial to the individual patient. Our data may rather help to guide clinicians on multidisciplinary tumor boards.

Repeat surgery, especially where complete resection of the recurrence can be achieved [38], should not be withheld as a treatment option for patients with recurrent gliomas for fear of a higher risk of postoperative infarction or new neurologic deficit than the primary surgery. Adjuvant treatment is nonetheless warranted.

Conclusion

Repeat surgery for gliomas does not per se carry a higher risk of development of new postoperative DWI lesions than first resection, if meticulous microsurgical techniques are applied. Thus, weighing risk and benefits, repeat surgery should not be withheld as a treatment option for patients with recurrent gliomas for fear of a greater risk of postoperative infarction or new neurologic deficit than the

primary surgery. The main risk factor for new postoperative DWI lesions seems to be tumor location in the insular, opercular, or temporal region.

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Conflict of interest The authors declare that they have no conflict of interest.

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