14 Recurring Glioblastoma: A Case for Reoperation?

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Doi: http://dx.doi.org/10.15586/codon.glioblastoma.2017.ch14

Abstract: Unlike newly diagnosed glioblastoma, no clear or widely accepted standard of care is available for patients with a recurrence. A purely radiological diagnosis of recurrence or progression can be hampered by flaws induced by pseudoprogression, pseudoresponse, or radionecrosis. Based on parameters like tumor location and volume, patient's performance status, time from initial diagnosis, and availability of alternative salvage therapies, reoperation can be considered as a treatment option to extend the overall survival and quality of life of the patient. The achieved extent of resection of the relapsed tumor—especially with the intention of having a safe, complete resection of the enhancing tumor—most likely plays a crucial role in the ultimate outcome and prognosis of the patient, regardless of other modes of treatment. Validated scores to predict the prognosis after reoperation of a patient with a recurrent glioblastoma can help to select suitable candidates for surgery. Safety issues and complication avoidance are pivotal to maximally preserve the patient's quality of life. Besides a possible direct oncological effect, resampling of the recurrent tumor with detailed pathological and molecular analysis might have an impact on the development, testing, and validation of new salvage therapies.

Key words: Prognosis; Recurrence; Relapse; Reoperation; Resampling

In: *Glioblastoma*. Steven De Vleeschouwer (Editor), Codon Publications, Brisbane, Australia
ISBN: 978-0-9944381-2-6; Doi: http://dx.doi.org/10.15586/codon.glioblastoma.2017

Introduction

Maximal safe debulking surgery is well accepted as the mainstay treatment for newly diagnosed glioblastoma (GBM), and postoperative radiochemotherapy was determined in 2005 as the standard of care (SOC) by a pivotal phase 3 randomized trial by the European Organisation for the Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trials Group (NCIC) (1, 2). According to this trial, adult patients, up to the age of 70, with newly diagnosed GBM are being treated with 6 weeks of radiotherapy with concomitant temozolomide chemotherapy, followed by six adjuvant cycles of adjuvant temozolomide. However, despite multimodal therapy, prognosis for GBM patients remains poor with a median progression-free survival (PFS) of only 6.9 months, median overall survival (OS) of 14.6 months, and a 5-year survival rate of 9.8%. The low PFS is also reflected in the fact that less than 50% of patients completed the six cycles of adjuvant temozolomide in the EORTC–NCIC trial.

Notwithstanding intense preclinical research and clinical trials, standard therapy has not changed over the past decade. New agents with promising results in Phase 1 and/or Phase 2 trials, for example, the Vascular Endothelial Growth Factor-A (VEGF-A) Inhibitor bevacizumab or the integrin inhibitor Cilengitide, failed to improve survival in randomized phase 3 trials (3, 4). Moreover, in an effort to optimize the current chemotherapy, a dose-dense schedule of adjuvant temozolomide did not lead to improved survival (5). Recurrence, regrowth of tumor after a period of complete remission or stable disease, is universal. Unlike the well-defined treatment schedule in the newly diagnosed setting, no standard therapy exists for recurrent GBM. Treatment options in the recurrent setting include reoperation, re-irradiation, rechallenge temozolomide, or nitrosourea chemotherapy (e.g., lomustin [CCNU]), bevacizumab, or combinations of therapies (6). Given the absence of SOC, inclusion in clinical trials is optional upon recurrence. Whichever therapy is given, prognosis at recurrence is grim, with median survival in recent years estimated to be about 9 months and only one-third of patients alive after 1 year (7). Eventually, GBM will recur and lead to progressive neurological deterioration and death. Preserving quality of life (QoL) for as long as possible, therefore, becomes a priority in this palliative oncological setting.

Radiological Diagnosis of a Recurrence in Clinical Practice

During follow-up of GBM patients, most oncologists will perform an MRI scan every 2–3 months, or earlier upon clinical deterioration (8). This regular MRI scan will detect many recurrences in the early phase, often in asymptomatic patients. However, interpretation of these follow-up MRI scans can be challenging in the context of possible appearance of contrast enhancement due to radionecrosis or pseudoprogression in patients treated with radiotherapy and chemotherapy. Pseudoprogression is thought to occur in up to 50% of patients during the first 3–6 months after radiotherapy, whereas radionecrosis can occur up to several years after treatment and does not spontaneously regress without treatment (9).

As much as 15% of samples after reoperation showed only radionecrosis but no viable tumor in a series by Azoulay et al. (10). Moreover, bevacizumab, which is often used to treat recurrent GBM, compromises interpretation of follow-up MRIs as it normalizes leaky tumor vasculature and hence decreases T1 gadolinium enhancement and peritumoral edema (11, 12), sometimes resulting in only a pseudoresponse. To assess progressive disease, it is therefore recommended to use the recent Response Assessment in Neuro-Oncology (RANO) criteria that include evaluation of corticosteroid use, T2/FLAIR images, and restricted parameters to determine progressive disease during the first 3 months after radiochemotherapy, instead of the classical MacDonald criteria (13).

When there is a clear relapse or high suspicion of a (symptomatic) recurrence for which new treatment has to be initiated, a neurosurgeon should always be consulted to assess whether the patient is suitable for a repeat surgery. In general, it is estimated that only about 25% of patients can be considered for repeat surgery (6). Certainly, in the case in which clinical symptoms are due to mass effect, surgery remains the only treatment strategy that can drastically and rapidly decrease tumor load and possible symptoms. This can alleviate symptoms such as headache and (more rapidly) reduce the need for steroids to decrease peritumoral edema (14, 15). On the other hand a reoperation exposes patients to a risk of new temporary or permanent neurological deficits, general surgical and/or anesthesiological risks, and, at least temporarily, exclusion from other second-line treatments. Moreover, the oncological effect remains controversial (16).

Most recurrences appear locally in or close to the resection cavity of the first surgery (14). In a study by Brandes et al. on 79 patients with a recurrent GBM after initial treatment with standard therapy, almost 80% of recurrences occurred inside or at the margin of the radiotherapy field, where radiotherapy was administered at the contrast-enhancing mass with a margin of 2–3 cm (17). Rapp et al. reported on 97 recurrent GBM patients and found pure local recurrences in 79.3%, and combined local and distant recurrences in another 10.3% of patients (18). Obviously, diffuse, multifocal recurrences or deep infiltrative lesions are not surgical indications, contrary to a local well-circumscribed lesion. However, many patients will present with a local but poorly delineated lesion, for which a surgical indication cannot be advocated based on radiology alone.

Clinical Outcome after Surgery for Recurrent GBM

INHERENT SELECTION BIAS LEADS TO BETTER OUTCOME IN SURGICALLY TREATED RECURRENT PATIENTS

No randomized trials exist that randomize patients for surgery in the relapse setting, and most reported surgical series in recurrent GBM are retrospective (15). An overview of selected surgical outcome series is given in Table 1. Several authors have reported better outcome after surgery for recurrent GBM, compared to control nonsurgical populations. However, we have to take into account that these reports inherently suffer from selection bias, as patients who are selected for reoperation usually tend to be younger and have a better Karnofsky Performance Scale (KPS), and hence belong to a more favorable prognostic group (19). Azoulay et al. compared 68 reoperated patients with a matched

TABLE 1 **Selected Surgical Series Reporting Outcomes after Reoperation for Recurrent GBM**

Ref.	Number of patients reoperated (only GBM)	Age at reoperation (median, unless otherwise specified)	Adjuvant therapy after reoperation	Median OS total	Median OS after reoperation	Control group
(25)	39	45.5 years	Chemotherapy (not further specified)	82 weeks	36 weeks	AA: median OS after reoperation: 88 weeks
(24)	35 (20 AA)	48 years (grades 3 + 4, not given for GBM separately)	55%: CT 13%: CT and radiotherapy 7%: Radiotherapy (grades 3 + 4, not given for GBM separately)	76.4 weeks (GBM only)	29 weeks (GBM only)	AA: median OS after reoperation: 61.1 weeks
(40)	60	48 years (mean)	22%: CT 22%: Radiotherapy and CT 8%: Radiotherapy	72.5 weeks	18.5 weeks	AA: median OS after reoperation: 55 weeks
(41)	20	51 years(only reoperation) 52 years (reoperation and CT/SRS)	45%: Only reoperation 45%: CT 10%: SRS	Not given	13 weeks (only reoperation) 34 weeks (reoperation and CT/SRS)	Nonsurgical recurrent GBM patients: median OS after reoperation: 28 weeks

TABLE 1 **Selected Surgical Series Reporting Outcomes after Reoperation for Recurrent GBM** (Continued)

Ref.	Number of patients reoperated (only GBM)	Age at reoperation (median, unless otherwise specified)	Adjuvant therapy after reoperation	Median OS total	Median OS after reoperation	Control group
(22)	168: 1 reoperation 41: 2 reoperations 15: 3 reoperations	51 years (mean) (1 reoperation) 46 years (mean) (2 reoperations) 40 years (mean) (3 reoperations)	Not given	15.5 months (1 reoperation) 22.4 months: (2 reoperations) 26.6 months: (3 reoperations)	Not given	None (only case control between patients with 1, 2, or 3 reoperations matched for other prognostic variables)
(27)	33	59 years (mean) (whole group, also nonsurgical patients)	48%: Adjuvant therapy (not further specified)	Not given	6 months: (only reoperation) 14 months: (reoperation and adjuvant therapy)	Nonsurgical recurrent GBM patients that received CT alone (24 patients): median OS after recurrence: 8 months Group that received palliative treatment (19 patients): median OS after recurrence: 5 months
(52)	40	58 years	7.5%: Radiotherapy 48%: CT 7.5%: CT and radiotherapy	21.7 months	13.0 months	None
(20)	20	53.5 years (mean)	40%: CT 10%: Radiotherapy 20%: CT and radiotherapy 30%: Palliative treatment	25.4 months (reoperation) 11.6 months (nonsurgical group)	13.5 months (reoperation) 5.8 months (nonsurgical group)	Nonsurgical recurrent GBM patients (45) Median OS after recurrence: 5.8 months

Table continued on following page

TABLE 1 **Selected Surgical Series Reporting Outcomes after Reoperation for Recurrent GBM** (Continued)

Ref.	Number of patients reoperated (only GBM)	Age at reoperation (median, unless otherwise specified)	Adjuvant therapy after reoperation	Median OS total	Median OS after reoperation	Control group
(21)	49	59 years	Not given	20.1 months	7.6 months	Nonsurgical recurrent GBM patients (155): median OS 13.4 months
(26)	48	Not given	81.3% additional systemic therapy of which: 71.8% chemotherapy 23.1% fotemustine and bevacizumab 5.1% re-irradiation and temozolomide	21 months	7 months	None
(30)	503	58 years	57.1%: CT 25.5%: Palliative treatment 14.4%: CT and radiotherapy 3.1%: Radiotherapy	25 months	11.9 months	None
(10)	69	56 years	59.4% radio and/or CT	Not given	9.8 months	Matched nonsurgical group of 68 patients: median OS 5.3 months versus 9.6 months in matched reoperated patients

AA, Anaplastic Astrocytoma; CT, Chemotherapy; GBM, Glioblastoma; SRS, stereotactic radiosurgery.

cohort of nonsurgically treated recurrent GBM patients, based on initial extent of resection (EOR) and subventricular zone involvement (10). Median OS in the surgical subgroup was 9.6 months versus 5.3 months in the nonsurgical group, which was statistically significant. They concluded that reoperation, combined with additional rescue therapies, can induce prolonged survival in recurrent GBM. Chen et al. described 65 recurrent GBM patients, of whom 20 were reoperated. Median OS after recurrence in the surgical group was statistically higher with 13.5 months versus 5.8 months in the nonsurgical group (20). However, KPS at recurrence was also significantly higher in the surgical group, and 77.8% of the nonsurgical group received only palliative therapy. Tully et al. described 204 GBM patients of whom 24% were reoperated at recurrence, and they found a significantly improved survival of 20.1 months in reoperated patients compared to 9.0 months in recurrent patients who were treated nonsurgically (21). In their series, reoperated patients were younger, had a smaller initial tumor diameter, and were more likely to have an initial EOR of ≥50% at first resection. Moreover, reoperated patients had a significantly higher percentage of completion of adjuvant therapy (79.6% vs. 35.9%). To compensate for this selection bias, patients that were *a priori* unlikely to be selected for reoperation based on age or performance scale were excluded in a subgroup analysis. A much less significant, though still present, advantage for the surgical group was found at first recurrence, but not anymore at second recurrence. Moreover, reoperation was no longer an independent predictor of OS in a multivariate analysis. The authors suggested that the improved OS in the surgical group might be more of a reflection of favorable patient characteristics than surgery itself. Chaichana et al. showed a survival benefit resulting from repeat resections using a multivariate analysis and case control evaluation to correct for selection bias (22). In their series, median survival was 6.8 months for patients that had one resection versus 26.6 months for patients that underwent four resections. Very often, a more favorable course of disease and pattern of recurrence render these patients eligible for reoperation rather than vice versa (Figure 1).

On the other hand several authors did not find a survival advantage for surgery. Franceschi et al. reported outcomes of a retrospective study on 232 recurrent GBM patients of whom 102 were treated with reoperation and chemotherapy, and compared these patients with 130 recurrent patients who were treated only with chemotherapy. They did not find a survival advantage in the reoperation group (23). In a large prospective registry database, including >1000 patients treated from 1997 to 2010, Nava et al. did not find better survival after recurrence in patients that underwent a reoperation. However, this study did not provide data on patient stratification at recurrence or EOR (7).

KARNOFSKY PERFORMANCE SCALE AND AGE AT RECURRENCE

The importance of patient characteristics at recurrence cannot be overestimated. Several older surgical outcome series have identified preoperative KPS as an important factor related to survival (24) or prolonged high QoL survival after recurrence (25). Also, KPS at recurrence in many studies turned out to be associated with better OS (19, 26–30). Patients with a poor performance scale are generally not proposed to undergo repeat surgery. A KPS of ≥70, which means the patient is able to take care of himself or herself but cannot perform normal

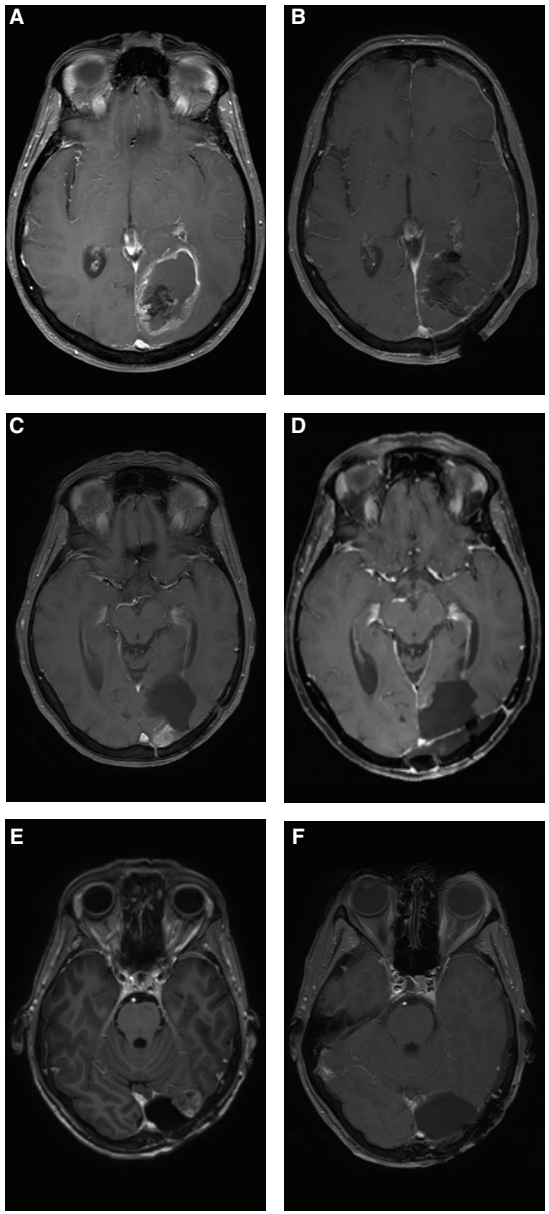

Figure 1 A 57-year-old lady was diagnosed with a left occipital glioblastoma (A), for which a total resection was performed (B). She was treated with standard radiotherapy, temozolomide chemotherapy, and experimental dendritic cell vaccination. An asymptomatic recurrence in the medial wall of the resection cavity was seen in a routine follow-up scan 16 months after the first surgery **(C)**. A second total resection was performed **(D)**, after which combined CCNU and bevacizumab was given in the EORTC 26101 study. A second asymptomatic local recurrence at the lateral side of the resection cavity was seen 14 months later **(E)**, and again a total resection was performed **(F)**. Nine months later she developed a multifocal progression, resistant to temozolomide. She died 42 months after the first surgery.

daily work, is generally accepted as a cut-off to select patients fit for surgery. The influence of age *per se* seems to be less pronounced in the absence of a good KPS, and reoperations in selected elderly patients were reported to be still feasible (31).

SCALES TO PREDICT SURVIVAL AFTER SURGERY FOR RECURRENT GBM

Two helpful prognostic scales to select patients for recurrent surgery are available. In 2010, Park et al. published a scale based on factors significantly associated with poor postoperative survival: involvement of ≥2 eloquent/critical brain regions, KPS ≤ 80, and tumor volume of ≥50 cm^3 (32). An additive scale based on these three variables stratified patients into good, intermediate, and poor postoperative survival groups. The authors were able to validate their score in a cohort of 109 recurrent GBM patients with a median survival of 9.2, 6.3, and 1.9 months in the three respective predictive groups. Patients with a poor prognosis as defined by this scale do not seem to have a benefit from reoperations. The applicability of this scale has been questioned, as the estimation of eloquent brain regions (referred to as MSM-score after involvement of motor or speech areas or involvement of middle cerebral artery areas) is somewhat subjective, and tumor volume is not always easy to measure. In 2013, Park et al. introduced a simpler prognostic scale (33) that combined one clinical parameter with one radiological parameter. A 0–2 points score was given based on KPS (≥70 or <70) and the presence or absence of ependymal involvement in contrast MRI. This score distinguished patients with good, intermediate, and poor prognosis with median OS of 18.0, 10.0, and 4.0 months, respectively. For patients with a poor prognosis, surgery was not recommended.

Extent of Resection in the Recurrent Glioblastoma

EXTENT OF RESECTION: EQUALLY IMPORTANT AT RECURRENCE?

In a newly diagnosed GBM, it is generally accepted that an improved EOR is an independent prognostic factor for better outcome. A significant benefit on OS was present when EOR was at least 78%, with a further stepwise improvement with an EOR in the 95–100% range (34). The survival benefit for complete versus incomplete resection was estimated to be almost 5 months in a post hoc analysis on patients initially included in the 5-ALA trial by Stummer et al. (35).

In recurrent GBM patients, the importance of improving EOR is less universally accepted with highly variable survival rates in the literature. However, in recent years, several authors have reported a better OS when a higher EOR was achieved in the recurrent setting. McGirt et al. described a significantly improved OS after gross total (GTR) or near resection (NTR) compared to a subtotal resection (STR) in a study on 294 reoperated patients. Median survival for GTR and NTR were 11 and 9 months, respectively, versus 5 months for STR (28). Also, Bloch et al. showed in a series of 107 patients undergoing reoperation for recurrent GBM that EOR at reoperation was a significant predictor of OS. Interestingly, EOR at first resection was not a statistically significant factor when EOR at reoperation was included in a Cox proportional hazards model, suggesting that a

complete resection at reoperation could overcome an initial STR (19). A large retrospective study by Ringel et al. described outcomes in 503 reoperated patients (30). In this series, EOR at reoperation was also found to be significantly associated with better outcome. Also, these authors concluded that a complete resection at first recurrence could compensate for an incomplete resection at the initial surgery. The authors of the two last mentioned studies favored an aggressive surgical resection in recurrent GBM, as the improved survival with higher EOR suggested a real oncological effect, not a reflection of the selection of younger patients with higher KPS for recurrence surgery. Oppenlander et al. reported on 170 patients reoperated for recurrent GBM. They also found EOR to be significantly associated with OS following repeat resection. A threshold of at minimum 80% EOR was calculated to offer a significant survival benefit, suggesting usefulness of repeat surgery even if only a STR can be achieved (36). Also, Perrini et al. found EOR at reoperation to be associated with longer OS in a multivariate analysis of 48 reoperated patients (26).

In a smaller series, however, De Bonis et al. did not find a survival advantage for patients who received a GTR (11 patients) versus partial resection (22 patients) (27). Suchorska et al. analyzed post hoc the influence of reoperation in patients of the DIRECTOR trial, originally designed to test different dosing schemes of temozolomide administered at recurrence. Patients who were reoperated before entry into the study had similar prognostic factors (age, KPS, MGMT promotor methylation) than patients who were not reoperated. OS was not different between the two groups. However, the subgroup of patients that had a complete resection had a significantly better OS than nonsurgical patients, and patients with an incomplete resection showed a trend toward a worse prognosis than nonsurgical patients. The authors concluded that reoperation improved survival if complete resection of contrast-enhancing tumor (CRET) could be achieved (37).

IMPROVING RESECTION IN THE RECURRENT SETTING

Surgery for recurrent GBM can be technically more demanding, as the tumor is usually more invasive, and anatomical margins are less-defined than initially due to post-treatment gliosis (14). Given the growing evidence to obtain a maximal resection in the recurrent setting, surgical adjuncts such as intraoperative navigation, functional mapping, intraoperative ultrasound, and/or intraoperative MRI can be useful. To maximize EOR, the use of 5-aminolevulinic acid has been shown to lead to more complete resection and improved PFS in newly diagnosed GBM (38). In surgery for recurrent GBM, the use of 5-ALA has also been shown to have a high predictive value for detection of tumor cells and, importantly, did not seem to be affected by prior radiotherapy and/or chemotherapy (39).

Surgical Risks and Complications at Reoperation

In 1987, Ammirati et al. reported an early mortality rate of 1.4% and surgical morbidity of 16% per procedure. In their series on reoperated malignant glioma patients, they found that 46% of patients improved on performance scale

after surgery but also found worsening in 25% of patients. Harsh et al. had a 5.1% mortality and 7.7% morbidity (25). Sipos and Afra found a 3.4% mortality rate in 60 reoperated GBM patients (40). In their series, patients with a lower preoperative KPs were more likely to deteriorate postoperatively. In a series of 20 reoperated GBM patients, Mandl et al. found a mortality of 15%, and permanent neurological morbidity of 15% (41). Moreover, 40% of patients had a worse KPS postoperatively. More recently, in a series of 503 reoperated patients, Ringel et al. found a nonneurological complication rate of 7.4% (30). New neurological deficits appeared in 16.8% of patients, of which 9.2% were transient and 7.6% were permanent. The authors concluded that complications in reoperations are higher than in primary surgery, but the increase is rather small, and the overall complication rate stayed fairly small. D'Amico et al. published a retrospective study of 28 patients aged ≥65 years operated for recurrent GBM (31). In their study, no postoperative mortality was seen after reoperation, and the overall complication rate in reoperated patients was 17.9% at first surgery and 25.8% at reoperation. This difference was not statistically significant, and the authors concluded that age itself should not exclude patients from repeat surgeries. In summary, combined mortality and morbidity rates of repeat surgery can be estimated to be around 12–30%. This should always be taken into account, as the goal of surgery in recurrent GBM is essentially prolonging survival with good QoL.

Beyond Cytoreduction: Additional Benefits of Surgery

TISSUE DIAGNOSIS AND SUBCLASSIFICATION

Surgery has the advantage over other treatment strategies by providing clinicians with a new tissue diagnosis. This can be important when radiology remains uncertain about possible pseudoprogression, real progression, or radionecrosis. If the diagnosis of a recurrence based on radiology, supplemented with nuclear imaging techniques, remains uncertain, surgery provides a unique opportunity for tissue confirmation of tumor regrowth or presence of viable tumor tissue (42), although no wide consensus exists about resampling pathology as the gold standard to confirm or definitively exclude pseudoprogression. Although currently not part of clinical practice, there is growing interest in the molecular subclassification of GBM to propel (personalized) experimental salvage treatments. Several subtypes of GBM have been described based on gene-expression profiles (43) and DNA methylation patterns (44). These subclassifications are already used to stratify and/or select patients in early clinical trials evaluating new anti-tumoral agents. For example, it has been shown that the mesenchymal subtype correlates with poor radiation response and shorter survival (45) but may be more immunogenic and respond better to immunotherapy (46). Moreover, Phillips et al. showed that upon recurrence, a class switch toward the mesenchymal subclass is frequently seen, showing that initial molecular diagnosis might not be easily extrapolated in the recurrence setting (47). As it is believed that these molecular genetic data will become part of clinical trials, the possibility of obtaining new tissue at recurrence will be of interest for researchers and neurooncologists.

SURGERY TO OBTAIN A STATE OF MINIMAL RESIDUAL DISEASE

Surgery is unique due to the fact that it rapidly leads to at least a substantial reduction of the tumor mass. This can result in a (macroscopically) state of *minimal residual disease*, which can be of benefit for other therapies. Keles et al. published a study on 119 GBM patients who were treated with temozolomide upon recurrence. They showed that the residual tumor volume was a significant predictor for "time to progression" and "survival," even when adjusted for age, KPS, and time from initial diagnosis. They dichotomized between residual tumor volume of <10 cm^3, 10–15 cm^3, and >15 cm^3; this was correlated with 6 and 12 months of PFS and OS, respectively. Although only three patients (3%) were reoperated before the start of chemotherapy in this series, the authors suggest that debulking surgery with the intent to reduce tumor volume to less than 10 cm^3 could be considered before chemotherapy is commenced (48). Stummer et al. described that a complete resection not only improves survival by itself but also may enhance the efficacy of adjuvant therapies such as radiochemotherapy and BCNU wafers, based on post hoc analyses on data from three separate randomized phase 3 trials in newly diagnosed GBM (49).

SURGERY TO START LOCAL CHEMOTHERAPY

After resection of a recurrent GBM, the resection cavity can be implanted with carmustine wafers (Gliadel). The effects were evaluated in a randomized trial. Patients with recurrent GBM had a 50% increased survival (56% vs. 36%), without increased complications or toxicity (50). However, in a retrospective study comparing recurrent GBM patients treated with Gliadel with a matched cohort group, Subach et al. did report on increased complications without survival benefit (51). Currently, Gliadel is rarely being used in Europe (52), although Quick et al reported in their recent publication that some form of chemotherapy was used after reoperation in more than 50% of cases all together (52) (table 1).

Conclusion

No prospective randomized trials directly evaluating the effect of reoperation for recurrent GBM have been published, and almost all available outcome data in surgical series are blurred by the inherent selection bias of patients with a high performance score and local recurrences. However, literature provides some evidence for an oncological advantage when a high EOR (or a CRET) can be obtained. This judgment needs to be made by a multidisciplinary oncological team with oncological neurosurgeons. Besides a cytoreductive effect, surgery can have an important role in obtaining tissue. Given the future expected importance of subclassification of glioblastoma and/or detection of specific druggable mutations, surgery probably will remain an important treatment strategy in the recurrent setting.

Conflict of interest: Dr. S. De Vleeschouwer organizes Gliolan (5-ALA) training sessions for neurosurgeons, for which a fee is received from Medac GmbH.

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