Moving Second Courses of Radiotherapy Forward: Early Re-Irradiation After Surgical Resection for Recurrent Gliomas Improves Efficacy With Excellent Tolerability

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BACKGROUND: Generally, re-irradiation (Re-RT) is offered to patients with glioma recurrences with macroscopic lesions. Results are discussed controversially, and some centers postulate limited benefit of Re-RT. Re-RT is generally offered to tumors up to 4 cm in diameter. Re-resection is also discussed controversially; however, recent studies have shown significant benefit.

OBJECTIVE: To combine proactive re-resection and early Re-RT in patients with recurrent glioma.

METHODS: We included 108 patients treated between 2002 and 2016 for recurrent glioma. All patients underwent surgical resection for recurrence; Re-RT was applied with a median dose of 37.5 Gy (range 25 Gy-57 Gy/equivalent dose in 2Gy fractions [EQD2]) with high-precision techniques. All patients were followed prospectively in an interdisciplinary follow-up program.

RESULTS: Median follow-up after Re-RT was 7 mo. Median survival after surgery and Re-RT was 12 mo (range 1-102 mo). Complete resection had a significant impact on the outcome (P = .03). The strongest predictors of outcome were MGMT-promotor methylation and Karnofsky Performance Score and time interval between primary and second RT.

CONCLUSION: Proactive resection of tumor recurrences combined with early Re-RT conveys promising outcome in recurrent glioma. Complete resection and early Re-RT lead to improved survival. Thus, moving Re-RT to an earlier timepoint during the treatment of recurrent glioma, eg after complete macroscopic removal of the tumor, may be crucial for treatment optimization. Using advanced RT techniques, side effects are low. Currently, this concept is evaluated in the GLIOCAVE/NOA 17 trial.

KEY WORDS: Recurrent glioma, Surgical resection, Re-irradiation, Survival

RECURRENT GLIOMAS ARE A CHALLENGE FOR THE INTERDISCIPLINARY NEUROONCOLOGY TEAM; INDEPENDENT OF PRIMARY HISTOLOGY, SUBSTANTIAL TREATMENT RESISTANCE CHARACTERIZES MOST RECURRENCES. GENERALLY, THE OUTCOME FROM ANY MODALITY IS ONLY MODEST. SINCE RADIOTHERAPY (RT) IS A CENTRAL PART IN PRIMARY TREATMENT FOLLOWING NEUROSURGICAL RESECTION OR BIOPSY, MUCH CONTROVERSY EXISTS REGARDING ANY ADDITIONAL RADIATION TREATMENT. ON THE ONE HAND, THE FEAR OF EXCEEDING NORMAL TISSUE TOLERANCE AND THE ATTRIBUTED RISK OF SYMPTOMATIC SIDE EFFECTS HAVE DISTRACTED RADIATION ONCOLOGISTS FROM DELIVERING SECOND COURSES OF RT WITH HIGH DOSES.1-3 PRECLINICAL AND CLINICAL DATA HAVE REVELED THAT RADIATION MEMORY OF NORMAL TISSUE IS ONLY LIMITED OVER TIME. DEPENDING ON THE TIME INTERVAL BETWEEN PRIMARY AND SECOND RT, RE-IRRADIATIONS (RE-RT) EVEN WITH HIGHER LOCAL DOSES ARE SAFE.4 Thus, Re-RT concepts have evolved over time becoming a fundamental tool in the armamentarium at tumor recurrence.

ABBREVIATIONS: GBM, glioblastoma multiforme; EOR, extent of resection; EQD2, equivalent dose in 2Gy fractions; FSRT, fractionated stereotactic radiotherapy; KPS, Karnofsky Performance Score; MRI, magnetic resonance imaging; PTV, planning target volume; Re-RT, re-irradiation; RT, radiotherapy; WHO, World Health Organization

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Early studies applied only modest doses of Re-RT, and clinical results were not convincing. The availability of more precise radiation modalities has enabled the radiation oncologist to deliver local doses to precisely defined target volumes while sparing normal tissue: techniques such as radiosurgery, for smaller volumes, or fractionated stereotactic radiotherapy (FSRT) made widespread application of Re-RT in recurrent glioma possible. The first series reporting on a large group of patients with recurrent glioma prescribed 36 Gy in 2 Gy single fractions, and many centers initially followed this concept. Especially for patients with short intervals between primary and second RT, and/or with larger target volumes, such dose and fractionation concepts are safe; subsequent combination studies with systemic agents often retained this concept, avoiding any treatment-related side effects.

To allow for short survival times and the often-palliative situation, many argued for shorter treatment concepts; thus, hypofractionated regimens with single doses of 3 Gy or higher were utilized. However, doses of 5 Gy or higher have shown to be associated with a significantly increased risk of symptomatic necrosis requiring additional neurosurgical intervention. Considering these data, it seems there is a small therapeutic window for dose escalation, perhaps with smaller single doses, but increased total dose the dose-response relationship may be exploited more beneficially.

While most single-armed or retrospective studies report a favorable outcome of Re-RT, it must be kept in mind that most treatment decisions are individual concepts based on a highly selected patient population, especially against the background of very early and very large tumor recurrences in patients with poor performance status, where only the best supportive care may be recommended. Additionally, some randomized trials have questioned the value of Re-RT in recurrent glioma.

To address the question of why data on Re-RT appear controversial, and to exploit the full power of RT in a recurrent setting, detailed assessment of RT characteristics beyond time intervals, dose and fractionation are crucial. Target volume definition for Re-RT of recurrent glioma generally includes any contrast enhancing lesions on T1-weighted magnetic resonance imaging (MRI), adding a safety margin of approximately 5 mm. To encompass the real dimension of the tumor, the additional benefit of amino acid positron emission tomography (PET) has been evaluated and is currently being assessed in a prospective clinical trial.

One important factor on the outcome is extensive neurosurgical resection of glioma recurrences, where several groups have shown that the extent of resection (EOR) is correlated with outcome. Several smaller series have confirmed that surgery is a valuable tool at tumor recurrence, if safe maximal resection is feasible. A randomized prospective trial of the German Neurooncology Community (NOA) has shown that surgery at first recurrence of glioblastoma multiforme (GBM) improves outcome if complete resection of contrast-enhancing tumor is achieved. However, in alleged completely resected glioma recurrences, Re-RT is withheld—most likely due to historical reasons.

In this paper, we evaluate the impact of early Re-RT after neurosurgical resection in patients with recurrent gliomas as a preparation for a prospective clinical trial.

### METHODS

From the prospective institutional database of the Departments of Neurosurgery and Radiation Oncology, all patients with recurrent glioma treated with re-resection and Re-RT were selected. Of all 207 patients treated with Re-RT, 108 patients fulfilled these inclusion criteria. The study was approved by the local ethics committee (vote number 408/14). Patient informed consent was obtained for data collection and analysis when entering treatment in our center.

Of all patients, 65 were male (60%) and 43 were female (40%). Primary histology was categorized as World Health Organization (WHO) grade I in 1 patient (1%), grade II in 19 patients (17%), grade III in 18 patients (17%), and grade IV/GBM in 70 patients (65%). At recurrence, histology obtained from re-resection was classified as grade III in 26 patients (24%) and grade IV/GBM in 82 patients (76%). Detailed information on patient characteristics is shown in Table 1.

Indication for surgery was determined by the interdisciplinary tumor board depending on size and location as well as the patient performance score. Surgery was conducted as published previously, aiming at safe maximal resection based on contrast-enhanced CT and MR imaging taking into account mapping examinations as needed anatomically. Postoperative MR imaging within 48 h after surgery was performed in all patients. After surgery, all patients were treated with Re-RT. The median time between surgery and beginning of Re-RT was 2 mo (range 1-4 mo). Treatment planning was based on contrast-enhanced CT and MR imaging using a slice thickness of 1 to 3 mm. RT was delivered as high-precision RT in stereotactic setup using the Brainlab immobilization.
Dose and fractionation regimens were chosen depending on the size of the treatment volume, the time interval between first and second RT, as well as other patient-individual factors such as overall performance score. The gross tumor volume was defined as any contrast-enhancing regions including any parts of the resection cavity where postoperative enhancement was present which was not distinguishable between postoperative changes and tumor residuals. A safety margin of 5 to 10 mm was added for the clinical target volume including any nonenhancing tumor tissue. The median planning target volume (PTV) treated with Re-RT was 101 mL (range 2-480 mL). A median total dose of 37.5 Gy (range 25-57 Gy/ equivalent dose in 2Gy fractions [EQD2]) was applied. Most patients were treated with a total dose of 36 Gy in 2 Gy or 3 Gy single fractions. Dosing schedules depends on individual factors, such as time between initial RT and Re-RT, treatment volume as well as the physician’s preference. The anticipated and in most patients applied dose was 36 Gy in 2 Gy or 3 Gy single fractions based on institutional standard operations procedures.

All patients were enrolled into a tight clinical follow-up including regular imaging every 2 to 3 mo. Generally, contrast-enhanced MR imaging was scheduled, and additional CT and/or PET imagings were performed as needed clinically. Any further treatment decisions were made in an interdisciplinary tumor board. The mean follow-up time of re-treatment was 7 mo (range 1-91 mo). Survival times were calculated using the Kaplan-Meier method. Prognostic factors were evaluated using the log-rank test. All analyses were performed using the Statistica 6.1 Software (Statistica, StatSoft Inc, Tulsa, Oklahoma).

RESULTS

Treatment Tolerability

Re-RT after surgical resection could be completed without any high-grade side effects and without any interruptions of treatment. Common side effects included focal hair loss, nausea, fatigue, and headache. Steroids were not given on a routine basis, only if signs of elevated intracranial pressure, ie headache or nausea, were present.

The median time interval between first and second RT was 20 mo (range 3-229 mo). We did not see any correlation with treatment-related side effects and time to second RT. Notably, we did not see any symptomatic necrosis related to Re-RT.

Survival After Re-RT: Impact of Resection Status

To provide hard data on the effect of treatment, we focused on survival after Re-RT since progression-free survival might be biased by several factors, such as additional systemic treatment modifying imaging results, pseudo progression vs progression after Re-RT. The median survival after surgery and Re-RT was 12 mo (range 1-102 mo), calculated from the first day of Re-RT. Treatment failures were all within the RT fields and/or at the field borders. No out-of-field recurrences were observed.

Since all patients had a surgical intervention prior to Re-RT, we evaluated the impact of surgical extent on the outcome, calculated from surgical resection; patients with complete tumor resections showed a significant benefit in terms of survival compared to patients where only a partial resection of the tumor was possible (Figure 1; \( P = 0.033 \)).

Prognostic Factors for Outcome

The primary goal of the present work was to determine factors predicting outcome after Re-RT, including known prognostic factors such as age, gender, Karnofsky Performance Score (KPS), histology, MGMT-promotor methylation as well as the time between primary RT and Re-RT. The strongest predictors of outcome were MGMT-promotor methylation \(( P < 0.001; \text{ Figure 2A})\) and the time between first and second RT \(( P = 0.003; \text{ Figure 2B})\). In line with the literature, histology \(( P = 0.01), \text{ age } (<50 \text{ yr } \text{ vs } >50 \text{ yr}; \text{ P } = 0.03), \text{ KPS } (P = 0.02), \text{ and dose } (P = 0.02)\) were significant prognostic factors. However, gender did not show difference with respect to survival \((P = 0.2)\). The treatment volume (PTV) did not influence outcome significantly \((P = 0.056), \text{ but was close to the significance level.} \)

We subdivided treatment groups according to the total dose applied for tumor recurrence: group 1 received doses \( \leq 36 \text{ Gy} \), group B was treated with doses \(< 36 \text{ Gy} \) and \( \leq 38 \text{ Gy} \), group C was treated with total doses over \( 38 \text{ Gy} \) and \( \leq 40 \text{ Gy} \), and group D received doses beyond \( 40 \text{ Gy} \). Survival was significantly correlated with dose \((P = 0.02); \text{ however, group B was the largest group in the series thus deforming a clear linear dose-response relation (Figure 3).} \)

We performed multivariate analysis of prognostic factors on outcome after Re-RT; here, only the extent of neurosurgical resection \((P = 0.01), \text{ MGMT-methylation } (P = 0.001), \text{ time between initial RT and Re-RT } (P = 0.046), \text{ and KPS } (P = 0.003)\) were strong prognostic factors for survival after Re-RT; treatment volume remained close to the significance level \((P = 0.056)\). Results from the multivariate statistical analysis are shown in Table 2.

DISCUSSION

Although discussed controversially, the value of re-resection in recurrent glioma is considerable and should be evaluated for every patient. Followed by early Re-RT, the benefit of locally intensified treatment contributes to prolonged outcome and demonstrated increased efficacy compared to other Re-RT strategies. Even in patients with completely resected lesions, Re-RT is a powerful tool to consolidate tumor control and subsequently extend survival. In this paper, we report on the outcome of resection of recurrent glioma followed by early Re-RT; compared to all data on Re-RT in the literature, this is the first report on Re-RT following neurosurgical resection. The novelty of the present data is underlined by the fact that the patients with complete removal of the recurrence followed by Re-RT to the resection cavity present with the longest survival times. This is in contrast to most Re-RT studies guiding the dose to macroscopic tumor remnants.

While all treatment decisions in cases of glioma recurrences remain individual to a certain extent, the value of surgery and Re-RT cannot be rationalized. Due to the anatomical extensions of some tumors, the eloquence of certain structures, as
FIGURE 1. Survival after surgery and Re-RT: EOR has a substantial impact on outcome ($P = .03$).

well as volume limitations and the patients’ clinical performance status, surgery may not be a recommendable option in all patients. Indications have to be evaluated on a case-by-case basis. Keeping in mind maximal safe resection, however, the value of additional interventions in cases of recurrence has been shown by several groups. Only recently, a multicenter analysis by the German Neurosurgical Society reported survival times of 11.9 mo after resection at first recurrence in 503 patients with recurrent gliomas. The EOR had a significant impact on the outcome, as well as KPS or any additional chemotherapy. While many institutions had contributed and anatomical situations varied, still the rate of new permanent deficits after first re-resection was as low as 8%. Bloch et al also demonstrated in 107 patients with recurrent glioma that the gross tumor resection at recurrence had a significant impact on survival. Oppenlander et al postulated that the benefit is only if resection is beyond 80%; others prefer to limit indication to symptomatic patients. Thorough clinical workup and extensive and recent neuroimaging are essential for decision making. Additionally, intensive discussion with patients and their families on the potential risks and side effects is essential. An exact prediction of outcome cannot be made in all cases; intensive counseling on the risks and benefits is essential.

Re-RT has been established as a central pillar for the treatment of recurrent gliomas. Initially, lower doses of Re-RT of up to 30 Gy were applied, with small single doses. This was mostly due to the fear of treatment-related side effects with older radiation techniques, where normal tissue could not be spared effectively. Therefore, only limited patients were treated, with only modest benefit. With the advent of more precise radiation techniques and the increasing knowledge on normal tissue tolerance, Re-RT was offered to continuously increasing numbers of patients, and innovative dosing schedules were used. One of the first studies reported on 172 patients with recurrent glioma treated with FSRT with a median dose of 36 Gy in 2 Gy single fractions: median survival after Re-RT was 8 mo in GBM, 16 mo in grade 3 tumors, and 22 mo in patients with low-grade gliomas. While some centers adhered to smaller single doses while increasing total dose, others focus on more hypofractionated regimens with single doses of 3 Gy, 3.5 Gy or even higher. To reduce overall treatment time and to take into account the palliative nature of the clinical situation, many groups have argued for high single doses, even up to 5 Gy or 6 Gy: In these series, high rates of symptomatic necroses requiring neurosurgical interventions were reported, while on the other hand a benefit of doses exceeding 40 Gy was observed.

While patient populations are generally heterogeneous, all studies on Re-RT had 1 fact in common: the indication was seen only in patients with macroscopic tumors. In cases where neurosurgical resection was possible and the tumor could be removed, radiation oncologists did generally not indicate Re-RT. In those patients, often a wait-and-see strategy or systemic treatments were prescribed. However, local control is the central problem in glioma patients; thus, local treatment intensification is perhaps the most effective treatment. Therefore, even in patients with...
FIGURE 2. Prognostic factors for survival after surgery and Re-RT: MGMT-promotor methylation (A, \( P = .001 \)), and time between first and second radiotherapy (B, \( P = .046 \)) were the strongest prognostic factors.
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FIGURE 3. Total dose applied for Re-RT is correlated with survival after Re-RT ($P = .056$).

Table 2. Multivariate Analysis of Prognostic Factors on Survival From Re-irradiation.

<table>
<thead>
<tr>
<th>Multivariate analyses</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>7.073</td>
<td>0.079–633.556</td>
<td>.166</td>
</tr>
<tr>
<td>Age (≥50 yr vs &lt;50 yr)</td>
<td>4.286</td>
<td>0.377–48.736</td>
<td>.241</td>
</tr>
<tr>
<td>Time between primary RT and Re-RT (&gt;12 min vs ≤12 min)</td>
<td>0.136</td>
<td>0.019–0.965</td>
<td>.046</td>
</tr>
<tr>
<td>KPS (≥80% vs &lt;80%)</td>
<td>16.367</td>
<td>2.671–100.315</td>
<td>.003</td>
</tr>
<tr>
<td>Extent of resection</td>
<td>0.091</td>
<td>0.015–0.557</td>
<td>.01</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>1.568</td>
<td>0.274–8.953</td>
<td>.613</td>
</tr>
<tr>
<td>PTV (&lt;50 mL vs &gt;50 mL)</td>
<td>0.200</td>
<td>0.039–1.040</td>
<td>.056</td>
</tr>
<tr>
<td>MGMT-promotor (methylated vs not methylated)</td>
<td>0.015</td>
<td>0.001–0.195</td>
<td>.001</td>
</tr>
<tr>
<td>Dose group</td>
<td>0.866</td>
<td>0.089–8.394</td>
<td>.516</td>
</tr>
</tbody>
</table>

To further improve treatment, the combination of Re-RT and systemic treatments, such as temozolomide, or other systemic agents, e.g., bevacizumab or APG 101, were evaluated. Depending on prior treatments, such combination regimens might further improve outcome. However, past combinations only modestly showed an increase in the outcome, while toxicity profiles seemed to add up, especially with older agents.
Summing up all data from the literature, it seems necessary to rethink Re-RT in terms of target volumes, dosing regimens or the ideal time point. Previously, Grosu et al. postulated that target volumes for Re-RT should be based on amino-acid PET imaging in addition to MRI. Others have confirmed the additional importance of PET imaging for target delineation, and the impact of imaging on the outcome after Re-RT is currently being assessed in a prospective randomized trial. In our view, based on the present data, Re-RT should not be restricted to situations with macroscopic tumor residuals, but should be brought forward in the sequence of treatment events to early phases after complete resections of recurrent lesions. As stated above, EOR has a significant impact on outcome; the present data support this idea and demonstrate that the outcome after Re-RT is correlated with EOR. Palmer et al. however reported on 231 patients treated with re-resection and Re-RT but could not show a benefit from surgery; however, no distinction between EOR has been made. Fogh et al., while applying a more hypofractionated Re-RT regimen, did also not find a better outcome after surgery and Re-RT; again, no imaging-based resection determination was made. Additionally, patient subgroups available for statistical evaluation are consistently smaller compared to the present analysis. Of course, further evaluation is necessary, especially with modern pre- and postoperative imaging, perhaps intraoperative imaging, when available, as well as improved information on target delineation and dose prescription recommendations. Moreover, a clear limitation of the present analysis is that no standardized chemotherapy regimens were applied at recurrence. Consistently, however, no avastin failures were included into this study.

The most crucial point is that radiation oncologists should rethink the ideal time point of Re-RT: an early application also in patients with complete tumor removal is safe and most likely the most effective timepoint for Re-RT.

However, this present analysis certainly has limitations, mainly due to the retrospective nature of the disease, the single-center bias and the small patient numbers. Generation of prospective evidence is necessary. Therefore, currently, the concept of early Re-RT after complete resection is evaluated within a prospective multicenter, randomized trial (GlioCAVE/NOA 17). A prospective multicenter trial is currently underway investigating the value of early Re-RT after complete resection in recurrent GBM (GlioCAVE-trial/NOA 17).

**Disclosure**

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

**REFERENCES**


COMMENTS

The authors present a relatively large series of patients who have received a second course of radiation for high-grade glioma, both in patients with surgically resected and intact tumors. The novelty of the series is the use of aggressive surgical resection followed by a second course of radiotherapy. A prior series has shown a survival benefit in patients with recurrent glioma with additional surgical resection if the tumor can be gross-totally-resected. Re-irradiation in this setting has not been standardly offered. However, in the current series, the longest survival was found in these patients who had gross-total resection followed by re-irradiation. It will be important that these data are validated prospectively as retrospective series of recurrent glioblastoma are fraught with significant patient selection bias. The NOA-17 study will be looking at early re-irradiation of glioblastoma and its results will hopefully help to answer the remaining controversy regarding the role of early re-irradiation.

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