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CLINICAL STUDY

# Combined salvage therapies for recurrent glioblastoma multiforme: evaluation of an interdisciplinary treatment algorithm

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**Abstract** Glioblastoma multiforme patients presenting with recurrence following multimodality therapy have limited palliative treatment options when the major modalities of therapy including surgery, radiochemotherapy and adjuvant chemotherapy have been exhausted. The authors introduce a clinical and radiological indication-solving algorithm and provide outcome rates of a glioblastoma recurrence cohort. Sixty six consecutive adult patients with recurrent glioblastoma who underwent a combined scheme of salvage treatments consisting of reoperation, high dose rate (HDR) brachytherapy and chemotherapy were included in this prospective study and were compared to a historical control group of 24 recurrent glioblastoma patients who have been treated with intensive temozolomide chemotherapy as the only treatment modality. Median follow-up was 32 months (range 28–36 months). Median survival was 9 months for the entire cohort after salvage treatment and can be translated into a 3-month improvement in survival compared to the control group of patients with glioblastoma recurrence treated with temozolomide alone ($P = 0.043$). Toxicity and adverse events of reoperation, HDR brachytherapy combined with chemotherapy were quite favourable compared to intensive temomozolomide chemotherapy as the only treatment. Our experience suggests that a combined salvage treatment plan appears to be both feasible and effective and can be considered in selected patients affected by recurrent high grade gliomas. The authors' clinical and radiological indication-solving algorithm may assist in providing the best possible salvage treatment for this difficult population.

**Keywords** Glioblastoma multiforme · Recurrence · Surgery · Radiosurgery · HDR brachytherapy · Salvage therapy

**Abbreviations**

| | |
|---|---|
| CTCAE | Common terminology criteria for adverse events |
| ddTMZ | Dense dose temozolomide |
| FSRS | Fractionated stereotactic radiosurgery |
| HDR | High dose rate |
| KPS | Karnofsky performance status |

## Introduction

Patients with recurrent high grade gliomas represent a unique challenge to the treating physicians, despite the advancements made in the fields of neurosurgery, neuro-oncology, medical oncology, and radiation oncology [1, 2].

A multimodal and interdisciplinary approach to a patient with a recurrent high grade glioma may involve re-resection and chemotherapy, depending on the clinical status and extension of the tumor. The feasibility of re-irradiation is limited by the potential for complications and

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radiosensitivity to previously irradiated surrounding non tumor tissue [3].

Improved outcomes with the application of a multimodality management of patients with recurrent malignant glioma have been reported in several series [4], yet no standardized treatment algorithm exists that approaches this challenging pathological entity in a systematic, logical, and concise manner. Various modalities are employed for recurrent gliomas, ranging from non-invasive techniques with three-dimensional (3-D) conformal external RT [5], intensity modulated radiotherapy (IMRT) [6], stereotactic radiosurgery (SRS) [7, 8], stereotactic radiotherapy (SRT) [9] or systemic use of temozolomide as dense dose treatment modality to invasive techniques such as re-operation (with or without chemotherapy with local therapy using Gliadel wafers) and brachytherapy (interstitial or intracavitary) [9–14]. There is evidence that suggests improved outcome with the combination of focal re-irradiation and a humanized monoclonal antibody which targets VEGF. Gutin et al. published results regarding 25 patients with recurrent grade III–IV gliomas using fractionated SRT and concurrent bevacizumab [15]. The Duke group recently reported its single-institution retrospective data on recurrent high-grade gliomas, treated with re-irradiation using SRS techniques combined with bevacizumab therapy [16]. A current multi-institutional randomized phase II trial of the RTOG investigates safety and efficacy regarding the combination of re-irradiation and bevacizumab in improving overall survival in recurrent glioblastoma patients.

Resurgery, dose escalation with interstitial high dose rate (HDR) brachytherapy delivered with an automatic computer controlled afterloading device of a single $^{192}$Ir source and consecutive intensive temozolomide chemotherapy might prolong survival in patients with this devastating disease. In three retrospective studies we have reported the safety and feasibility of HDR brachytherapy and a survival benefit in comparison to conservative treatment for patients with recurrent glioblastoma [2, 17, 18]. We designed a prospective study in order to report not only a treatment algorithm of combined therapeutic modalities used in patients with recurrent high grade gliomas but also to provide long-term follow-up and results of treatment side effects on all enrolled subjects.

## Materials and methods

Between 2008 and 2011, 66 consecutive adult patients with recurrent high grade gliomas were prospectively analyzed and compared to a historical control group. The study cohort consisted of patients who underwent a multimodal treatment according to a clinical and radiological algorithm decided prior to the beginning of the series at Sana Klinikum Offenbach, Germany. This project was approved by the Ethics Board at Sana Klinikum Offenbach, and informed consent was obtained from all study subjects and/or guardians at the time of registry into a prospective database. We employed a control group of patients who were treated in the outpatient institute of Sana Klinikum Offenbach between 2006 and 2008, prior to the introduction of the above mentioned algorithm. Eligibility criteria included (1) histology proven diagnosis of glioblastoma (WHO grade 4), (2) age $\geq$18 years, (3) primary treatment with initial surgery and radiotherapy with concomitant temozolomide, (4) patients with good neurological function (KPS $\geq$80), and (5) provided informed consent for salvage therapy after recurrence. The exclusion criteria were the use of any other investigational agent and conscious impairment. Multifocality of the recurrence and involvement of eloquent regions was not considered a contraindication for further salvage treatment.

All patients were treated for recurrence, having following possible combinations of treatment (treatment variables): (a) Resurgery and HDR brachytherapy followed by temozolomide, (b) HDR brachytherapy followed by temozolomide, (c) Resurgery followed by temozolomide. These different treatment groups were compared to patients who have been treated with intensive temozolomide chemotherapy as the only treatment modality.

Table 1 shows the patient's characteristics and KPS profiles at the time of glioblastoma recurrence. With the exception that the rate of frontal tumors was higher in the combined salvage treatment group in comparison to the control group of sole ddTMZ (27 vs 8 %), the two groups didn't show any significant differences in the other parameters including among others Karnofsky performance score (KPS) rates, age, sex, eloquent regions.

The clinical and radiological indication-solving algorithm illustrated in Fig. 1 was utilized to determine management decisions and was decided prior to the beginning of this series.

Resurgery was undertaken using a 5-aminolevulinic acid fluorescence visualization technique whereas resection was limited to a neurologically safe maximal tumor resection as considered possible by the responsible surgeon. MR imaging with and without contrast enhancement were performed in the first 48 h after resurgery in order to accurately determine tumor size and the extent of tumor resection. A gross total removal was defined as a reduction >98 % of the tumor volume based on volumetric measurements. Follow-up MRI scans were performed at 3-month intervals for both combined salvage treatment and ddTMZ groups.

HDR brachytherapy consisted of an interstitial $^{192}$Ir implant delivered with an automatic computer-controlled afterloading device through catheters. Tumor demarcation

**Table 1** Salvage therapy data of patients with recurrent GBM

| Parameters | Combined salvage treatment group | ddTMZ |
|---|---|---|
| No. of cases | 66 | 24 |
| Age (in years) | 58.1 | 56.7 |
| Sex (female), n (%) (no. of cases) | 32 (48 %) | 11 (46 %) |
| Standard follow up (range) (in months) | 33 (27–35) | 31 (29–36) |
| KPS score | 90 | 90 |
| 100 (no. of cases) | 16 (24 %) | 4 (17 %) |
| 90 (no. of cases) | 32 (48 %) | 12 (50 %) |
| 80 (no. of cases) | 18 (27 %) | 8 (33 %) |
| Time since initial diagnosis (in months) | 9.4 | 9.1 |
| Side of tumor location (no. of cases) | | |
| Left | 42 (64 %) | 14 (58 %) |
| Right | 24 (36 %) | 10 (42 %) |
| Predominant lobe of tumor location (no. of cases) | | |
| Frontal | 18 (27 %) | 2 (8 %) |
| Temporal | 20 (30 %) | 7 (29 %) |
| Parietal | 22 (33 %) | 6 (25 %) |
| Occcipital | 6 (9 %) | 9 (37.5 %) |
| Eloquent/critical regions involved (no. of cases) | | |
| 0 | 26 (39 %) | 10 (42 %) |
| 1 | 28 (42 %) | 9 (37 %) |
| 2 | 6 (10 %) | 4 (17 %) |
| 3 | 6 (9 %) | 1 (4 %) |
| Tumor volume ($cm^3$) | 38.1 | 36.8 |
| Seizures (no. of cases) | | |
| Yes | 39 (58 %) | 11 (46 %) |
| No | 28 (42 %) | 13 (54 %) |
| Midline shift (no. of cases) | | |
| Yes | 40 (61 %) | 13 (54 %) |
| No | 26 (39 %) | 11 (46 %) |
| Cerebral edema (no. of cases) | | |
| None | 4 (6 %) | 2 (8 %) |
| Perifocal $\leq$ 2 cm | 26 (39 %) | 8 (33 %) |
| Perifocal $\geq$ 2 cm | 36 (55 %) | 14 (58 %) |

Mean values

with planning target volume (PTV) was performed with a 3D planning system (Prosoma, Medcom, Darmstadt, Germany) and was defined preoperatively as the enhanced lesion demonstrated by postcontrast MR imaging. PTV coverage was defined as the proportion of the PTV receiving 100 % of the prescribed dose, and the prescribed fractional dose of 5 Gy as the mean dose value on the PTV surface, representing also the 100 % isodose line. Catheter implantation was implemented using interactive CT guidance under local anaesthesia and sedoanalgesia.

Resurgery and HDR brachytherapy were followed by TMZ chemotherapy as an adjunctive treatment with a dose of 100 mg/$m^2$ for 5 days in 28-day cycle. In patients treated with sole chemotherapy, we used the 1 week on/1 week off temozolomide with a daily dose of 150 mg/$m^2$, until documented disease progression or unacceptable toxicity. We chose this more rigorous dose regimen of TMZ according to the publications of Wick et al. who reported a 3 months PFS as high as 48 % with an overall survival for 12 months of 81 % [19]. The primary endpoint of this study was disease-specific survival after salvage treatment. Secondary endpoints were complication rates, adverse events, mortality and morbidity due to toxicity.

Progression was evaluated according to Macdonald criteria defined as ">25 % increase in size of enhancing tumor or any new tumor on CT or MR imaging, or neurologically worsening (that is, increase in the NIH-SS score $\geq$1 compared to preceding visit) in case of stable or increased use of steroids" [20]. All patients were observed until the time of death or last follow-up. Median follow-up was 32 months (range 28–36 months). KPS score was estimated in both groups as an important parameter of quality of life before and after initiation of salvage treatment, as well as every 3 months during treatment.

## Statistical analysis

All statistical analyses were conducted with BiAS software program (2006, Frankfurt, Germany). Mann–Whitney *U* test was applied as non-parametric significance test. In addition, Chi-quadrate ($Chi^2$)test and Fisher's exact test were performed to analyze the difference in patient characteristics, surgical parameters and complications for each surgical approach. P values less than 0.05 were regarded as statistically significant. Kaplan–Meier survival analysis was obtained using log-rank tests.

## Results

Out of the 66 patients with recurrent glioblastoma, 30 underwent resurgery and 36 underwent HDR brachytherapy due to eloquence of the affected region, multifocality and involvement of both hemispheres. The salvage treatment groups consisted of 20, 26 and 20 patients in the group 1 (resurgery and HDR brachytherapy followed by temozolomide), group 2 (HDR-Brachytherapy followed by temozolomide), and group 3 (resurgery followed by temozolomide) respectively. The salvage therapy data are summarized in Table 2. The median survival was 8 months

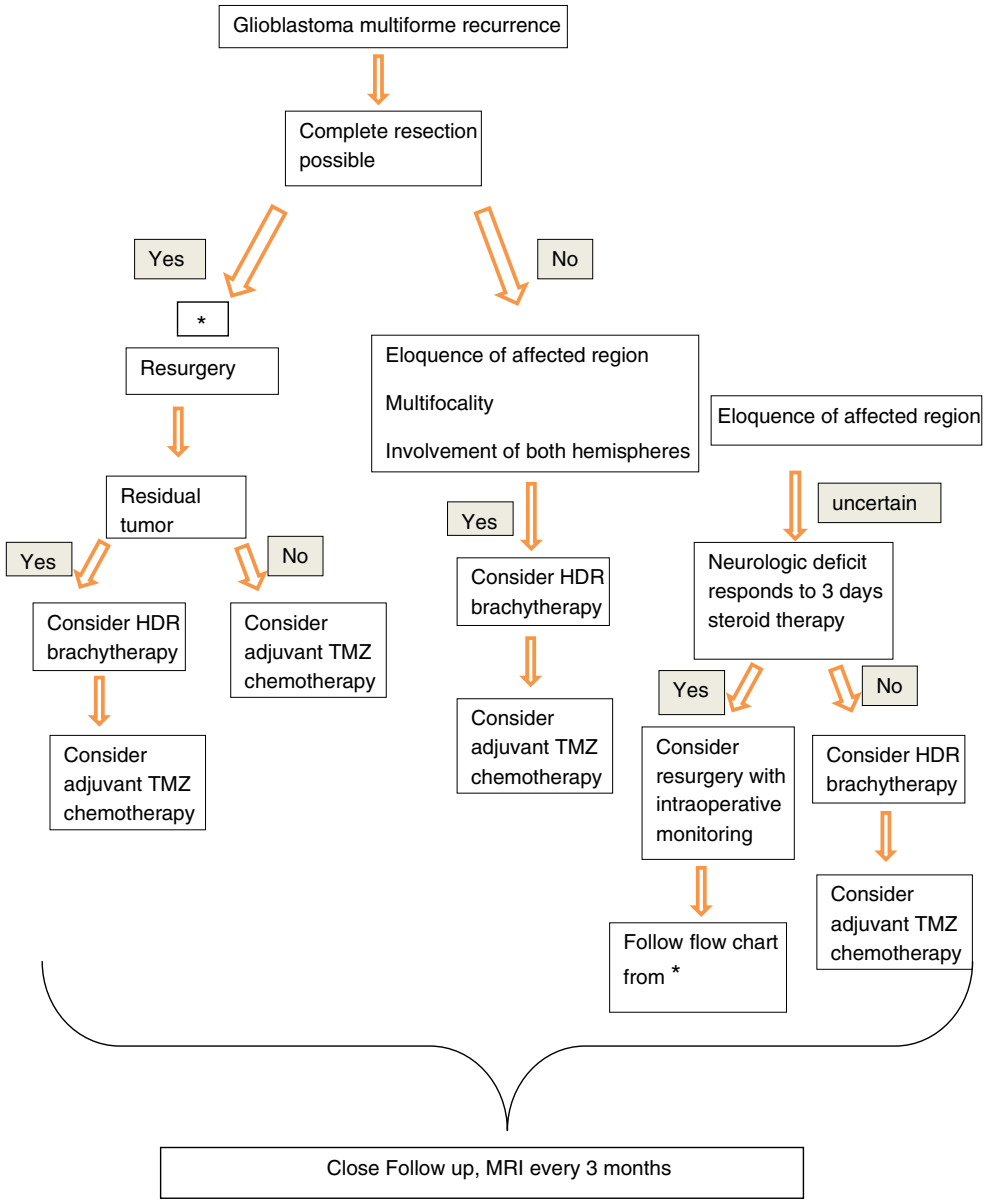


**Fig. 1** A retrospective placed paradigm showing the flow chart of the therapeutic modalities on the multimodal treatment group

for the entire cohort after combined salvage treatments compared to 5 months in the sole ddTMZ group. The additional 3-month improvement in medial survival time in patients with recurrent high grade gliomas represented a statistically significant increase compared to the sole ddTMZ group ($P = 0.043$). We used a non-parametric test for the comparison of survival between the two groups (log rank test). Fig. 2 graphically demonstrates this increase in survival for the patients with recurrent glioblastoma by 3 months for the group of combined salvage treatment compared to ddTMZ group. We examined the different combined salvage treatment modules in detail and an average medial survival time for group 1, group 2 and group 3 of 7.8, 8.2 and 8.0 months respectively. There were no significant differences in survival rates comparing these different combinations of salvage treatments.

The median KPS of the entire patient population was 80 at the time of salvage treatment. At the first 3-month evaluation periods, the median KPS was 80 for the combined salvage treatment group and 70 for the sole chemotherapy control group, respectively. Therefore, there was no severe deterioration regarding function in the first 3 months immediately following salvage treatment in any of the groups.

Table 3 summarizes the side effects of the different combined salvage treatment as graded by the CTCAE criteria. There were no serious adverse HDR brachytherapy related effects and no grades 3 or 4 acute or late toxicities.

**Table 2** Salvage therapy data of patients with recurrent GBM

| Parameters | Combined salvage treatment group | ddTMZ |
|---|---|---|
| Median survival after treatment | 8 months | 5 months |
| Group 1 | 7.8 months | |
| Group 2 | 8.2 months | |
| Group 3 | 8 months | |
| Overall survival | 20.5 months | 14 months |
| Group 1 | 20 | |
| Group 2 | 21 | |
| Group 3 | 20.5 | |
| Progression free survival | 7 months | 3.5 months |
| Group 1 | 7 | |
| Group 2 | 7.5 | |
| Group 3 | 7 | |

Mean values are presented as the mean

Group 1: Reop., HDR-BRT, TMZ

Group 2: HDR-BRT, TMZ

Group 3: Reop., TMZ

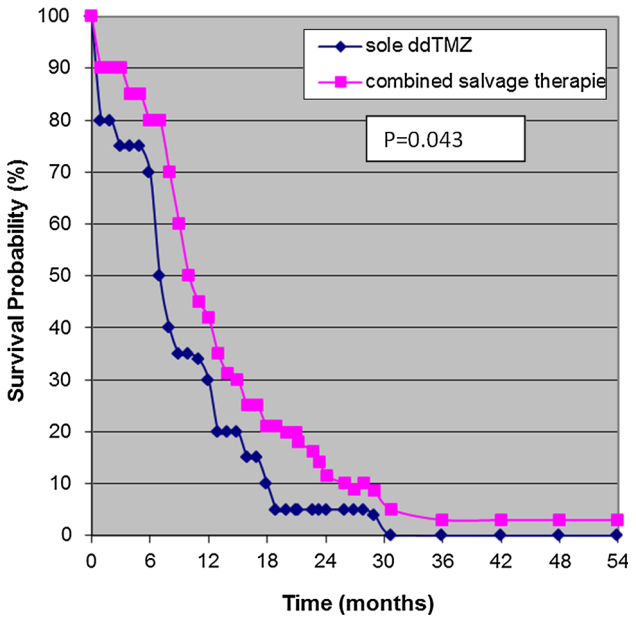


**Fig. 2** Kaplan–Meier plots of survival probability after salvage treatment of patients stratified according to therapeutic modality

Acute headache, vomiting and nausea (grade 1–2) was reported in 22/66 (33 %) of patients which resolved after increase steroid administration. Of the subjects enrolled, 2/66 experienced cerebral spinal fluid (CSF) leak at the time of re-surgery. The infections (2 meningitis and 2 wound infection) that occurred in patients undergoing combined salvage treatments were treated successfully

**Table 3** Complication rates and adverse events (AEs) stratified by treatment group

| Parameters | Combined salvage treatment group | ddTMZ |
|---|---|---|
| No. of cases | 66 | 24 |
| AEs due to toxicity | | |
| All | 22 | |
| Grade 3/4[a] | 0 | 8 |
| Thrombocytopenia | | |
| Grade ¾ | 0 | 3 |
| Leucopenia | | |
| Grade ¾ | 0 | 3 |
| Elevated transaminases | | |
| Grade ¾ | 0 | 1 |
| Infection | | |
| Grade 4 | 0 | 1 |
| Wound healing disturbance | | 0 |
| Grade 3 | 2 | |
| Cerebral fluid leak | | |
| Grade 3 | 2 | |
| Intracerebral bleeding | | 0 |
| Grade ¾ | 2 | |
| Bacterial mengitis | | 0 |
| Grade 4 | 2 | |
| Radiation necrosis | | 0 |
| Grade 3 | 4 | |
| Overall complications | | |
| Grade 3/4 | 12 (18 %) | 8 (33 %) |

[a] According to the common toxicity criteria

with antibiotics. Only 4 patients developed a symptomatic radiation necrosis identified on the follow-up MRI imaging. Eight patients in the ddTMZ control group developed adverse events. Seven patients discontinued TMZ due to toxicity: grade 3 and 4 (3), persistent grade 3 and 4 leucopenia (3) and grade 4 elevated transaminases (1). One patient in the ddTMZ group developed a pneumocystis jirovecii pneumonia and died.

## Discussion

Glioblastoma multiforme tend to recur within 6–10 months after treatment. The patterns of recurrence and failure studies examining recurrence of glioblastoma multiforme after primary therapy have demonstrated that majority of the patients experience recurrence immediately near the resection bed (within 2 cm) [21, 22]. Disease progression is followed shortly by death. Therefore, local therapies administered as surgical resection or radiotherapy in combination with systemic chemotherapy may offer an

advantage in local control and potentially survival. The importance of complete surgical resection has been discussed in the literature [23, 24]. Barker et al. reported that patients who did undergo reoperations experienced clinically and statistically significantly longer survival periods. However, this was determined to be partially because of selection bias and resurgery posed several technical challenges, including bigger tumor volumes, significant gliosis and adhesions, and proximity of the tumor to eloquent brain areas [25]. Dirks et al. reported a death rate after reoperation of 4.6 % and that reoperation alone confers a modest increase in survival if the interval between operations is greater than 50 weeks [26]. On the other hand, dose escalation with external beam radiotherapy in preirradiated areas did not result in benefit of improved survival and was likely to result in complications and injury to the normal brain tissue with radionecrosis. Re-irradiation of normal perilesional brain tissue can easily result in exceeding the cumulative biologic effective tolerance dose (BED) of >100 Gy (in equivalent doses of 2-Gy fractions) that is considered critical for the development of radionecrosis in the brain [27].

A number of attempts have been reported to escalate the dose with interstitial brachytherapy while limiting doses received by the healthy brain tissue [9, 12, 28]. Several trials reported that radiation necrosis dampened the results of treating recurrent glioblastoma with HDR temporary $^{125}$I seed implants [9, 12, 28]. Repeated operations for radio necrosis has generally occurred within 6 months of the end of RT in 26–64 % of treated patients [9, 28, 29]. Moreover, this treatment modality requires a stereotactic frame placement and drilling of multiple holes in the skull for seed delivery. Low-dose-rate (LDR) interstitial brachytherapy with permanent $^{125}$I implants does not require a stereotactic frame or drilling of holes in the skull for seed placement and reduces the incidence of such complications as symptomatic radio necrosis [12, 28]. However, both HDR and LDR $^{125}$I seed placement in the surgical cavity can produce an inhomogeneous dose distribution which in turn may have led to radiation necrosis in the over-dosed areas and recurrence in the under-dosed regions. Lack of improvement in survival in patients with recurrent glioblastoma treated with HDR and LDR interstitial brachytherapy with $^{125}$I implants may be explained by deficiencies in dose distribution [4].

The addition of SRS in combination to chemotherapy could have beneficial effects. Previous studies show the effectiveness of fractionated stereotactic radiosurgery (FSRS) as an option for the treatment of recurrent glioblastoma [30, 31]. Combs et al. reported 5 months progression-free survival after FSRT and 21 months median overall survival [32]. However, SRS is not recommended for recurrent lesions >40 mm in diameter and the fulfilment of this restriction immensely limits patient's eligibility for treatment [7].

The HDR-Brachytherapy delivered through catheters with an automatic computer controlled after loading device of a single $^{192}$Ir source as practiced in our hands, is an attractive form of highly localized doses of radiation implanted not only in solid and cystic parts of the tumor but also in the former resection cavity while minimizing dose deposition to the surrounding tissues. Further, this method allows the delivery of radiation dose to areas most at risk of recurrence while addressing the limitations of interstitial (seed) and intracavitary brachytherapy (Gliasite). HDR brachytherapy offers radiobiological advantages in comparison to radiosurgery in the treatment of larger tumor recurrence. On the other hand, some of the limitations of HDR brachytherapy are the invasivity of this procedure which requires drilling of the skull bone for the placement of the catheters. The fact that HDR brachytherapy can be delivered percutaneously under local anaesthesia, makes this approach attractive but can cause discomfort to the patient. Possible adverse events such as radiation necrosis around the implant site with marked mass effect and worsening of focal neurologic deficits on the first days after implantation and re-irradiation, although not reported as statistically significant in our study, still remain on the focus of such salvage treatments and should be carefully monitored. Moreover, although we tried to standardize decision making through this algorithm, each patient had to be uniquely discussed in our tumor board and this might lead to selection and to a considerable source of bias, thus careful interpretation of these results is needed.

In contrast to brachytherapy, the data on chemotherapy use in the setting of a glioblastoma recurrence are plentiful. There are many studies of temozolomide alone for recurrent GBM in different schedules, some show a marginal efficacy and others provide a wide range of improved overall median survival up to 6 months [13, 33–35]. Other studies on different new chemotherapeutic agents report a range of overall median survival, from 4–9 months [19, 36–38].

At present, the decision on the best management of a glioblastoma recurrence is based on surgeon's preference and varies among centers. To the best of our knowledge, there are no reports available based on an algorithm of combined treatments including interstitial brachytherapy. In the present study, 66 patients received salvage treatment according to the indication solving algorithm depicted in Fig. 1. There were 12 complications, yielding an 18 % complication rate in this challenging patient population; in comparison the ddTMZ group presented a 33 % complication rate due to toxicity. We have to acknowledge that the ddTMZ temozolomide alone group received a dose dense therapy while the study cohort received less drug

dose. As expected, the ddTMZ group showed a higher incidence of grade 3–4 cytopenias. Our present study showed that combined therapies could achieve better long-term survival outcomes to those seen with sole temozolomide chemotherapy in patients with recurrent glioblastoma. It is obvious that a non randomized comparison of combined salvage treatments with ddTMZ on which the above conclusions are drawn is complicated by bias of patient selection. Moreover, it was not the aim of this study to determine the most appropriate first-line chemotherapy at first recurrence. We chose TMZ for our patients with recurrent glioblastoma because it is well tolerated, has good oral bioavailability, and is convenient to administer as an outpatient regimen. Additionally, there is no clear benefit when comparing PCV with TMZ [39]. Bevacizumab has been adopted into regular clinical practice, though there is no phase III evidence of its efficacy and based on the current literature there is a modest response rate and effect on progression-free survival.

The rate of infection was within the expected range for this population, in which the patients who experienced infection had previously undergone numerous treatments, including surgical manipulation. The small number of radiation necrosis in this study cohort suggests that patients may tolerate this regimen better than the one with interstitial seed brachytherapy.

None of our patients required surgical intervention to address radiation necrosis. Same results regarding radiation necrosis reported Wernicke et al. with a regimen of GliaSite brachytherapy [4]. HDR brachytherapy offers a possibility of further dose escalation with the potential to improve the efficacy of this treatment while avoiding the morbidity associated with high rates of radiation necrosis and implantation-explantation surgery. The rate of the acute and long-term toxicities was acceptable.

This report gives a full account of 66/66 (100 %) patients treated with resurgery, HDR brachytherapy combined with dense dose chemotherapy and examines survival and complication rates, as well as compares and contrasts the outcomes and toxicity rates to a control group of patients treated with ddTMZ alone. Our CTCAE based toxicity profile is quite favourably compared to the prior reports and is devoid of any high grade toxicity, including radiation necrosis, hydrocephalus, intracranial haemorrhage, or meningitis. We developed a treatment algorithm guiding the neurotherapist through the decision making process. The present results might therefore help neurotherapists to put different treatment modalities into perspective.

Though we report long-term follow-up, data on treatment failures and toxicity in all patients in this study, we have to acknowledge the limitations of our study. The number of patients is small, and there was no randomization regarding choices of treatment. We could not withhold rechallenge with a multimodal treatment in patients with recurrence of this devastating disease and for this reason inclusion and exclusion criteria between the different multimodal treatments were not strict and an ethics committee approval was not considered necessary. The fact that the patient population was not homogeneous and that for example the rate of frontal tumors was higher in the combined salvage treatment group in comparison to the control group of sole ddTMZ (27 vs 8 %) might be a source of bias; although in this series frontal lesions didn't show to be more amenable to larger surgical resection.

All cases in our series were managed in an interdisciplinary way. The best approach involved collaborative interactions and decisions made by a team of neurosurgeon, radiotherapist and oncologist. The decision to treat with resurgery was dependent mainly on whether complete resection was possible and whether eloquent brain areas were affected and was based also on morphology and topography of the tumor progression in relation to speech, motor, brainstem and sylvic fissure and also on multifocality of the recurrence as illustrated by the algorithm in Fig. 1. The size of the tumor recurrence played also a role for the decision making in some patients although not statistically significant. These facts made the three different possible salvage treatments not comparable. Sixteen out of the 20 patients of group1 (Reop., HDR-BRT, TMZ) showed no eloquence of the affected region but a residual or progressive tumor on control MRI. On the other hand, 19 out of 20 patients of group 3 (Reop., TMZ) showed no residual tumor after surgery and therefore were not rechallenged with reirradiation. All patients in group 2 (HDR-BRT, TMZ) showed either eloquence of the affected region or multifocality. These major draw backs of our study point up the necessity of randomized prospective studies to support these results.

## Conclusions

The objective of this prospective study was to assess survival rates of combined salvage treatments after recurrence of glioblastoma and to evaluate side effects. This study demonstrates that HDR brachytherapy in combination with resurgery and chemotherapy can be valuable tools for therapeutic escalation in patients with recurrent CNS malignancy. We propose the aforementioned clinical and radiological indication solving algorithm to systematically assist therapists in their efforts to provide the best possible salvage treatment in this difficult patient population.

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

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