Recurrent Glioblastoma Treatment

- Hybrid Therapy for Newly Diagnosed and Recurrent Glioblastoma: Staged Procedure Integrating Open Surgical Resection With Laser Interstitial Thermal Therapy
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There is no consensus as to the standard of care as no therapeutic options have produced substantial survival benefit for Glioblastoma recurrences (Glioblastomas) [1) 2)].

A purely radiological diagnosis of recurrence or progression can be hampered by flaws induced by pseudoprogression, pseudoresponse, or radionecrosis

There is sufficient uncertainty and equipoise regarding the question of reoperation for patients with Glioblastoma recurrence to support the need for a randomized controlled trial [3)].

Based on parameters like localization and tumor volume, patient's Karnofsky Performance Score, 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 Glioblastoma recurrence can help to select suitable candidates for surgery. Safety issues and complication avoidance are pivotal to maximally preserving 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 [4)].

Options

Options include repeat surgical resection, repeat fractionated radiation, radiosurgery.

Bevacizumab (BEV) plus daily temozolomide (TMZ) as a salvage therapy has been recommended for recurrent glioma.

In a study, Hundsberger et al investigated which treatments are currently being used for recurrent Glioblastoma within a single nation (Switzerland) and how clinicians are deciding to use them [5)]

The authors surveyed Swiss hospitals with comprehensive multidisciplinary neuro-oncology practices (neurosurgery, radiation therapy, medical neuro-oncology, and a dedicated neuro-oncology tumor board) about treatment recommendations for recurrent Glioblastoma. They identified relevant clinical decision-making criteria, called diagnostic nodes or “dodes,” and compared treatment recommendations using a decision-tree format.

Eight hospitals participated. The most common treatment options for recurrent Glioblastoma were combination repeat surgical resection with temozolomide or bevacizumab, monotherapy temozolomide or bevacizumab, and best supportive care. Alternative therapies, including radiotherapy, were less common. Despite widespread disagreement between centers in clinical decision-making, the decision-tree analysis found agreement (>63%) between most centers for only 4 specific clinical scenarios. Patients without an appropriate performance status were usually managed with the best supportive care. Patients with rapid recurrence, nonresectable tumors, unmethylated O(6)-methylguanine DNA methyltransferase (MGMT) promoter, and high-performance status were usually managed with bevacizumab. Patients with late recurrence, nonresectable tumors, overt clinical symptoms, methylated MGMT promoter, multifocal disease, and high-performance status were usually managed with repeat temozolomide therapy. Patients with late recurrence, nonresectable tumors, no clinical symptoms, methylated MGMT promoter, tumor multifocality, and high-performance status were usually managed with temozolomide. The findings of this study underscore the lack of effective first- and second-line treatments for Glioblastoma, and the interhospital variability in practice patterns is not surprising. It seems likely that similar heterogeneity would also be noted in a study of American neuro-oncology centers. It is interesting to note that despite the availability of an increasing number of molecular markers for Glioblastoma stratification, MGMT promoter methylation appears to be the only biological marker widely used across multiple centers in this study. It remains to be seen when and how broadly other markers such as the epidermal growth factor receptor variant III or isocitrate dehydrogenase mutations will be adopted for clinical decision-making. The authors are to be congratulated for identifying core clinical decision-making criteria that may be useful in future studies of recurrent Glioblastoma. This decision tree is an excellent reference for clinical trial development, and several active clinical trials already target the dudes identified in this study. Subsequent studies may help to determine whether similar decision trees exist in American neuro-oncologic centers now or will exist in the future [6)].

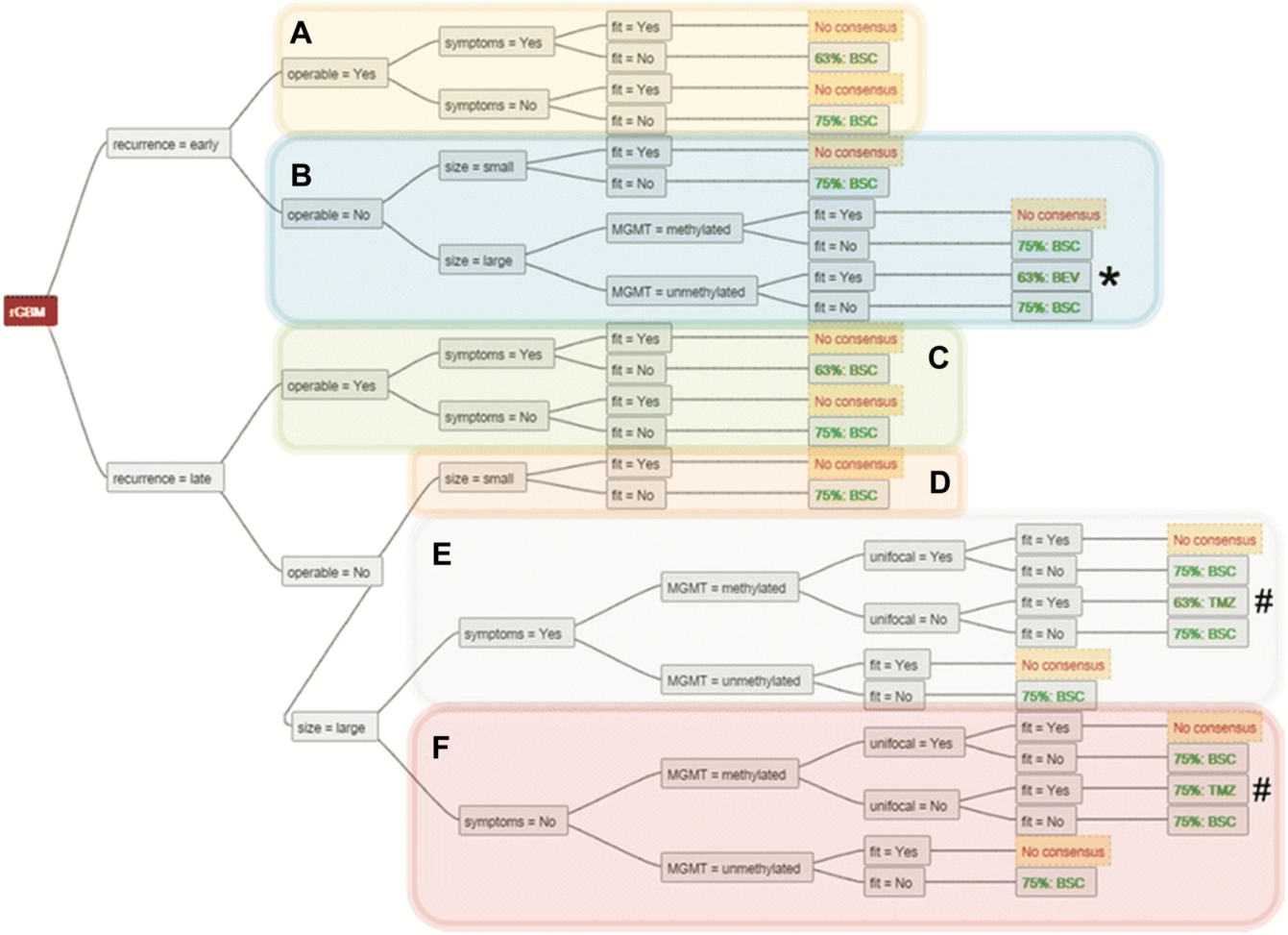

Figure. A through F, clinical decision-making tree for Glioblastoma recurrence multiforme (Glioblastoma) based on clinical scenarios that achieved a majority recommendation (ie, at least 5 of 8 Swiss hospitals). BEV, bevacizumab; BSC, best supportive care; rGlioblastoma, Glioblastoma recurrence multiforme; TMZ, temozolomide. Modified with kind permission from Springer Science+Business Media: Journal of Neuro-Oncology, Patterns of care in Glioblastoma recurrence in Switzerland: a multicenter national approach based on diagnostic nodes (published online ahead of print October 12. 2015), Hundsberger T, Hottinger AF, Roelcke U, et al [doi: 10.1007/s11060-015-1957-0. Available at: http://link.springer.com/article/10.1007%2Fs11060-015-1957-0].

Resection

see Glioblastoma recurrence resection.

Fractionated Stereotactic Radiotherapy

see Fractionated Stereotactic Radiotherapy for Glioblastoma recurrence.

Temozolomide

Temozolomide rechallenge is a treatment option for MGMT promoter-methylated Glioblastoma recurrence. Alternative strategies need to be considered for patients with progressive glioblastoma without MGMT promoter methylation [7].

Bevacizumab

see Bevacizumab for Glioblastoma recurrence.

Intraarterial chemotherapy

Intrarterial chemotherapy is a viable methodology in recurrent Glioblastoma patients to prolong survival at the risk of procedure-related complications and in newly diagnosed patients with the benefit of decreased complications [8].

Low-dose fractionated radiotherapy LD-FRT and chemotherapy for recurrent/progressive Glioblastoma have a good toxicity profile and clinical outcomes, even though further investigation of this novel palliative treatment approach is warranted [9].

Second surgery plus carmustine wafers followed by intravenous fotemustine

Second surgery plus carmustine wafers followed by intravenous fotemustine in twenty-four patients were analyzed. The median age was 53.6; all patients had KPS between 90 and 100; 19 patients (79%) performed a gross total resection > 98% and 5 (21%) a gross total resection > 90%. The median progression-free survival from second surgery was 6 months (95% CI 3.9-8.05) and the median OS was 14 months (95% CI 11.1-16.8 months). Toxicity was predominantly haematological: 5 patients (21%) experienced grade 3-4 thrombocytopenia and 3 patients (12%) grade 3-4 leukopenia.

This multimodal strategy may be feasible in patients with Glioblastoma recurrence, in particular, for patients in good clinical conditions [10].

Immunotherapy

The HSPPC-96 vaccine is safe and warrants further study of efficacy for the treatment of recurrent Glioblastoma. Significant pretreatment lymphopenia may impact the outcomes of immunotherapy and deserves additional investigation [11].

Laser induced interstitial thermotherapy

see Laser interstitial thermotherapy.

Galldiks et al monitored the metabolic effects of stereotaxy-guided LITT in a patient with a recurrent Glioblastoma using amino acid positron emission tomography (PET). Serial 11C-methyl-L-methionine positron emission tomography (MET-PET) and contrast-enhanced computed tomography (CT) were performed using a hybrid PET/CT system in a patient with recurrent Glioblastoma before and after LITT. To monitor the biologic activity of the effects of stereotaxy-guided LITT, a threshold-based volume of interest analysis of the metabolically active tumor volume (MET uptake index of ≥ 1.3) was performed. A continuous decline in metabolically active tumor volume after LITT could be observed. MET-PET seems to be useful for monitoring the short-term therapeutic effects of LITT, especially when patients have been pretreated with a multistep therapeutic regimen. MET-PET seems to be an appropriate tool to monitor and guide experimental LITT regimens and should be studied in a larger patient group to confirm its clinical value [12].

CP-673451

CP-673451 for glioblastoma recurrence.

Lomustine

Adjuvant lomustine to other chemotherapy may provide no obvious benefits for the glioblastoma recurrence treatment [13].

Outcome

A more favorable prognosis following surgery for recurrence or progression is associated with younger age, smaller tumor volume (~50%), motor speech-middle cerebral artery scoring and preoperative Karnofsky performance score (KPS) >80% [14] [15].

Systematic Reviews

Schettini et al. conducted a systematic review and Bayesian trial-level network metaanalysis (NMA) to identify the regimens associated with the best outcomes. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS) and overall response rates (ORR). They estimated separate treatment rankings based on the surface under the cumulative ranking curve values. Only phase II/III prospective comparative trials were included.

Twenty-four studies (3733 patients and 27 different therapies) were ultimately included. Twenty-three different regimens were compared for OS, 21 for PFS, and 26 for ORR. When taking lomustine as a common comparator, only regorafenib was likely to be significantly superior in terms of OS (hazard

ratio: 0.50, 95% credible interval: 0.33-0.75). Regorafenib was significantly superior to other 16 (69.6%) regimens, including NovoTTF-100A, bevacizumab monotherapy, and several bevacizumab-based combinations. Regarding PFS and ORR, no treatment was clearly superior to the others.

This NMA supports regorafenib as one of the best available options for relapsing/refractory glioblastoma. Lomustine, NovoTTF-100A, and bevacizumab emerge as other viable alternative regimens. However, evidence on regorafenib is controversial at best. Moreover, most studies were underpowered, with varying inclusion criteria and primary endpoints, and no longer adapted to the most recent glioblastoma classification. A paradigmatic change in clinical trials' design for relapsing/refractory glioblastoma and more effective treatments are urgently required [16)]

Schettini et al.'s systematic review and Bayesian NMA make an important contribution to understanding the relative efficacy of available therapies for relapsing/refractory GBM, particularly by highlighting regorafenib as a potentially effective option. However, the study is hindered by limitations inherent to the included trials and the analytical framework, including the heterogeneity of studies, underpowered designs, and outdated glioblastoma classifications.

The findings underscore the pressing need for a paradigm shift in GBM clinical trials. Future research should prioritize large, well-powered, multicenter trials incorporating molecularly stratified patient cohorts and harmonized endpoints. Additionally, the exploration of novel therapeutic strategies is critical to advancing the treatment landscape for this devastating disease. While regorafenib appears promising, its clinical utility must be validated in robust, contemporary trials to establish its place in the therapeutic arsenal for GBM.

Optimal treatment for recurrent High-grade glioma continues to evolve. Currently, however, there is no consensus in the literature on the role of reoperation in the management of these patients.

An analysis, of reoperation in patients with World Health Organization grade III or IV recurrent gliomas, focusing on how reoperation affects outcome, perioperative complications, and quality of life. An extensive literature review was performed through the use of the PubMed and Ovid Medline databases for January 1980 through August 2013. A total 31 studies were included in the final analysis. Of the 31 studies with significant data from single or multiple institutions, 29 demonstrated a survival benefit or improved functional status after reoperation for recurrent high-grade glioma. Indications for reoperation included new focal neurological deficits, tumor mass effect, signs of elevated intracranial pressure, headaches, increased seizure frequency, and radiographic evidence of tumor progression. Age was not a contraindication to reoperation. Time interval of at least 6 months between operations and favorable performance status (Karnofsky Performance Status score ≥70) were important predictors of benefit from reoperation. Extent of resection at reoperation improved survival, even in patients with subtotal resection at initial operation. Careful patient selection such as avoiding those individuals with poor performance status and bevacizumab within 4 weeks of surgery is important. Although limited to retrospective analysis and patient selection bias, mounting evidence suggests a survival benefit in patients receiving a reoperation at the time of high-grade glioma recurrence [17)].

Case series

2018

Twenty patients with recurrent glioma were treated with BEV (5-10 mg/kg, i.v. every 2 weeks) plus daily TMZ (daily, 50 mg/m2). The treatment response was evaluated via the RANO criteria. HRQL were measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 (QLQ-C30) and Brain Module (QLQ-BN20).

Twenty patients received a total of 85 cycles of BEV with a median number of 4 cycles (range: 2-10). No patients showed complete response (CR) to treatment. Twelve patients had partial response (PR), stable disease (SD) in 5 patients with, and 3 patients showed progressive disease (PD). In the functioning domains of QLQ-C30, physical functioning, cognitive functioning and emotional functioning significantly improved after the second cycle of BEV compared to baseline, with the mean score of 45.0 vs. 64.0 ($p = 0.020$), 55.8 vs. 71.7 ($p = 0.020$) and 48.3 vs. 67.5 ($p = 0.015$), respectively. In the symptom scales, the scores of pain and nausea/vomiting significantly decreased compared to baseline from the mean score of 39.1 to 20.0 ($p = 0.020$) and 29.2 to 16.7 ($p = 0.049$), respectively. Score of global health status also increased from 47.5 to 63.3 ($p = 0.001$). As determined with the QLQ-BN20, motor dysfunction (43.3 vs. 25.0, $p = 0.021$), weakness of legs (36.7 vs. 18.3, $p = 0.049$), headache (38.3 vs. 20.0, $p = 0.040$), and drowsiness (50.0 vs. 30.0, $p = 0.026$) after the second cycle of BEV also significantly improved compared to baseline.

BEV plus daily TMZ as a salvage therapy improved HRQL in patients with recurrent glioma [18].

2016

Quick-Weller et al. performed tumour resections in seven patients with rGlioblastoma, combining 5-ALA (20 mg/kg bodyweight) with iMRI (0.15 T). Radiologically complete resections were intended in all seven patients.

They assessed intraoperative fluorescence findings and compared these with intraoperative imaging. All patients had early postoperative MRI (3 T) to verify final iMRI scans and received adjuvant treatment according to interdisciplinary tumour board decision.

Median patient age was 63 years. Median KPS score was 90, and median tumour volume was 8.2 cm(3). In six of seven patients (85%), 5-ALA induced fluorescence of tumour-tissue was detected intraoperatively. All tumours were good to visualise with iMRI and contrast media. One patient received additional resection of residual contrast enhancing tissue on intraoperative imaging, which did not show fluorescence. Radiologically complete resections according to early postoperative MRI were achieved in all patients. Median survival since second surgery was 7.6 months and overall survival since diagnosis was 27.8 months.

5-ALA and iMRI are important surgical tools to maximise tumour resection also in rGlioblastoma. However, not all rGlioblastomas exhibit fluorescence after 5-ALA administration. They propose the combined use of 5-ALA and iMRI in the surgery of rGlioblastoma [19].

Old publications

In some case series reoperation extends survival by an additional 36 weeks in patients with glioblastoma, and 88 weeks in anaplastic astrocytoma [20) 21)] (duration of high-quality survival was 10 weeks and 83 weeks, respectively, and was lower with pre-op Karnofsky score < 70). In addition to Karnofsky performance score, significant prognosticators for response to repeat surgery include: age and time from the first operation to reoperation (shorter times → worse prognosis) [22)]. Morbidity is higher with reoperation (5–18%); the infection rate is ≈ 3x that for first operation, wound dehiscence is more likely

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