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The algorithms of adjuvant therapy in gliomas and their effect on survival.

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Abstract

The treatment of gliomas became more sophisticated during the last decades. As by now, adjuvant treatment after maximum safe resection is considered an important and effective treatment strategy in most gliomas, yet the decision is based on several factors. This review summarizes the available evidence for the current adjuvant treatment algorithms with a focus on the impact on the survival of glioma patients. The review is based on the current guidelines, but it also includes new insights which have not yet been included into the official guidelines.

Key-words

Glioma, Glioblastoma, Oligodendroglioma, adjuvant treatment, Radiotherapy

Introduction

The adjuvant treatment of gliomas has undergone important changes within the past years [1, 2], which now involves surgical, medical as well as technical therapies side by side. Within the past two centuries, important improvements in all of these therapeutic strategies have improved the outcomes of our patients. Beginning with neurosurgery, microsurgical techniques with the use of intraoperative CT- and MR-imaging, neuro-navigation as well as 5-alpha-aminolevulinat (ALA) enhanced resections, among others, have improved the safety as well as the extent of resection of glioma patients. This development has led to an improvement of the prognosis [3, 4]. Not only the surgical techniques, but also the pathological review has made a large step forward. With the advent and inclusion of molecular findings into the diagnosis of primary brain tumors, the accuracy of the diagnosis has improved and the prognostication has become more accurate [5]. The molecular factors in the new WHO classification are also predictive for the following adjuvant treatments [6, 7]. Systemic treatments are now a standard of care in most primary brain tumors, where the choice of the treatment regimen is largely influenced by the molecular pattern of the disease [1]. Radiotherapy has undergone fundamental changes within the past years, too. Modern linear accelerators, enhanced by modern computer based planning algorithms, allow highly conformal dose distributions to the tumor with simultaneous protection of adjacent organs at risk. Furthermore, the precision of the treatment delivery has reached a millimeter or even sub-millimeter level with the use of stereotactic or image-guidance techniques. Besides this, the advent of particle therapies now allows further dose escalations. All of these techniques went hand-in-hand with improvements in neuroimaging, which evolved from anatomic imaging towards functional and metabolic visualisation which now allows to capture the heterogeneity within subvolumes of the tumor [8].
All of these improvements have led us to a plethora of trials, many of them comparing different adjuvant treatments. In this review, we present the milestone trials and their results and generate an algorithm for the adjuvant treatment of gliomas. The algorithm takes into account the 2017 EANO guidelines as well as the 2018 NCCN guidelines [1, 9]. However, we modified the recommendation, where appropriate, to include novel results. The target volume recommendations for radiation therapy are based on the recommendation from the EORTC as well as the ESTRO[10].

Low-Grade Glioma

The treatment of low-grade gliomas (LGG) is currently shifting towards a more intense treatment [11]. After maximum safe resection, national as well as international guidelines recommend adjuvant treatment in all patients who fulfill a set of risk factors [1][9]. The definition of these risk factors has changed over the past two decades, thereby focussing on the age of ≥40 years and a subtotal resection as risk factors. Additional clinical features, such as a tumor size of >6cm or the presence of neurologic deficits, which were suggested earlier by Pignatti et al. [12], have currently lost their influence. Currently, molecular factors have gained more attention which is discussed in detail later in this article.
The regimen with the highest level of evidence (IB) in the adjuvant situation in LGG is the RTOG 9802 regimen. The trial included patients with diffuse gliomas: Patients with low-risk features as defined above were observed, while patients with high-risk-features were randomized to receive either a mono-radiotherapy or radiotherapy (RT) followed by six cycles of combination chemotherapy (ChT). The radiotherapy dose was 54 Gy in 30 fractions. The adjuvant combination chemotherapy included procarbazine (60 mg/m²/d8-21, q56), CCNU (110 mg/m²/d1,q56) and Vincristine (1.4mg/m²/d8+29,q56)(PCV). As anticipated, the combination regimen was associated with an increased rate of hematologic and serologic side effects, and the average number of cycles was 3 for procarbazine and 4 for CCNU and vincristine. Besides this, the two regimens were equally tolerated. The long-term results of RTOG 9802 were published in 2016 and showed a significant improvement in the long term-survival of LGG patients. The median overall survival (mOS) was increased from 7.8 to 13.3 years, with an even more pronounced effect in patients with oligodendroglial histology [13]. Accordingly, the adjuvant treatment with an RT to 54 Gy in 30 fractions, followed by six cycles of PCV is the best-established standard for high-risk LGGs. The RT is prescribed to the resection cavity as

well as mass like hyperintensities in the fluid-attenuated inversion recovery (FLAIR) sequence plus an anatomically adapted margin of 1.0 to 1.5 cm (clinical target volume, CTV), a margin of 0.3 to 0.5 mm is added to account for positioning uncertainties (planning target volume, PTV).

As PCV is associated with an increased rate of hematologic as well as liver toxicities, especially when combined with temozolomide (TMZ), many centers use TMZ instead of PCV for the adjuvant treatment of diffuse astrocytomas [11]. The evidence for this regimen is based on three arguments. Firstly, the phase II study RTOG 0424 showed a favorable outcome in patients receiving RT with concomitant and adjuvant TMZ as compared to historical controls from EORTC 22844 and 22845 [12, 14]. The 3-year survival in this regimen was 73.1%. A recent secondary analysis further validated the prognostic impact of O6-Methylguanin-DNA-methyltransferase (MGMT) promoter methylation status as well as IDH1/2 mutations in LGGs [15]. Secondly, EORTC 22033-26033 showed the general efficacy of TMZ as a stand-alone treatment. The randomized trial patients to receive either RT to 50.4 Gy in 28 fractions or 12 cycles of TMZ (150-200mg/m²/d1-5,q28). The trial was designed to detect a 13% increase in the progression-free survival (PFS) at five years of follow up in favor of TMZ. As the trial was formally negative, a mono-therapy with TMZ is currently not recommended. None the less, TMZ was at least not significantly inferior to a mono- RT, which argues in favor of its efficacy [16]. Thirdly, the results from NOA-04 are frequently quoted, although the trial only included patients with high-grade gliomas (HGG). The trial randomized HGG patients to receive either a mono RT with 59.4 Gy in 33 fractions or chemotherapy. The chemotherapy-arm was divided in either TMZ or PCV. The important strength of this trial was the inclusion of a molecular analysis which was able to stratify an increased efficacy for PCV to patients with a co-deletion of 1p19q (loss of heterogeneity, LOH) [7]. As the less toxic TMZ was not inferior to PCV in patients without a co-deletion of 1p19q, TMZ is considered to be equally effective to PCV in diffuse astrocytomas. The obvious limitation of this argumentation is that NOA-04 only included HGGs.

Currently, the results from the CODEL-trial are pending (NCT00887146). This originally four-armed trial randomized patients with either grade II or III oligodendrogliomas, as defined by a co-deletion of 1p19q, to receive either RT alone, TMZ alone, RT with concomitant TMZ followed by 12 cycles of TMZ or RT followed by six cycles of PCV. The mono-TMZ arm was closed early after an interim analysis due to a worse PFS and OS; the mono-RT arm was closed after the results from RTOG 9402/EORTC 26951 were published [17].

While the general indication for high-risk LGGs is relatively clear, the evidence for the adjuvant treatment of low-risk LGGs is less established. Prospective data from the observation arm of RTOG 9802 supplies the best evidence for this situation. As reported by an abstract in 2006, the 111 patients in the observation arm, the 2- and five years OS was 99% and 94%; the PFS was 82% and 50% [18]. While the OS times thus were superior to the RT+PCV-Arm of the trial, the PFS was inferior to the RT-PCV arm at least at five years. Noteworthy, patients in the RT-PCV were considered to have an unfavorable prognosis as defined by the inclusion criteria [13].

Noteworthy, newer data stress the importance of the molecular pattern of LGGs as risk factors, even beyond the clinical features [6]. While some of these molecular features have already been implemented into the new WHO classification of brain malignancies [5], other markers seem to have an impact on the prognosis of LGG patients, too. The MGMT promoter methylation status is among these markers [15]. As IDH wild-type and nonmethylated MGMT promotors seem to be negative prognostic markers, these patients should undergo active treatment, even despite the presence of clinical low-risk features [1, 11].

Based on these considerations, we propose an adjuvant treatment algorithm as depicted in Figure 1.

INSERT FIGURE 1

Anaplastic Gliomas

Comparable to LGGs, anaplastic gliomas are now preferably treated with a multimodal adjuvant approach. After maximum safe resection, usually, RT is prescribed. The RT is 59.4 to 60 Gy in 33 or 30 fractions of 1.8 or 2.0 Gy. The target volume encompasses the resection cavity, contrast

enhancements on computed tomography (CT) or magnetic resonance imaging (MRI) T1-Sequences as well as mass-like FLAIR hyperintensities defined as gross total volume (GTV). A 1.5-2.0cm margin is added and adapted to account for anatomic barriers (CTV), the PTV encompasses additional 0.3-0.5 mm.

Different trials support the systemic treatment in anaplastic astrocytomas (AA) and anaplastic oligodendrogliomas (AO). Based on the results of NOA-04, AO, as defined by a LOH 1p19q, seemed to respond better to PCV as compared to TMZ [7]. As NOA-04 showed similar efficacies of mono RT and mono ChT for AA and AO, thereby proofing the stand-alone efficacy of both modalities, the RTOG as well as the EORTC started two trials to clarify the efficacy of a multimodal approach with RT with neoadjuvant (RTOG 9402) or adjuvant (EORTC 26951) PCV [19, 20]. RTOG 9402 was formally negative, with a similar OS of 4.6 and 4.7 years for patients treated with or without neoadjuvant PCV before RT [20]. Noteworthy, patients with anaplastic oligo-astrocytoma (AOA) as well as with AO could enter the trial. When the patients were stratified by LOH 1p19q, patients with a co-deletion significantly benefited from a multimodal approach (OS 14.7 vs. 7.3 years) [20]. In opposite to RTOG 9402, EORTC 26951 was positive for the entire study cohort which also included patients with AO and AOA as defined by histology (OS 42.3 months vs. 30.6 months for RT+PCV vs. RT) [19]. Also in EORTC 26951, the subgroup of patients with LOH 1p19q significantly benefited from the addition of PCV (OS not reached vs. 112 months in RT+PCV vs. RT) [19]. When comparing the tolerability of both regimens, EORTC 26951 had a better treatment compliance with 95% receiving the standard RT as compared to 76% in RTOG 9402; ChT was tolerated equally with 12%, 9%, 22% and 54% receiving 1,2,3 or 4 cycles of PCV in RTOG 9402 vs. 11%, 22%, 17% and 49 receiving 1,2,3 or 4-6 cycles in EORTC 26951 [20, 21]. The reduced RT-compliance might be a reason for the primary negative result of RTOG 9402. In conclusion, a multimodal approach with upfront RT followed by up to six cycles of PCV is the current standard of care in AO. Whether there is a role of TMZ in AO is currently unknown, as the final results from CODEL are still pending.

For AA the optimal management was less clear until the publication of the preliminary results of the CATNON trial in 2017 [22]. The large phase 3 trial randomized patients to either receive RT, RT with concomitant TMZ (RChT; 75 mg/m²/d), RT with adjuvant TMZ (12 cycles, 150-200 mg/m²/d1-5,q28) or RChT with adjuvant TMZ. A planned interim analysis showed a significantly better five year-OS for patients receiving an adjuvant ChT with TMZ as compared to patients not receiving an adjuvant ChT (55.9 vs. 44.1%) [22]. The current EANO guidelines did already include these results [1]. As the data for the concomitant ChT are not available yet, the current algorithm for AA is to treat patients with an adjuvant RT with or without concomitant TMZ, followed by up to 12 cycles of adjuvant TMZ. The treatment algorithm for WHO Grade III gliomas (AA, AO, AOA) are summarized in Figure 2.

INSERT FIGURE 2

Glioblastoma

The EORTC 26981/22981/NCIC trial by Stupp et al. defined in 2005 the current standard of care in GBM patients younger than 70 years who are in a good performance status [23]. The trial tested an adjuvant treatment with RT alone (60 Gy in 30 fractions) vs. a multimodal regimen with RT and concomitant TMZ (75 mg/m²) followed by 6 adjuvant cycles of TMZ (150-200 mg/m²/d1-5, q28). The PTV in this trial included the resection cavity as well as contrast enhancing lesions with a 1.5 – 2.0 cm margin, adapted to anatomic barriers (CTV); for positioning uncertainties, a 0.5 cm margin was added (an example can be found in Figure 3). The investigative arm gained a significantly improved survival (12.1 vs. 14.6 months), with an additional advantage for patients with methylated MGMT promoter [24]. Meanwhile, several trials investigated combination regimens with additional Bevacizumab against this standard, but they of them failed to their primary objectives [25, 26]. Only recently, the results of two trials were presented which suggested new treatment options for GBM patients. The first one investigated the effect of the addition of TTFields to the adjuvant treatment in GBM. The trial randomized 695 patients – who did not progress after standard-of-care RT with concomitant

TMZ – to either receive up to six cycles of TMZ or the same number of TMZ cycles with the concomitant use of TTFields. The trial was randomized but not blinded, which is one of the critics to the trial. However, after a median follow-up of 40 months, a significant median survival benefit of 4.9 months was evident (20.9 vs. 16.0 months) [27]. The health-related quality of life was equal in both arms of the trial [28]. Secondly, the results from the German CeTeG-Trial have been reported at the SNO conference in 2017. The trial focussed on patients with a methylated MGMT promoter, and randomized these patients into two arms. Patients in the standard arm received a standard RT with 60 Gy together with concomitant TMZ, followed by up to six cycles of adjuvant TMZ. Patients in the investigational arm received the same RT, but the systemic treatment consisted of up to six courses of CCNU (100 mg/m², d1, q42) and TMZ (100 mg/m² d2-6, q42). The primary endpoint was the median OS in the modified intention to treat-cohort (mITT). The mITT included all patients who did receive the first dose of the study-drug. The survival was analysed after a pre-specified inverse probability weighting. This technique was used to up- or down-weight patients from centers with a distribution of RPA classes that was different from the whole population. The trial randomized 141 patients and reported a significant improvement of the median OS in the mITT cohort from 31.4 months in the standard arm to 48.1 months in the investigational arm. Noteworthy, there was neither a difference in median OS between the groups when all patients were compared in the unbalanced cohort nor there was a difference in the PFS. The toxicity was higher in the investigational arm, which was mostly driven by the hematologic toxicities. Taken together, the standard of care for all patients in a good performance status is a RT to 59.4-60 Gy with concomitant TMZ followed by up to six courses of adjuvant TMZ. Especially in patients with no progression after concomitant RT/ChT TTFields can be considered. In thoroughly selected patients with methylated MGMT promotor and a very good performance status, the CeTeG regimen can be an option, too. Noteworthy, there are results from several promising trials pending, among these are trials with an intraoperative RT-boost (INTRAGO II, NCT02685605), early TTFields (Bonn…) and checkpoint-inhibition (BMS CA209-498 and BMS CA209-548).

While the former algorithm is appropriate for patients in good performance status, a different algorithm should be used for elderly and/or frail patients. The best results are achieved when patients are treated with a short-course RT (40.67 Gy in 15 fractions) with concomitant TMZ (75 mg/m²/d) followed by up to 12 cycles of TMZ (150-200 mg/m² d1-5, q28). This regimen is based on the results from NCIC CTG CE.6. The standard arm of this trial was based on the results from Roa et al., who compared a standard RT (60 Gy, 30 fractions) to a short-course RT (40.67 Gy in 15 fractions) without ChT. The mOS in this trial was not different (median OS 5.1 vs. 5.6 months) [29]. The investigational arm used the same RT but combined it with the ChT mentioned above. The investigational regimen resulted in a significant survival benefit (median OS 9.3 vs. 7.6 months), the subgroup of patients with a methylated MGMT promoter had a greater benefit (median OS 13.5 vs. 7.7 months) [30]. When patients are not considered to be fit enough to undergo multimodal adjuvant treatment, mono-therapies should be considered. The efficacy of mono RT in elderly patients was proven by a French trial which randomized GBM patients older than 70 years to either receive a standard RT (60 Gy, 30 fractions) or best supportive care (BSC). The addition of RT resulted in an improved OS (29.1 vs. 16.9 weeks) [31]. Given the poor prognosis even after addition of RT, several trials investigated shorter course RT regimens with similar results with 40.67 Gy in 15 fractions, 34 Gy in 10 fractions or 25 Gy in 5 fractions (median OS 5.6 vs. 5.1 months (34 Gy vs. 60 Gy) [29], 7.5 vs. 6.0 (40.05 Gy vs. 60 Gy) months [32] and 7.9 vs. 6.4 months (25 Gy vs. 40.05 Gy) [33]). Despite this, treatment with ChT only can be considered especially in elderly and frail patients who are presenting with a methylated MGMT promoter [32, 34].

According to the 2017 EANO guidelines, BSC is considered as a best choice, when patients are presenting with a very unfavorable prognosis, namely a Karnofsky performance score (KPS) of less than 50% (bed bound patients) as well as for patients who are not able to consent into the treatment [1]. These criteria should not be based on a single visit, as reversible conditions might, such as infections, epileptic convolutions or reversible brain edema might be present. Caregivers, therefore, should thoroughly search for this conditions, initiate an effective treatment and re-evaluate the performance status after an appropriate interval.

A summary of the presented algorithm can be found in figure 4.
INSERT FIGURE 3 AND 4

Recurrent Glioma

Depending on the grade of the disease as well as of other risk factors, many patients are challenged by recurrences throughout their disease. Currently, it is not possible to define an ideal algorithm for the treatment of recurrences, yet a multimodal approach is increasingly considered as an option for these patients. While it is beyond the scope of this review to discuss all possible treatments of recurrent gliomas, it seems germane to briefly discuss the current evidence of second surgery with a focus on adjuvant treatments.

A second surgery can be considered as a first step in the treatment whenever it is possible with a reasonable risk-profile, yet prospective data are missing for LGG and HGG. In GBM, the data from the DIRECTOR trial were secondarily analyzed for the value of a second surgery. While the trial did not show a benefit for all patients with second surgery, it did show an improved survival for a subgroup of patients with gross total resection (GTR) after second surgery (11.4 vs. 9.8 months). Patients with a subtotal resection after (STR) second surgery had a worse prognosis when compared to patients without surgery (6.5 vs. 9.8 months) [35]. The authors concluded that second surgery should only be performed when a safe GTR can be achieved. This conclusion is discussed very controversial, as pooled data from 20 centers came to different results, thereby supporting the efficacy also for STR [36].

While all patients in the DIRECTOR trial received an adjuvant ChT after the surgery, but no adjuvant Re-RT, the multi-institutional report from Ringel et al. reported on patients with surgery but with different adjuvant regimens. This enabled the authors to analyze their cohort for the value of adjuvant therapies after the second surgery. A significant benefit for patients who received an RT after second surgery was found (median OS after second surgery 8.5 vs. 13.4 months) [36]. This finding is in line with other reports [37–39]. Importantly, the indication for a second RT is re-thought currently. While Re-RT classically was prescribed only in cases with a macroscopic tumor, newer approaches now investigate the value of a second RT even after GTR of a recurrent glioma [38, 40, 41]. This approach is supported by the efficacy of adjuvant RT in the primary situation, the efficacy of Re-RT in macroscopic disease as well as by the good safety profile of Re-RT with modern RT techniques. As by now, the evidence for a routine indication of adjuvant Re-RT after GTR of recurrent gliomas is still too weak for a general recommendation. Therefore, patients with recurrent gliomas should be discussed in an interdisciplinary context and included in clinical trials as possible.

Concerning systemic treatments after a second surgery, there is no standard defined yet and recommendaions thus are based on the general efficacy of systemic protocolls in recurrent GBM without privious surgery. Nitrosurea, a re-challenge with TMZ or Bevacizumab alone or a combination ot f these drugs are frequently used [1, 42].Notably, Bevacizumab has no approval for this indication in the european union, treamtents therefore have to be requested at health insurance providers on an individual bases. Besides the traditional approaches of ChT and RT, alternating electric fields (TTFields) have proven equal efficacy as compared to best investigator choice ChT in recurrent HGG and GBM in a multicenter phase III trial [43].

Conclusion

Adjuvant treatment of gliomas has evolved to follow complex and highly differentiated algorithms. All of those clearly state that adjuvant treatment in gliomas is essential, independently of primary histology. Radiation therapy has improved over time and is now highly precise and well targeted. So normal tissue can be spared, and treatment-related sequelae can be minimized. Chemotherapy can enhance the effect of radiotherapy, which has been confirmed to subgroups of low-grade gliomas comparable to high-grade gliomas.

In the future, molecular stratification will most likely increase and will further differentiate treatments. Until then, it is important that interdisciplinary decision making takes place and that any

adjuvant treatment is offered in a modern and state-of-the-art manor including advanced radiotherapy techniques.

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Christoph Straube: received a scholarship from Medac GmbH; received a travel grant from NovoCure Ltd.;
Bernhard Meyer: work as consultants for BrainLab and Nexstim
Benedikt Wiestler: received speaker honoraria from Bayer AG
Friederike Schmidt-Graf: served as author for Medac GmbH
Claus Zimmer: has served on scientific advisory boards for Philips and Bayer Schering; serves as co-editor on the Advisory Board of Clinical Neuroradiology; has received speaker honoraria from Bayer-Schering and Philips and has received research support and investigator fees for clinical studies from Biogen Idec, Quintiles, MSD Sharp & Dome, Boehringer Ingelheim, Inventive Health Clinical UK Ltd., Advance Cor, Brainsgate, Pfizer, Bayer-Schering, Novartis, Roche, Servier, Penumbra, WCT GmbH, Syngis, SSS International Clinical Research, PPD Germany GmbH, Worldwide Clinical Trials Ltd., Phenox, Covidien, Actelion, Medivation, Medtronic, Harrison Clinical Research, Concentric, Penumbra, Pharmtrace, Reverse Medical Corp., Premier Research Germany Ltd., Surpass Medical Ltd. and GlaxoSmithKline.
Stephanie E. Combs: has served on Advisory Board of Bristol-Myers-Squibb (BMS), Advisory board and Speaker's Bureau for BrainLab; Advisory Board of Roche, Daiichi Sankyo and Varian Medial Systems. Has received Speakers Honoraria from BrainLab, Tomotherapy, Dr. Sennewald, BMS, Varian Medical Systems, Elekta, Novocure and Medac GmbH.

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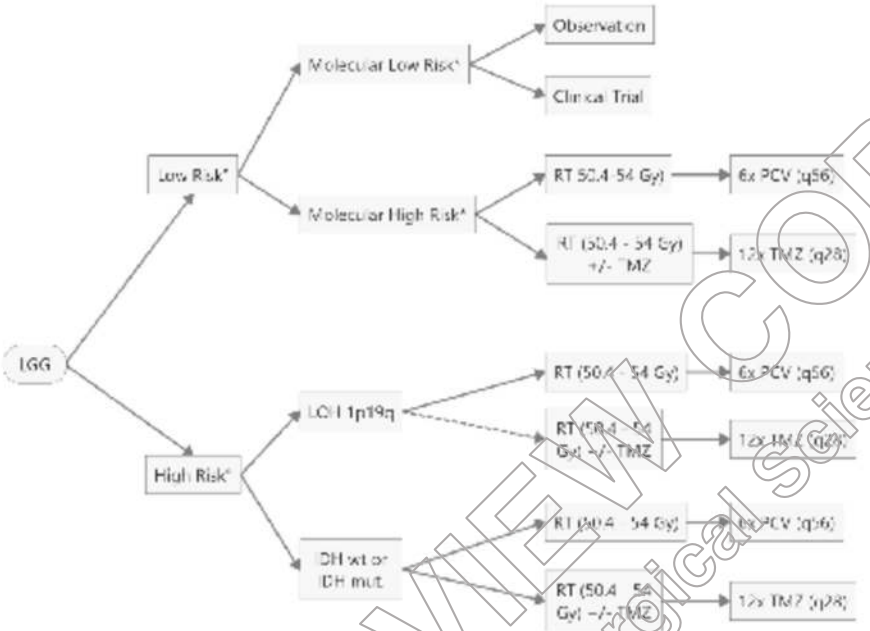

Figure 1. Treatment algorithm in LGGs. *Clinical high-risk features: subtotal resection and/or age ≥40 years. *Molecular high-risk: IDHwt and/or MGMT not methylated.

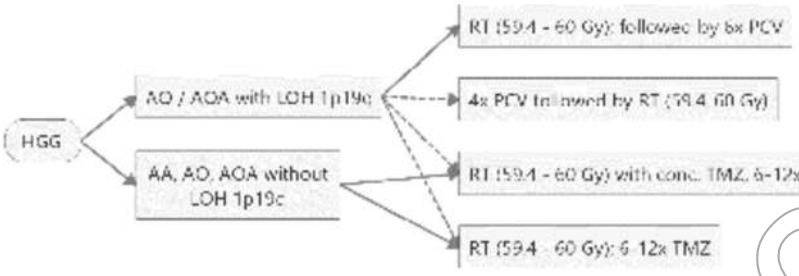

Figure 2: Adjuvant treatment algorithm for high-grade gliomas. Solid lines represent 1st choice recommendation, dashed lines represent 2nd choice recommendations.

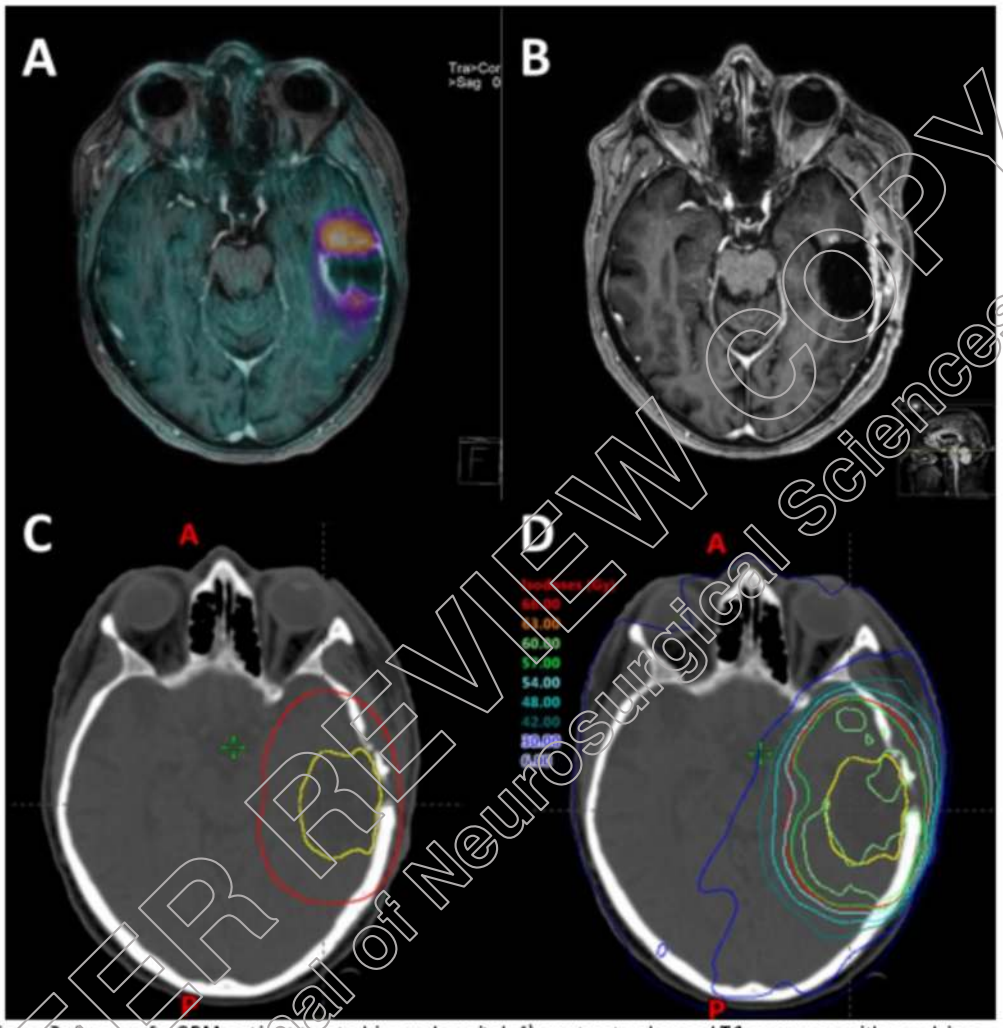

Figure 3: A case of a GBM patient treated in our hospital. A) contrast enhanced T1 sequence with overlying FET-PET image before resection. B) contrast enhanced T1 sequence after resection. There is a small remnant at the rostral edge of the resection cavity. C) Planning CT, PTV (red) resection cavity (yellow). D) Dose distribution of the RT-plan.

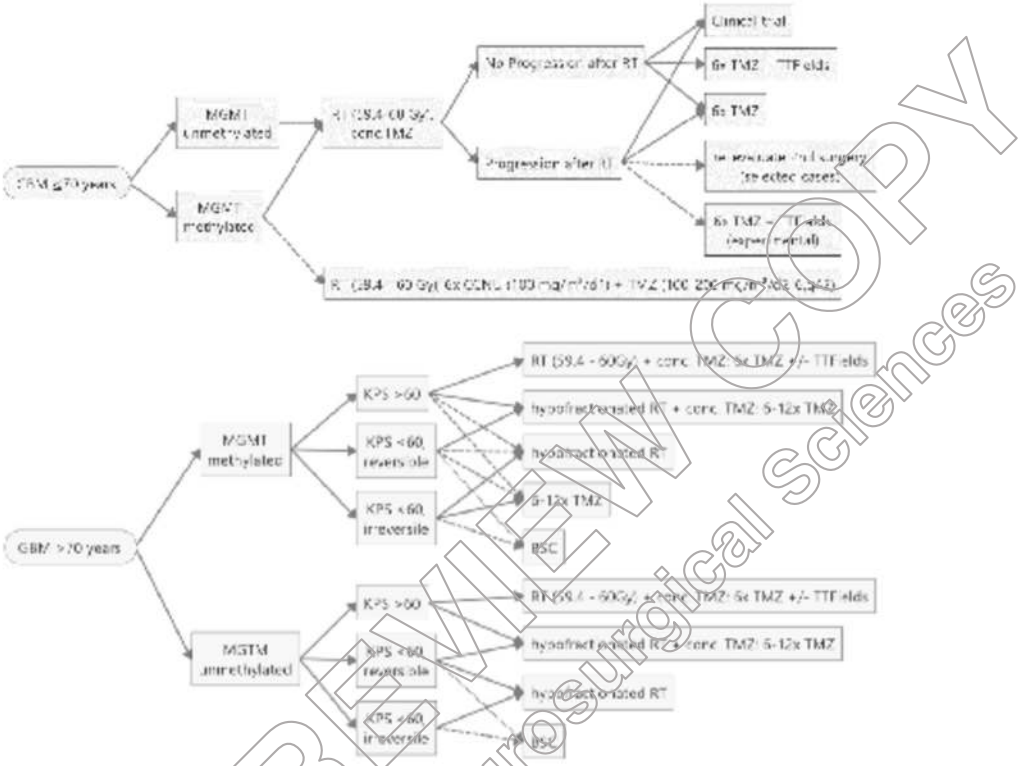

Figure 4. Adjuvant treatment in GBM. Solid lines represent the recommended strategies, whereas dashed lines are second and spotted lines are third choice options.