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Review

Radiation and concomitant chemotherapy for patients with glioblastoma multiforme

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Abstract

Postoperative external beam radiotherapy was considered the standard adjuvant treatment for patients with glioblastoma multiforme until the advent of using the drug temozolomide (TMZ) in addition to radiotherapy. High-dose volume should be focal, minimizing whole brain irradiation. Modern imaging, using several magnetic resonance sequences, has improved the planning target volume definition. The total dose delivered should be in the range of 60 Gy in fraction sizes of 1.8–2.0 Gy. Currently, TMZ concomitant and adjuvant to radiotherapy has become the standard of care for glioblastoma multiforme patients. Radiotherapy dose-intensification and radiosensitizer approaches have not improved the outcome. In spite of the lack of high quality evidence, stereotactic radiotherapy can be considered for a selected group of patients. For elderly patients, data suggest that the same survival benefit can be achieved with similar morbidity using a shorter course of radiotherapy (hypofractionation). Elderly patients with tumors that exhibit methylation of the O-6-methylguanine-DNA methyltransferase promoter can benefit from TMZ alone.

Key words Glioblastoma multiforme, radiotherapy, chemotherapy, concomitant treatment

High-grade gliomas account for 50% of primary malignant brain tumors, glioblastoma multiforme (GBM) being the most frequent (80%). Despite new advances in treatment, prognosis remains poor, with a 2-year survival rate below 25%. Generally, maximal surgical resection is recommended, taking into account postoperative morbidity and eloquent areas.

Adjuvant radiotherapy has an important role in the treatment of GBM, doubling survival when compared with surgery alone. Traditionally, GBM has been considered very refractory to chemotherapy. During the late 1990s, the drug temozolomide (TMZ) was tested. An European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) phase III trial demonstrated an increase in survival when adding TMZ to radiotherapy[1]. Patients who benefited most from this treatment were those who had a methylation of the O-6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter[2]. Most recently, new drugs that target vascular endothelial growth factor (VEGF) were introduced and are potentially attractive either as new line monotherapy or in combination with other drugs[3].

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Prognostic factors are key tools in selecting patients for inclusion in clinical trials. The prognostic significance of recursive partitioning analysis (RPA) from the Radiation Therapy and Oncology Group (RTOG) was validated in the EORTC 22981/26981-NCIC CE3 randomized trial. The factors analyzed in this trial were age, mental status, performance status, and type of surgery[4].

Malignant gliomas predominantly recur locally, whereas a few recur in the cerebrospinal fluid or outside the central nervous system[5]. In spite of well defined standards of care, the entire population of GBM patients does not undergo the full schedule of best surgery, radiotherapy, and chemotherapy. Between 2008 and 2010, 834 cases of GBM were recorded in a Spanish survey. In a community setting, 57% of all patients with GBM and 32% of older patients underwent radiotherapy with concomitant and adjuvant TMZ. In patients with surgical resection who were eligible for chemoradiotherapy, initiation of radiotherapy within 42 days since the operation was associated with better progression-free survival (PFS)[6].

The purpose of this article is to present an update on adjuvant treatment in patients with GBM after surgery.

Radiotherapy

Radiotherapy or no radiotherapy

Five trials demonstrated a statistically significant survival benefit from postoperative radiotherapy compared with supportive care only

or with different chemotherapy schedules without radiotherapy[5]. The 5 positive trials were well balanced with respect to the major prognostic factors such as age and baseline Karnofsky performance status (KPS).

The value of radiotherapy in elderly patients was demonstrated retrospectively[7]. Prospectively, a French randomized trial that compared radiotherapy with best supportive care in GBM patients 70 years or older confirmed a better outcome when radiotherapy was used. Median survival following a radiotherapy of 50 Gy over 5 weeks was 29.1 weeks compared with 16.9 weeks when supportive care only was given. PFS was 14.9 weeks versus 5.4 weeks, respectively. Radiotherapy did not impair cognition or quality of life[8].

Radiation volume and doses

Before computed tomography (CT) and magnetic resonance imaging (MRI) were available, whole brain irradiation was the standard radiotherapy technique according to most reports on the management of malignant glioma. However, the last 30 years have presented a paradigm shift with the use of partial fields with margins around tumor bed on the order of 2 cm (**Figure 1**). This has been due in part to the better tumor localization associated with imaging, to many reports documenting that the primary cause of treatment failure was related to tumor recurrence at the original site in over 90% of cases, and to the wish to reduce morbidity associated with whole brain irradiation[9]. Radiotherapy has evolved to more conformal plans with the use of multiple noncoplanar fields. In the recent years, groups such as the EORTC have implemented quality assurance programs to reduce errors delivering radiation[10].

Conventionally fractionated radiotherapy is the most used scheme for delivering radiation. The Medical Research Council randomized trial for grades 3 and 4 gliomas compared 45 Gy in 20 fractions with 60 Gy in 30 fractions[11]. Survival was significantly better when 60 Gy in 30 fractions were administered. An American trial had previously found that higher total doses or larger volumes did not lead to a difference in overall survival (OS)[12].

Hyperfractionated radiotherapy

Hyperfractionation involves the use of a larger number of small-sized fractions to a total dose that is higher than that delivered with conventional radiotherapy in the same overall treatment time. Glioma cells divide relatively rapidly, and an increased number of daily fractions have greater potential to irradiate these cells at a more sensitive phase of their cell cycle. With smaller radiotherapy doses per fraction, cell killing is less dependent upon oxygen, which might be advantageous given the prevalence of hypoxia in these tumors. However, a number of studies have failed to demonstrate any benefit with hyperfractionation, and this approach has been abandoned by large research groups and in clinical practice.

The largest trial on hyperfractionation showed no benefit in malignant gliomas[13]. This randomized trial included 712 patients,

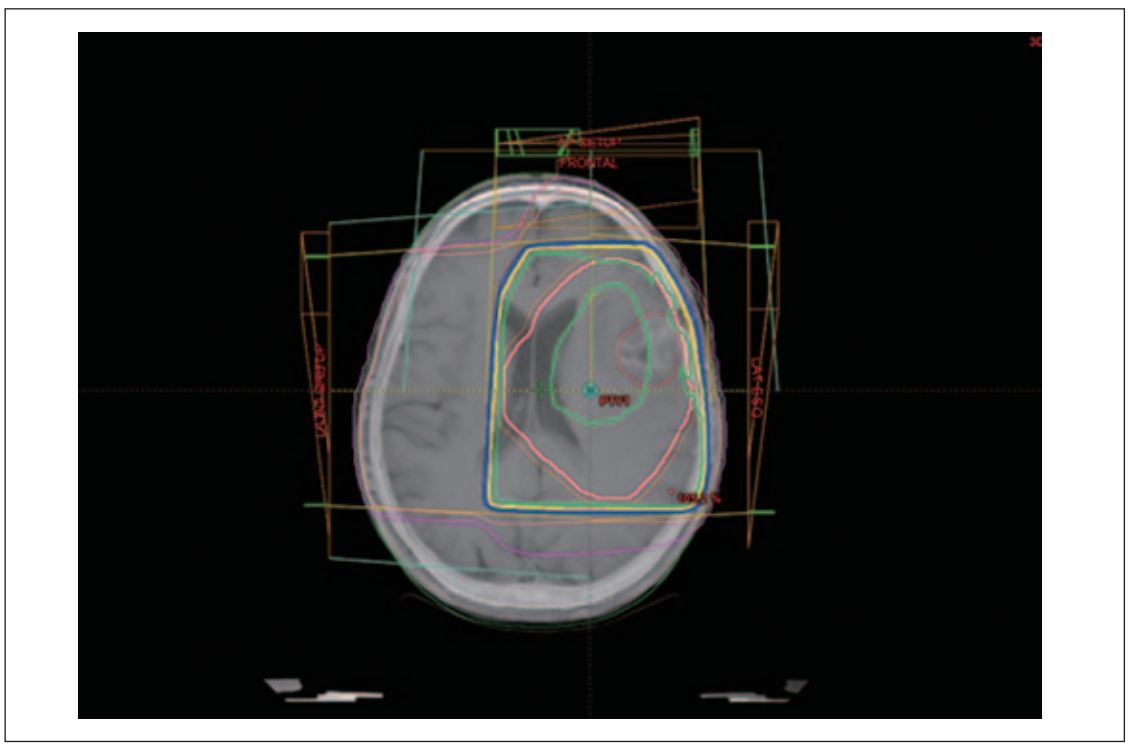

Figure 1. **Example of the technique for conventional 3-dimentional radiation therapy in a patient with glioblastoma multiforme affecting the left hemisphere (40 Gy in 15 fractions). Three fields are encompassing gross tumor vouume (GTV; red line), clinical target volumn (CTV; pink line), and planning target volumn (PTV; orange line) for this only biopsied tumor in an old woman.**

and the overall and subgroup analyses demonstrated no significant difference in median survival for hyperfractionated radiotherapy compared with conventional radiotherapy. However, in an older randomized trial reported by the Radiation Therapy Oncology Group (RTOG), the experimental arm that entailed 72 Gy in 60 fractions proved to be better than conventional 60 Gy in 30 fractions[14].

Accelerated fractionated radiotherapy

The aim of accelerated fractionation is to reduce overall treatment time so that tumor repopulation during radiotherapy is minimized. This is achieved by delivering 2 or 3 fractions per day with normal-sized fractions. An accelerated regimen was evaluated in a trial conducted by the EORTC[15]. Patients were randomly assigned to conventional radiotherapy or accelerated radiotherapy with or without misonidazole. Accelerated fractionation consisted of 3 fractions of 2 Gy per day to deliver 30 Gy in 1 week. This scheme was repeated after a 2-week break for a total dose of 60 Gy. There was no difference in survival between the treatment groups and no increased toxicity with accelerated radiotherapy.

Brada *et al*.[16] reported a single-arm study of accelerated fractionation in 211 patients with malignant astrocytomas. Radiotherapy consisted of 55 Gy in 34 twice-daily fractions delivered to the enhancing gross tumor with a 3-cm margin. Median OS was 10 months, which was similar to a matched cohort of patients who had received 60 Gy in 30 fractions.

Prados *et al*.[17] conducted a prospective phase III trial in patients with GBM. The authors observed no OS or PFS benefit with accelerated hyperfractionated radiotherapy to 70.4 Gy, nor was there any benefit with radiosensitizers.

Other authors have explored various total doses with an accelerated hyperfractionated regimen, as well as different tumor volumes. When a higher dose (70.4 Gy vs. 64.0 Gy) was delivered to smaller volumes, using hyperfractionated radiotherapy in both arms, survival was improved but not significantly[18].

Hypofractionation

Hypofractionation refers to the use of fewer large-sized radiation fractions to reduce the overall treatment time. Glinski[19] reported a randomized trial in 108 patients with high-grade gliomas comparing 50 Gy in 25 fractions to the whole brain with a hypofractionated regimen consisting of 3 courses of radiotherapy separated by a 1-month interval. The first two courses of hypofractionation were 20 Gy in 5 fractions to the whole brain, whereas the third course was a 10-Gy boost to the tumor bed in 5 days. An analysis of all 108 patients demonstrated no significant difference in survival between the two arms, but there was a significant survival benefit favoring hypofractionated radiotherapy compared with conventional radiotherapy in a subgroup of 44 patients with GBM (23% vs. 10% at 2 years). The improvement in techniques such as intensity modulation seems feasible and safe, and it can be used with hypofractionation. Nevertheless, this approach does not increase the time to disease progression or OS compared with historical experience[20,21].

Radiation treatment of brain tumors in the elderly is particularly challenging due to the declining mental function in this age group and the risk that radiotherapy will exacerbate this decline. Almost half of patients with GBM are aged 65 years or older and are excluded from the main trials. Over the last 2 decades, an increasing incidence of GBM in the elderly has been noted, partly due to the increased availability of CT and MRI for diagnosis. In this context, Roa *et al*.[22] reported a prospective phase III trial comparing an abbreviated course (hypofractionated) with conventional radiotherapy in older patients with GBM. They compared 60 Gy in 30 fractions with 40 Gy in 15 fractions, and observed no differences in survival. Patients had similar KPS scores and a similar decrease in need for corticosteroids. The authors concluded that this shorter schedule is reasonable for older patients. Therefore, this hypofractionated schedule or similar schedules can be considered not only for older patients but also for patients with very bad clinical conditions such as lower RPA classes.

An ongoing phase III trial (GBM in elderly) run by NCIC and EORTC is currently evaluating the role of TMZ given together with short-course radiotherapy in patients 65 years of age and older.

Sensitizer studies

Radiosensitizers are chemicals that increase the lethal effects of radiation. The two major classes of compounds investigated to date are hypoxic cell sensitizers and halogenated pyrimidines. Only a very old small trial showed a difference in survival with metronidazole, but admittedly, the survival in the radiotherapy alone arm was particularly low[23].

Radiosurgery

Stereotactic radiosurgery (SRS) refers to the delivery of a high-dose single fraction of radiotherapy using stereotactic techniques to conform the dose to the contrast-enhanced tumor only (**Figure 2**). The RTOG 93-05 phase III trial analyzed this approach and included 186 patients. The trial did not show an advantage to adding SRS as a boost before conventional radiotherapy in patients with small tumors (tumor size less than or equal to 40 mm). No differences were found in terms of OS for the entire population regarding RPA prognostic classes, preoperative tumor size less than or equal to 40 mm, SRS techniques, patterns of failure, quality of life, or minimental status examination[24]. The American Society of Radiation Oncology's (ASTRO's) evidence-based review did not find any sufficient criteria to implement a boost with SRS either on primary tumors or for recurrent disease[25]. A recent review by Binello *et al*.[26] concluded that only the RTOG 93-05 randomized trial has been defined as high evidence. Complete resection can influence the outcome of these patients. Also, tumor size, KPS, and tumor grade are prognostic factors. Consequently, SRS can be recommended only for a selected group of patients.

Radiation toxicity

Radiotherapy has long been recognized for its potential to cause

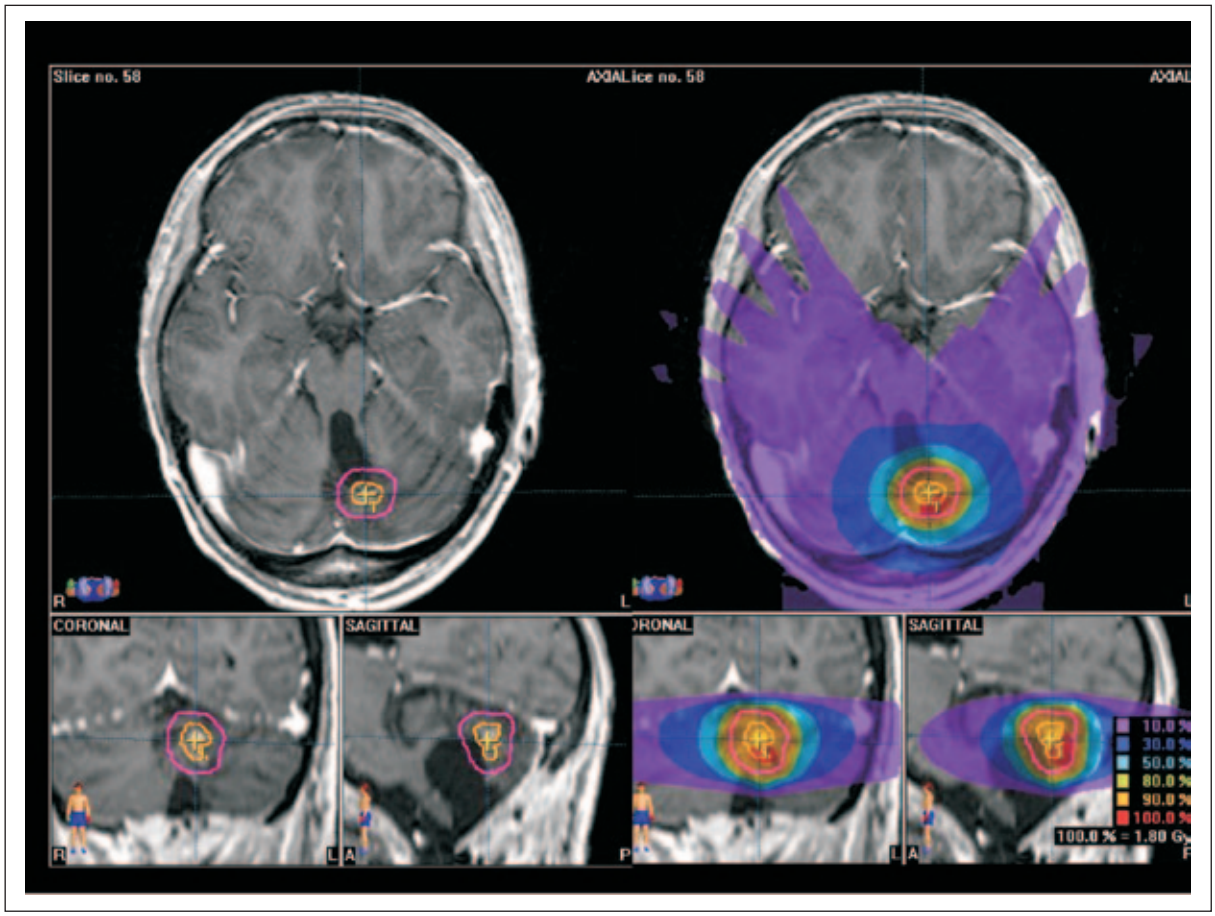

Figure 2. **High precision radiotherapy using stereotactic system. Example of hypofractionated stereotactic radiotherapy as a rescue after small relapse of glioblastoma multiforme.**

significant deleterious effects on normal brain tissue[27]. Radiation toxicity can sometimes be very difficult to ascertain in patients with GBM for two reasons: the short median survival is probably not long enough for late radiotherapy toxicity to become apparent in many of these patients; and these tumors are associated with large areas of necrosis, which may be mistaken for radiotherapy damage on imaging studies.

Adverse effects from radiation should be differentiated between acute (during radiation), early-delayed (up to 3 months post radiotherapy), and late (more than 3–6 months post radiotherapy). Symptoms related with encephalopathy include headache, drowsiness, fever, vomiting, and worsening of neurological deficits that are probably linked to blood-brain barrier disruption and increased edema. Symptoms of early-delayed complications include somnolence syndrome (mostly in children). Transitory cognitive disturbances mainly affecting short-term memory and attention have also been identified. Delayed complications include focal cerebral radionecrosis, a particularly severe radiation-induced complication that mainly affects the white matter. On neuropathologic examination, radionecrosis, which is related with increased dose of radiotherapy[24], is defined as necrosis with severe vascular lesions, namely stenosis, thrombosis, hemorrhage, and fibrinoid vascular necrosis. Late complications are unpredictable and depend on individual sensitivity to radiotherapy. The latency of such changes can be as short as 3 months. Symptoms associated with radionecrosis are non-specific and can mimic tumor recurrence. Similarly, radionecrosis cannot be discriminated from recurrent tumors with conventional MRI. Metabolic imaging techniques such as positron emission tomography (PET) with fluoro-deoxyglucose (FDG) and single photon emission computed tomography (SPECT) have been used, and their sensitivity ranges from 80% to 100%. The development of magnetic resonance spectroscopy seems promising. Advanced imaging with which to assess treatment response and toxicity will progressively be incorporated in daily practice[28].

Treatment of focal radionecrosis includes surgical resection and corticosteroids. To date, other approaches such as hyperbaric oxygen, alpha-tocopherol and deferoxamine, anticoagulants, and anti-VEGF drugs have not shown any benefit[27].

The most common and serious delayed complication of cerebral radiotherapy is cognitive dysfunction related to radiation-induced

leukoencephalopathy. Currently, there are no available treatments for this adverse effect, but a very careful radiotherapy planning, including avoiding sensitive structures like the hippocampus, may be a promising preventive strategy[29].

Chemotherapy as First-Line Treatment

Historically and prior to the development of TMZ, nitrosoureas [carmustine (BCNU), lomustine, procarbazine] were the drugs used most frequently to treat cerebral tumors because of their liposolubility, which enables them to cross the blood-brain barrier. Randomized studies failed to demonstrate that treatment with nitrosoureas following surgery and radiotherapy increases survival. However, an increase in the percentage of patients receiving carmustine who were alive at 18 months was noted. Furthermore, two meta-analyses have shown a marginal benefit for nitrosoureas in all age groups and subgroups of high-grade glioma[30,31].

The standard first-line treatment for GBM was established with the EORTC-NCIC randomized phase III trial[1]. This trial showed a significant improvement in survival in patients who had undergone tumor resection and were treated with a combination of radiotherapy and concomitant TMZ, with 6 cycles of subsequent TMZ after a 4-week break. This regimen conferred a benefit over radiotherapy alone both in PFS (6.9 vs. 5 months) and in OS (14.6 vs. 12.1 months). The unadjusted hazard ratio (HR) for death in the radiotherapy-plus-TMZ group was 0.63 [95% confidence interval (CI), 0.52–0.75; $P < 0.001$ by the log-rank test]. Moreover, 26.9% of the patients undergoing this treatment were progression-free at 12 months, 18.4% at 18 months, and 10.7% at 24 months. Long-term results corroborated the benefit, with 9.8% (6.4%–14.0%) of patients still alive if treated with TMZ and 1.9% (0.6%–4.4%) if treated with radiotherapy alone (HR, 0.6; 95% CI, 0.5–0.7; $P < 0.001$)[2]. Toxicity was tolerable, with a 7% grade III–IV hematologic toxicity in the concomitant phase and 14% in the adjuvant phase. So far, no other study has been able to improve upon these results. Thus, concurrent and adjuvant treatment with 6 cycles of TMZ was established as a standard following surgery in 2005[1].

TMZ acts as a DNA methylating agent. It is administered orally and penetrates the blood-brain barrier. High expression of the repair enzyme MGMT can overcome TMZ-induced DNA damage and confers drug resistance to the tumor. The MGMT enzyme is encoded by the *MGMT* gene. *MGMT* may be methylated at GpG islets, causing enzyme inactivity. *MGMT* methylation status is predictive of response to TMZ. In the pivotal EORTC-NCIC study, patients with methylated *MGMT* derived better benefit when treated with TMZ, 48.9% (33.7%–62.4%) of patients with tumors exhibiting methylated *MGMT* were alive at 2 years versus 14.8% (7.2%–25.0%) of patients with tumors exhibiting unmethylated *MGMT*[2]. However, determining *MGMT* methylation status may not be mandatory for therapeutic decisions because TMZ still provides a marginal benefit to patients in the unmethylated *MGMT* group. The current recommendation is to continue adjuvant TMZ for at least 3 cycles because of a phenomenon called pseudoprogression. Pseudoprogression represents a false radiological worsening on MRI with changes in gadolinium uptake. It is not a reliable indication of tumor growth, as the increase in the permeability of the blood-brain barrier can occur secondary to radiation, to radiation necrosis, or to the antitumor effect[32]. This phenomenon can occur in up to 20% of patients who have been treated with TMZ and/or radiotherapy and can explain the increase in lesion size after the end of treatment in about half of all cases. These false images can last for months and may confound the evaluation of residual disease but, paradoxically, have been related to longer survival[33].

The benefit of TMZ for older patients ($\geqslant$ 65 years old) was analyzed in the EORTC-NCIC trial only in subgroup analysis[1]. Two European trials (the NOA-08 and Nordic trials) have patients over 65 or over 60 years old, respectively, randomized to undergo radiotherapy only or chemotherapy with TMZ. Data from the two trials suggest that TMZ is not inferior to radiotherapy alone, and patients whose tumors harbor methylated *MGMT* can be treated with TMZ alone, which achieve similar results to those in patients treated with radiotherapy[34,35]. However, neither of these trials has compared TMZ with radiotherapy or chemoradiotherapy, the current standard regimen. Notably, the results of two trials (AVAGLIO and RTOG 08-25) that evaluated the addition of bevacizumab to the standard treatment have recently been reported at international meetings[3,36]. Bevacizumab is an antiangiogenic compound shown to be active in the recurrent setting. Neither the AVAGLIO trial nor the RTOG 08-25 trial demonstrated any differences in OS. The AVAGLIO trial found an increase in PFS from 6.2 to 10.6 months (HR, 0.64; 95% CI, 0.55–0.74; $P < 0.001$), with an improvement in the quality of life, a longer time to maintain KPS, and a decreased use of steroids. However, the results of the RTOG 08-25 trial were disappointing. Although a difference in PFS was detected (from 7.3 to 10.7 months; HR, 0.79; 95% CI, 0.66–0.94; $P = 0.007$), the data did not meet the pre-specified trial statistical considerations. Moreover, no improvement in quality of life has been found, and the data on neurocognitive impact and quality of life contradict the previously reported AVAGLIO trial.

Conclusions

Postoperative external beam radiotherapy with concomitant and adjuvant TMZ is the standard of care for patients with GBM. The high-dose volume should incorporate the contrast-enhanced tumor plus a margin using several MRI sequences for the planning target volume. The total dose delivered should be in the range of 60 Gy in fraction sizes of 1.8–2.0 Gy. Radiotherapy dose intensification and sensitizer approaches are not yet recommended as standard therapy. Stereotactic radiotherapy could be considered for a selected group of patients. For patients older than 65 years, data suggest that the same survival benefit can be achieved with similar morbidity using a shorter course of RT. Elderly patients with tumors exhibiting methylated

MGMT can benefit from TMZ alone, with deferred radiotherapy (**Table 1**). Other concomitant drugs deserve further investigation.

Table 1. Take-home points of care for patients with glioblastoma multiforme in terms of radiation and concomitant chemotherapy

List number	Points of care
1	Postoperative external beam radiotherapy is mandatory.
2	High-dose volume should be focal, eliminating the potential for whole brain irradiation.
3	Modern imaging, using several MRI sequences, has improved planning target volume definition.
4	The total dose delivered should be in the range of 60 Gy in fraction sizes of 1.8–2.0 Gy.
5	Temozolomide concomitant and adjuvant to radiotherapy is the main medical treatment.
6	Radiotherapy dose intensification and radiosensitizer approaches did not improve outcome.
7	Stereotactic radiotherapy could be considered for selected group of patients.
8	For elderly patients, similar local control and morbidity have been seen using hypofractionated radiotherapy. Patients with methylation of *MGMT* promoter can benefit from temozolomide alone.

MRI, magnetic resonance imaging; MGMT, O-6-methylguanine-DNA methyltransferase.

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