



Glioblastoma — treatment and obstacles

Farley Soares Cantidio , Gabriel Oliveira Bernardes Gil, Izabella Nobre Queiroz, Marcos Regalin

Hospital da Baleia, Belo Horizonte, Minas Gerais, Brazil

ABSTRACT

Background: Glioblastoma is the most common and aggressive primary tumor in adults. A narrative review of all the relevant papers known was conducted.

Materials and methods: Reviews, clinical trials, and randomized controlled trials published from 1981 through September 2021 and written, or at least abstracted, in English were analyzed.

Results: The standard of care for glioblastoma is the maximum safe resection possible, followed by radiation therapy and concurrent temozolomide (TMZ) and daily TMZ and tumor treatment fields (TTFields) after irradiation. There is no evidence to date of the benefit of brachytherapy, radiosurgery (SRS), fractional stereotactic radiotherapy (FSRT), and hyperfractionated radiotherapy over conventional external beam radiation therapy (EBRT) for the primary tumor. The assessment of age and performance status before treatment in the elderly enables hypofractionated radiotherapy. The research of tumor molecular signatures contributes to the choice of the best-targeted drug therapy. In recurrent glioblastoma, it is necessary to balance the risks and benefits of re-radiation and association with bevacizumab. Solid data confirming the role of immunotherapy in the treatment of malignant glioma are still lacking.

Conclusions: Although the treatment of glioblastoma has evolved in terms of local control, mortality remains close to 12 months after diagnosis. To obtain better results and reduce recurrence, future research needs to investigate the frontiers of knowledge, such as the elucidation of the molecular mechanisms related to the tumor, the optimization of drugs to overcome the blood-brain barrier effectively, and the discovery of new therapies aimed at the heterogeneous profile of this neoplasm.

Key words: glioblastoma; malignant glioma; radiation therapy; temozolomide

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Introduction

Glioblastoma or malignant glioma is the most common and aggressive primary tumor in adults [1]. A histological feature of this neoplasia is the cellular and morphological heterogeneity and cells with a diverse grade of differentiation [2]. The tumor bulk is organized into three major parts: the necrotic central area, the proliferative and angiogenic region, the brain adjacent to the tumor including

the invasive and escaping tumor cells [3]. Multiple foci lesions can be found in about one-third of patients with glioblastoma at diagnosis and have worsened prognostic because of surgical difficulties during gross safe maximal tumor resection [4]. The malignant glioma is derived from the neuroglial stem cells or progenitor cells [5] and neoplasia originate from somatic molecular defects in three pathways: initiating tumor growth, evading senescence, and enabling immortal growth [6].

Address for correspondence: Dr Farley Soares Cantidio, Physician at Hospital da Baleia, Belo Horizonte, Minas Gerais, Brazil, Hortencia Street, Esplanda, 454, Belo Horizonte, Brazil, tel: +55 (31) 996 276 511; e-mail: farleysoares@yahoo.com.br

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In contrast to other solid tumors, the malignant glioma cells do not spread by intravascular or lymphatic routes, but they use the perivascular space, glutamate-mediated Ca^{2+} changes, Ca^{2+} -activated K^+ channels, and the brain to infiltrate and invade the distant parenchyma. The invasive tumor cells migrate along blood vessels, leading to the displacement of astrocytic endfeet, degradation of tight junctions on endothelial cells, and breakdown of the basal membrane surrounding blood vessels. Hence, serum components leak into the cerebral parenchyma [7].

Glioblastomas are classified as a primary tumor and secondary neoplasm when originating from grade II or III gliomas [1]. The primary type or glioblastoma de novo is the most common and develops in elderly patients without clinical or histological evidence of a less malignant antecedent lesion. The secondary type comes from low-grade astrocytoma and anaplastic astrocytoma. They occur in young patients, have less necrosis, are especially found in the frontal lobe, and carry a better prognosis [8].

The World Health Organization (WHO) classifies this tumor as grade IV and the major histopathology findings are necrosis and endothelial proliferation [1].

They represent 45% of all gliomas with a 5-year relative survival of 5% [9]. With increased life expectancy and a higher incidence of glioblastoma in old people, the median age at diagnosis changed to 64 years [10]. Males tend to be more affected than women in proportion 1.7:1 [5]. Malignant gliomas are devastating tumors and the patient's death can occur within one year of diagnosis [7].

Glioblastoma is associated with genetic syndromes caused by Mendelian disorders, including neurofibromatosis, tuberous sclerosis, and Li-Fraumeni. The most significant risk factor studied related to malignant gliomas is exposure to ionizing radiation [9]. However, the latency period for neoplasia development is unknown [6].

Materials and methods

A narrative review of all the relevant papers known was conducted. MEDLINE and PubMed databases were searched using the keywords “glioblastoma”, “glioblastoma and radiation”, “glioblastoma and temozolomide”. Reviews, clinical trials,

and randomized controlled trials published from 1981 through September 2021 and written, or at least abstracted, in English were analyzed. In addition, more current studies published up to September 2021 were included in the review to discuss management of glioblastoma recurrence. The references which comprised mainly large and current articles were selected. The older original studies that have been referenced widely and are greatly respected were not excluded.

Molecular signature

The molecular markers for prognosis and treatment options determination are O6-methylguanydil DNA-methyltransferase (MGMT) and isocitrate dehydrogenase (IDH). Glioblastomas with MGMT promoter methylated have better prognosis, unlike tumors without isocitrate dehydrogenase 1 and 2 mutations and the telomerase reverse transcriptase (TERT) mutated [11], with a worse prognosis [12].

Most of the glioblastomas are IDH-wildtype [1], corresponding to 90% [5, 13] and another 10% are glioblastoma IDH-mutant that arises in the younger patients. The median age of diagnosis is 44 years for IDH mutant and 62 years for IDH-wildtype [13]. IDH mutations are associated with prolonged progression survival-free (PFS) [14].

There is another variant most detected in children and young adults classified as epithelioid glioblastoma present as superficial or diencephalic mass and frequently it has a BRAF V600E mutation [13].

Promoter methylation of the gene encoding the DNA repair protein, MGMT predicts benefit from alkylating chemotherapy with temozolomide and guides first-line treatment in elderly patients [1]. The DNA-repair enzyme MGMT inhibits the killing of tumor cells by alkylating drugs and its activity is controlled by a promoter. When promoter methylation is present there is silencing of the cancer gene and the cells no longer produce MGMT [15].

In a trial with the objective to explore whether the isocitrate dehydrogenase 1 (IDH1) or 1p19q status are associated with prognostic and predictive significance, the results indicated that MGMT promoter methylation was a predictive biomarker for benefit from alkylating agent chemotherapy in pa-

tients with IDH-wild type, but not IDH-1 mutant, malignant gliomas grades III/IV [16].

In patients with MGMT promoter methylated tumors, monotherapy with temozolomide is superior to radiotherapy alone. Similarly, the results of combined temozolomide-based chemoradiotherapy compared to radiotherapy alone are more consistent in patients with this methylation [17].

The analysis of MGMT promoter methylation by pyrosequencing is an appropriate and reliable method used with diagnostic samples and may be used to distinguish two or more prognostic groups in response to chemoradiotherapy [18].

The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein and a member of the tyrosine kinase receptor superfamily, which has been identified in glioblastomas, including amplification, deletions, and single nucleotide polymorphisms (SNPs) [19].

Diagnosis

The tumor sample is frequently required for a definitive diagnosis even if the computed tomography (CT) and magnetic resonance imaging (MRI) strongly suggest glioblastoma. Therefore, a biopsy or surgical resection is mandatory to allow for a better neoplasia characterization [17].

The diagnosis is based on a biopsy and shows an infiltrating glial fibrillary acidic protein immunopositive tumor with pleomorphism, brisk mitotic activity, microvascular proliferation, and necrosis. The cellularity is astrocytic, but in some cases, a group of tumor cells contains oligodendroglial or primitive neuroectodermal features [10].

Prognosis

Young age and good performance status are good prognostic indicators [5] and both points integrate the Recursive Partitioning Analysis of Malignant Glioma (RPA) that is associated with prognostic significance overall as well as in patients receiving radiation therapy (RT) with or without temozolomide (TMZ) for newly diagnosed glioblastoma, particularly III and IV grades. The trial results revealed in RPA classes III, IV, and V a median survival time of 17, 15, and 10 months and 2-year survival of 32%, 19%, and 11%, respectively [20].

Clinical presentation

The variable clinical presentation is related to the tumor location, but the headache is the most common symptom and is associated with mass effect [10]. The pain pattern is progressive, unilateral localization may awake the patient from sleep, accompanying focal deficits. Another symptom at the presentation of glioblastoma includes nausea, vomiting, cognition and personality changes, gait imbalance, urinary incontinence, hemiparesis, aphasia, hemineglect, visual field defect, and seizures [21].

Images

There is no evidence for early detection of glioblastoma. Magnetic resonance imaging is the more sensible method for diagnosis, however, once glioblastoma is suspected it is inevitably in an advanced state. The glioblastoma imaging reveals an infiltrative, heterogeneous, ring-enhancing lesion with central necrosis and surrounding peritumoral edema. Involvement of the deep white matter and the corpus callosum is common [10].

Most patients undergo computed tomography (CT) of the brain at diagnosis and when mass is identified and hemorrhage is excluded, a contrast-enhanced magnetic resonance imaging (MRI) is normally ordered, with standard T2-weighted (T2w), T2-fluid-attenuated inversion recovery (T2-FLAIR), gradient echo, T1-weighted (T1w) and T1-weighted contrast-enhanced (T1CE) sequences. The perfusion is increased because of the higher relative cerebral blood volume (rCBV) in the region of the mass tumor [22].

Glioblastoma often presents as a single peripheral enhancing lesion, but multiple enhancing images can be found, named multifocal if there is a connection between enhancing lesions as evidenced in FLAIR sequence, or multicentric when no communication is proven. Tumors with involved deep structures and located in the posterior fossa are associated with worse survival due to these key being structures affected [4].

Gadolinium-enhanced MRI showed to be important for evaluation of gross residual tumor when ordered during days 1 to 3 after the resection of a preoperatively enhancing high-grade glioma. This timing allows surgically-induced

contrast enhancement to be avoided and interpretative difficulties as post-operative artifacts to be minimized [23].

Radiation necrosis and pseudoprogression are usually considered opposite directions on the spectrum of radiation-induced injury, and imaging features may mimic disease progression [24].

Treatment

Since 2005, standard treatment of glioblastoma has been surgery, radiotherapy, and alkylating chemotherapy [1, 5]. Patients younger than 70 years should be managed with maximal safe surgical resection, followed by radiation therapy (RT) and concomitant TMZ [10]. In clinical trial results, the two-year survival rate was 26.5% with RT plus TMZ vs. 10.4% with RT alone [25]. 97% of patients in the radiotherapy alone group and 89% in the combined-treatment group died after five years of follow-up of this study and MGMT methylation status most likely benefited patients from the addition of temozolomide [26].

The oral alkylating agent temozolomide approved by the Food and Drug Administration (FDA) in 1999 [27] should be taken with a daily therapeutic dose of 75 mg/m² concurrent to RT and then with a daily dose of 150 to 200 mg/m² for five days of every 28-day cycle during 6 cycles [25].

The continuing temozolomide beyond 6 cycles in patients without disease progression did not increase overall survival, except for the progression-free survival that was associated with a slight improvement for patients, especially with methylated MGMT [28].

Because of immunosuppression risk, mainly lymphocytopenia in concomitant treatment, trimethoprim-sulfamethoxazole prophylactic is used for prevention of pneumocystis pneumonia [25].

The management of elderly patients is similar to that of younger ones but the performance status, as well as comorbidities, are important factors of individual decisions [17].

Complete resection is usual surgically difficult due to the infiltrative nature of this disease and, therefore, with high rates of relapse [29].

Except for prolonged progression-free, but not overall survival guaranteed from bevacizumab, a kind of vascular endothelial growth factor antibody, no pharmaceutical intervention has been

demonstrated to alter the course of disease [5]. However, bevacizumab increases the risk of severe hematological and thromboembolic events and current evidence shows little benefit in elderly patients outside clinical trials [30].

Antiepileptics are indicated in patients with seizures, but not for prophylactic purposes. Levetiracetam is preferred, given its excellent toxicity profile and lack of interactions with most chemotherapy agents [21].

Radiotherapy and chemotherapy with temozolomide might be considered as a standard of care in elderly glioblastoma patients and good Karnofsky Performance Status Scale (KPS). Patients with MGMT promoter-unmethylated tumors may still be candidates for radiotherapy only. Monotherapy with TMZ is an option if methylation is present and radiochemotherapy is not possible [17].

The inactivation of the MGMT promoter methylation increases the sensitivity of malignant cells to the DNA-damaging effects of alkylating agents (2). Instead, in the absence of silencing of the MGMT promoter, there is a smaller and statistically insignificant difference between the RT and RT plus TMZ treatment groups [18].

In a trial comparing a group of patients with methylated MGMT promoter versus unmethylated MGMT promoter, the median overall survival was 18.2 months and 12.2 months, respectively. The methylation MGMT promoter decreased the risk of death in 55% [31].

The radiation dose results from the study show that 60 Gy in 30 fractions over 6 weeks is better than 45 Gy in 20 fractions over 4 weeks with prolongation of median survival from 9 months to 12 months [32]. The trials with doses higher than 60 Gy demonstrated inferiority in survival of patients [33] and results comparable to historical controls [34].

In a study comparing the abbreviated course of RT in elderly ≥ 60 years, KPS ≥ 50 and glioblastoma, the patient treatment with 40 Gy in 15 fractions over 3 weeks and standard RT with 60 Gy in 30 fractions over 6 weeks did not show any difference in survival between patients. This option of fractionation is reasonable for old people with reduced treatment time and decreases corticosteroids necessity during irradiation [35].

In elderly people with glioblastoma, the addition of temozolomide to short-course radiotherapy

with 40.05 Gy dose in 15 fractions resulted in overall survival benefit compared to RT alone (13.5 vs. 7.7 months) [36].

The hyperfractionated treatment was compared to conventional radiation therapy in a study with 72 Gy in 60 fractions twice daily versus 60 Gy in 30 fractions given once daily. There was no trend or indication of a benefit to hyperfractionated radiotherapy in any subset of malignant glioma patients. In a follow-up study, there was no difference in median survival time [37].

There was no improvement in the quality of life or cognitive functioning with stereotactic radiosurgery (SRS) with dose from 15 Gy for largest to 24 Gy for smallest tumors (as in reference number 38, page 5 of the manuscript) respectively, followed by conventional external beam radiation therapy (EBRT) with 60 Gy in 30 fractions and carmustine (BCNU) 80 mg/m², days 1–3 every 8 weeks for six cycles. The median overall survival was 13.5 months in the SRS group as compared to 13.6 months for the EBRT with carmustine treatment [38].

The use of fractionated stereotactic radiotherapy (FSRT) with 5 Gy and 7 Gy in one fraction for lesions > 40 mm and ≤ 40 mm, respectively, was tested after 50 Gy in 25 fractions of EBRT, followed by BCNU 80 mg/m², days 1–3 every 8 weeks for six cycles. The results indicated no significant survival benefit in using this dose-intense RT regimen [39].

The brachytherapy with iodine-125 implants after EBRT with a dose of 50 Gy in 25 fractions delivering peripheral tumor dose of 60 Gy did not demonstrate a statistically significant improvement in survival in the initial management of patients with malignant astrocytoma [40]. In another trial, these iodine-125 seeds did not take a long-term survival advantage for patients [41].

The European Organization for Research and Treatment of Cancer (EORTC) recommends 2-3 cm margins around MRI or CT enhancing abnormalities on T1 for 60 Gy and Radiation Therapy Oncology Group (RTOG) includes target volumes with 2 cm margins on T2 signal abnormalities for the 46 Gy and 2.5 cm margin on T1 enhancement for a 14 Gy boost [42].

The tumor-treating fields (TTFields) is a device that emits medium frequency (200 kHz) with antimitotic action in glioblastoma cells division and organelle. In comparison to maintenance TMZ alone, TTFields with standard treatment maintenance

temozolomide showed increased progression-free survival (6.7 vs. 4.0 months) and median overall survival (20.9 vs. 16.0 months) [43]. Then, the TTFields addition to radiation therapy and TMZ for patients with glioblastoma resulted in increased survival without a negative impact on health-related quality of life, except for more itchy skin related to transducers [44].

Because of overexpression of vascular endothelial growth factor A (VEGF-A), a tumor angiogenesis factor, a trial investigated the effect of bevacizumab plus standard treatment of glioblastoma with radiochemotherapy and concurrent temozolomide versus placebo. This drug therapy did not improve survival although has been presented significantly progression-free survival, maintenance of baseline quality of life, and performance status. However, the grade three or higher adverse events were increased with bevacizumab as compared to placebo (32.5% vs. 15.8%) [45].

The corticosteroid dexamethasone 2 to 4 mg prescription can relieve the signals and symptoms during treatment, especially reducing the edema related to irradiation and afterwards this drug needs to be reduced. The prophylactic anticonvulsants are still controversial but if seizures occur, carbamazepine, phenobarbital and phenytoin are avoided and levetiracetam, lacosamide, lamotrigine, and pregabalin are preferred because of minor interactions with chemotherapeutic schema [46].

Recurrence

The recurrent glioblastoma increases the patient's mortality and develops from cells located close to the original tumor margin. These neoplastic cells probably migrate from the peripheral region tumors before debulking surgery or lay dormant in the tumor periphery. During the recurrence, the genomic profile usually has different genetic alterations from malign glioma at diagnosis that results in a more difficult tumor treatment [47]. These differences are larger in distant recurrent tumors than local relapse [48].

Malign glioma recurs within 2 cm from the tumor bed in 90–95% of cases [49]. In a trial with glioblastoma and anaplastic astrocytoma patients, 78% of recurrences occurred within 2.0 cm of the initial tumor bed and 56% were within 1.0 cm or less [50].

Positron emission tomography (PET) has also been employed towards the evaluation of brain tumors. Their role has been substantially improved over the last years, given the advent of various radiotracers that are currently used for several indications. PET has been used for the differentiation of necrosis from tumor recurrence. In necrosis, there is low or no tracer uptake in contrast to tumor recurrence in which there is profound radiotracer uptake. Several studies have been conducted so far; however, the major drawback was the lack of histological verification of the final diagnosis in most patients [51].

^{18}F -fluoro-ethyl-tyrosine (^{18}F -FET) can be used for the differentiation between post-therapeutic modifications and relapses. The radiotracer enters tumor cells through a specific amino acid transport system and is not metabolized or incorporated into proteins. ^{18}F -FET clinical applications include guiding biopsy, tumor delineation, scheduling and monitoring treatment (surgery or radiotherapy), and distinguishing between radiation necrosis and tumor recurrence. Another radiotracer in the differentiation between tumor recurrence and radiation necrosis is the [18F]-L-dihydroxyphenylalanine (^{18}F -FDOPA) with the superiority over ^{18}F -fluor-fluorodeoxyglucose (^{18}F -FDG), thanks to a higher contrast between tumor tissue and normal tissue [52].

Localized recurrent glioblastoma (without multiple lesions in different lobes/hemispheres) should be considered for local therapy. A recent study proposes the use of an oncology management algorithm. Patients with limited recurrent disease and survival greater than 3 months should be evaluated for prognostic factors (performance status, steroid requirement, and number and size of lesions). For cases with a good prognosis and reduced toxicity with retreatment, salvage surgery or reirradiation is possible (Fig. 1). In contrast, for patients with a life expectancy of less than 3 months, with a poor prognosis and high risk of toxicity with local therapies, systemic treatment should be considered [53].

In a trial that evaluated the efficacy of fractionated stereotactic radiotherapy (FSRT) performed as reirradiation in 71 patients with WHO grade 2 gliomas, 42 patients with WHO grade 3 gliomas, and 59 patients with glioblastoma, the treatment was well tolerated and may be effective in recurrence. The progression-free survival after irradiation was 5 months, 8 months, and 12 months, respectively [54].

Patients with glioblastoma (71%) and anaplastic astrocytoma grade III (29%) recurrent after initial treatment, when re-irradiated with hypofractionated stereotactic radiation therapy (H-SRT) with doses of radiation ≥ 35 Gy (3.5 Gy by a fraction)

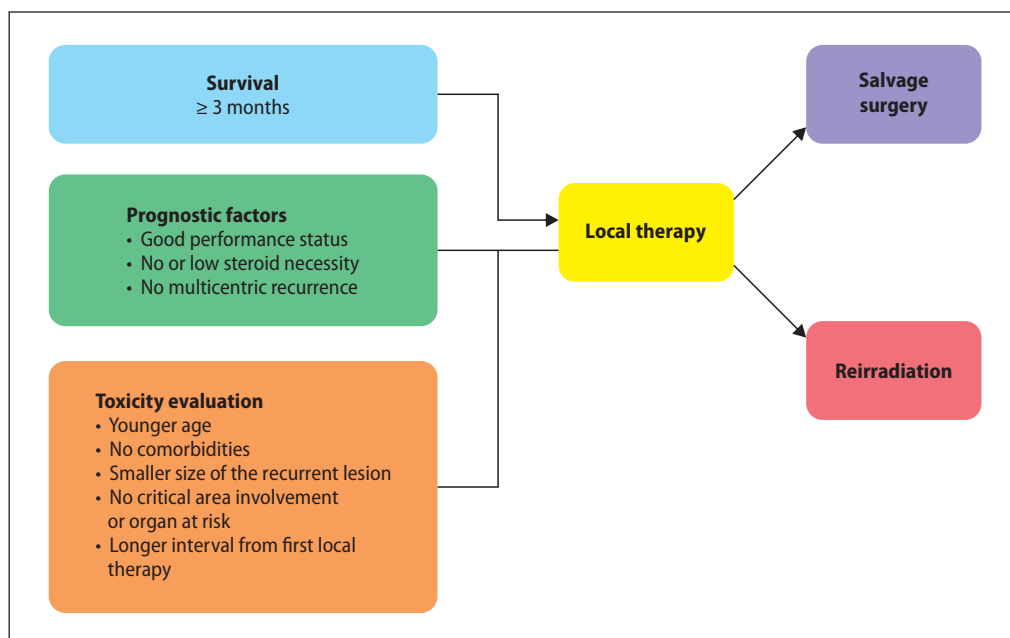


Figure 1. Recurrence flowchart. Evaluation of favorable factors for the use of local therapy. When local treatment is not suitable, the patient is evaluated for systemic therapy

were associated with unexpectedly good prognosis, and they should not be disqualified from H-SRT or other salvage therapy [55].

Reirradiation is an effective and safe treatment in the management of recurrent glioblastoma. For suitable patients, both SRS and SRT, either hypofractionated or conventionally fractionated regimens, are possible therapeutic options associated with similar median overall survival in the range of 6 to 12 months and relatively low toxicity. However, clinical deterioration due to radiation necrosis has been reported in up to 25% of patients. The risk remains generally low (less than 10%) for cumulative biological equivalent total dose normalized to 2 Gy/fraction (EQD2) doses around 100–110 Gy, but may increase up to 25% for cumulative EQD2 > 130 Gy [56].

Indications for surgery include unequivocal radiographic progression on surveillance imaging in accordance with either the MacDonald [57] or Response Assessment in NeuroOncology (RANO) criteria [58] and clinical decline including paresis or altered mental status as a manifestation of elevated intracranial pressure, mass effect, or seizures. Recommendation from a multidisciplinary tumor board is listed as an indication to proceed with reoperation, considering patients with good performance status and focal disease amenable to complete resection [59].

Follow-up

The choice method during follow-up patients is MRI. Radiographic worsening shortly after radiotherapy may reflect treatment effects (pseudoprogression), rather than tumor progression. Patients with sudden neurologic symptoms, such as severe headache, seizures, and fluctuations in neurologic symptoms, should be urgently evaluated (as in reference [21], page 7 of the manuscript).

Obstacles

The main obstacle for treatment efficacy is the diffuse invasion of the glioblastoma, which enables the tumor to evade complete resection and chemoradiation therapy [7].

The blood-brain barrier (BBB) is a major limiting factor that reduces the results of anti-cancer drugs in the treatment of glioblastomas. The re-

currence of this tumor after first-line therapy is related to invasive tumor cells protected from chemotherapy by the intact BBB in the surrounding brain tissue [3].

The molecular and cellular pathways altered in glioblastomas, such as the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), the p53 and the retinoblastoma (RB), or EGFR gene amplification or mutation, have failed to improve outcome, likely because of redundant compensatory mechanisms, insufficient target coverage to BBB, or poor tolerability and safety [5].

The temozolomide chemoresistance is related to O6-methyl adducts that allow DNA replication to continue. As drug resistance occurs, the downregulation of DNA methyltransferase-1 because of epigenetic de-repression of oncogenes such as SNGH12 that activate MAPK signaling, leads to inhibition of apoptosis and G/S1 transition [60].

Glioblastoma commonly recurs at surgery bed after radiation therapy but it was uncertain if changes in the tumor microenvironment caused by radiotherapy influenced the recurrence. One trial demonstrated after radiotherapy the recruitment of Ly6G+ inflammatory cells promoting conversion of glioblastoma cells to glioblastoma stem cells and dedifferentiation and tumor recurrence [61].

Immunotherapy has so far failed in glioblastoma and poor response is attributed to several factors like the high tumor heterogeneity and variable mechanisms of immunosuppression [62].

Conclusion

The standard of care for glioblastoma is the maximum safe resection possible, followed by radiation therapy and concurrent temozolomide and daily TMZ and tumor treatment fields (TTFields) after irradiation. There is no evidence to date of the benefit of brachytherapy, radiosurgery (SRS), fractional stereotactic radiotherapy (FSRT), and hyperfractionated radiotherapy over conventional external beam radiation therapy (EBRT) for the primary tumor. The assessment of age and performance status before treatment in the elderly enables hypofractionated radiotherapy. The research of tumor molecular signatures contributes to the choice of the best-targeted drug therapy.

In recurrent glioblastoma, it is necessary to balance the risks and benefits of re-radiation and association with bevacizumab. Solid data confirming the role of immunotherapy in the treatment of malignant glioma are still lacking.

Although the treatment of glioblastoma has evolved in terms of local control, mortality remains close to 12 months after diagnosis. To obtain better results and reduce recurrence, future research needs to investigate the frontiers of knowledge, such as the elucidation of the molecular mechanisms related to the tumor, the optimization of drugs to overcome the blood-brain barrier effectively, and the discovery of new therapies aimed at the heterogeneous profile of this neoplasm.

Conflicts of interest

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Data availability statements

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Author contribution

All authors contributed to the study conception and design. Material preparation and literature search were performed by F.S.C., G.O.B.G., I.N.Q., and M.R. The authors F.S.C., G.O.B.G., I.N.Q., and M.R have the idea for the article and performed the literature search and drafted revised the work. The first draft of the manuscript was written by F.S.C. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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