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REVIEW ARTICLE

Survival in glioblastoma: a review on the impact of treatment modalities

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Abstract Glioblastoma (GBM) is the most common and lethal tumor of the central nervous system. The natural history of treated GBM remains very poor with 5-year survival rates of 5 %. Survival has not significantly improved over the last decades. Currently, the best that can be offered is a modest 14-month overall median survival in patients undergoing maximum safe resection plus adjuvant chemoradiotherapy. Prognostic factors involved in survival include age, performance status, grade, specific markers (MGMT methylation, mutation of IDH1, IDH2 or TERT, 1p19q codeletion, overexpression of EGFR, etc.) and, likely, the extent of resection. Certain adjuncts to surgery, especially cortical mapping and 5-ALA fluorescence, favor higher rates of gross total resection with apparent positive impact on survival. Recurrent tumors can be offered re-intervention, participation in clinical trials, anti-angiogenic agent or local electric field therapy, without an evident impact on survival. Molecular-targeted therapies, immunotherapy and gene therapy are promising tools currently under research.

Keywords Glioblastoma · Survival · Prognosis · Radiotherapy · Chemotherapy · Tumor marker

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Introduction

Glioblastoma (GBM) is the most common and lethal tumor of the central nervous system [1]. It belongs to *malignant gliomas*, a group of heterogeneous and invasive brain tumors derived from glial cells. Despite optimal treatment, the usual course of GBM is poor. Population-based studies report median survivals of 42.4 % at 6 months and 17.7 % at 1 year [2]. According to the Central Brain Tumor Registry of the United States between 2007 and 2011, the 5-year survival rate for GBM is limited to 5 % [3]. Currently, the best that can be offered to these patients, by performing surgical resection plus concurrent chemoradiotherapy, is a modest 14-month median survival [4]. Survival in the elderly is even shorter and usually limited to no longer than 8.5 months on average [5]. Even though GBM has been the highest funded intracranial malignancy by the American National Institutes of Health over the past 40 years [6], overall survival has not significantly changed over time [7]. Despite a great effort in basic and clinical research, clinicians are as yet unable to provide a realistic curative therapy for malignant gliomas. Nevertheless, there has been a remarkable improvement in our understanding of the disease progression, genomics and clinical behavior.

The reasons why treating GBM remains a great challenge are diverse. These include the diffuse and infiltrative nature of the tumor, which limits the scope for surgical removal; the rapid proliferative rate of GBM malignant cells; the appearance of treatment resistant cell clones shortly after initial therapy; the relative impediment of the blood brain barrier, precluding access of systemic agents to the brain parenchyma; the activation of multiple signal transduction pathways and specific gene mutations within the tumor; and the special sensitivity of certain areas of the brain to radiation therapy [8].

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Specialists involved in the care of GBM patients commonly recognize this diagnosis as a delayed death sentence, since current therapies prolong life only to a very limited extent. However, 3–5 % of GBM patients are able to survive over 3 years [9]. Although the clinical and molecular factors associated with long-term survival are still unknown, it has been reported that younger female patients with good initial performance status and harboring the O6-Methylguanine-DNA methyltransferase (MGMT) promoter hypermethylation are overrepresented among these long-term survivors [10].

Recent studies on the molecular pathogenesis of gliomas have led to a re-classification of glial tumors according to three specific tumor markers: *1p/19q* codeletion, either isocitrate dehydrogenase-1 (*IDH1*) or *IDH2* mutation, and mutation of promoter of *TERT* (*telomerase reverse transcriptase*) [11]. According to combinations of these markers, gliomas can be classified in five principal groups with characteristic ages of onset, clinical behavior, genetic alterations, associated germ-line variants and possibly distinct mechanisms of pathogenesis. This molecular classification also implies different overall survival, already established for WHO grade II and III gliomas, although questionable for grade IV gliomas [11].

Advances in the treatment of malignant glioma include novel surgical techniques aimed at obtaining maximum safe resections, specific radiation therapy schemes and new systemic chemotherapy regimens. To date, these therapies have failed to qualitatively alter the natural history of GBM. In this review we focus on the impact that the various treatment modalities and combinations currently available have on survival, the historic evolution of glioblastoma survival throughout the last decades, the prognostic factors affecting survival and the prospects offered by emerging therapies.

Classification and natural history of glioblastoma

High-grade or malignant gliomas are classified into glioblastomas (60–70 % of all malignant gliomas), anaplastic astrocytomas (10–15 %), anaplastic oligodendrogliomas and anaplastic oligoastrocytomas (10 %) and some other less frequent subtypes [3]. The incidence of GBM is 3–5/100,000 people per year and it is 40 % more common in males compared to females [1].

Primary GBM comprise the great majority of GBM (about 90 %) and they occur de novo. Patients tend to be older in primary versus *secondary* GBM. Secondary GBM may develop from a low-grade diffuse astrocytoma or oligodendroglioma (or from their anaplastic variants). Since primary and secondary GBM evolve from different genetic precursors, they harbor distinct genetic alterations [12]. Overexpression of epidermal growth factor receptor (EGFR), phosphatase and tensin homolog (PTEN), mutations and loss of chromosome 10 are common in primary GBM, whereas IDH1 mutations, TP53 mutations and 19p loss are usually found in secondary GBM [13]. Interestingly, IDH1 mutations occur in a very large proportion of younger patients and in more than 80 % of secondary GBM, compared to less than 5 % of primary GBM [14]. This has been reported to be associated with better prognosis and increased overall survival [12]. Therefore, IDH1 mutation is currently considered a reliable and objective molecular marker for secondary GBM, although indistinguishable from primary GBM from a pathological perspective [15].

Based on genetic alterations and expression profiles and according to The Cancer Genome Atlas, GBM is classified into four subtypes: classical, mesenchymal, proneural and neural [16]. The *proneural* subtype is enriched in gene expression patterns seen in oligodendrocytes and characterized by alterations in TP53, platelet-derived growth factor receptor (PDGFR) and IDH1. It is also more common in younger GBM patients. This subtype is associated with better prognosis and increased survival compared to the rest [17]. However, chemoradiotherapy seems to be more effective in terms of decreased mortality in patients with classical and mesenchymal subtypes compared to proneural subtype [16].

The overall median age at time of diagnosis of GBM is 64 years, with patients being 10–15 years younger in secondary compared to primary GBM [1]. No etiological factor other than ionizing radiation has been conclusively associated to GBM [1]. Several rare genetic syndromes (Li-Fraumeni, Neurofibromatosis, Turcot) associate with gliomas, although most familial cases (5 % of all malignant gliomas) are sporadic [18]. Clinically, GBM patients usually present with sub-acute headache, nausea or vomiting, seizures, focal neurological deficit, confusion, personality changes or combinations of these symptoms. Since GBM patients present an increased risk of venous thromboembolism, anticoagulation (with low-molecular weight heparin) is generally recommended and considered safe unless intracerebral hemorrhage is present. The chronic use of corticosteroids in GBM, for peritumoral edema relief, commonly leads to Cushing's syndrome and steroid-induced myopathy [1].

The natural history of a typical GBM case is discouraging. GBM patients presenting with a large tumor and not receiving treatment at all, usually survive no longer than a few weeks depending on the severity of the mass effect provoked by the lesion. This survival period is actually unknown since only GBM patients in very poor condition are left untreated (or just on steroids), and the study needed to evaluate the natural history of untreated GBM is not

likely to be conducted for ethical reasons. Supportive care (including high-dose dexamethasone for tumor-related edema) provides a modest increase in survival from 3 to 4 months to no more than 6 months [1]. Surgical resection alone provides an additional 6 months medial survival [19]. Surgical resection plus radiation therapy extends median survival to about 12 months [20]. The addition of concomitant chemotherapy (Temozolomide) slightly improves survival to 14.6 months on average, and it also increases the survival rate at 2 years from 10.4 to 26.5 % [20]. These figures seem to have modestly improved over the last decades but the natural history of treated GBM remains poor and survivors after 5 years are extremely rare. Still, occasional reports of cured GBM can be found in the literature [21, 22].

According to historic epidemiological studies, overall survival in patients with malignant brain tumors has not improved significantly over the last 50 years [7, 23]. There has been minimal progress in survival for GBM in the last 30 years as compared to other brain tumors like medulloblastoma (20 % increase in survival, achieved in the 1970s and 1980s) [23]. The most important prognostic factors affecting outcome and increasing survival in high-grade gliomas are younger age, better performance status, histologic tumor type (oligodendroglial component) and several molecular factors still under clinical investigation (MGMT methylated status, 1p19q codeletion and mutation of IDH1 or IDH2) [24]. The impact of the extent of resection on survival is likely to be favorable but still under debate (see below). Table 1 summarizes the importance of prognostic factors in GBM survival.

Novel therapies other than surgical resection and concomitant chemoradiotherapy are also being researched. These include molecularly targeted therapies (including inhibition of angiogenesis pathways by vascular endothelial growth factor (VEGF) ligand blocker bevacizumab), immunotherapy and gene therapy. Recently, a fourth modality of treatment for GBM, an alternating electric field device (named NovoTTF-100A) aimed to disrupt tumor cell division, has been presented as a promising tool for delaying progression of GBM [25]. Table 2 summarizes the impact on survival of the various treatment modalities currently available or under investigation.

Impact of surgical resection

Surgical resection of GBM provides immediate mass effect relief and specimen for pathological confirmation. Resection is generally considered to be only cytoreductive

Table 1 Prognostic factors related to glioblastoma survival

Prognostic factor	Comment
Age, sex, KPS	Younger females with good preoperative status live longer. Long-survivors (over 3 years) mostly belong to this group (with accompanying MGMT hypermethylation). They are all independent factors for increased survival
Extent of resection	Resections over 70–80 % on the enhancing mass and especially over 90 % (or residual tumor less than 5 cm^3) significantly improves survival
Grade	Anaplastic glioma (WHO grade III) associates longer survival compared to glioblastoma (WHO grade IV)
	Oligodendroglial component within tumor mass provides better prognosis and overall survival
Molecular GBM Cancer Genoma Atlas expression subtypes	*Classical* Enriched in gene expression patterns of astrocytes, mostly EGFR overexpression and loss of chromosome 10
	Mesenchymal Enriched in gene expression of astrocytes, mesenchymal markers and mutations in genes NF1 and PTEN deletions. Aggressive chemoradiation significantly decreases mortality in patients with classical or mesenchymal subtypes, but not in proneural subtype
	Proneural Enriched in patterns seen in oligodendrocytes. Alterations in: p53, PDGFR and IDH1. Youngest age at diagnosis. Typically seen in secondary GBM. Better prognosis and overall survival compared to the other subtypes
	Neural Enriched in gene expression seen in normal neurons
Mutations in biological markers	MGMT promoter hypermethylation (significantly increases survival), 1p19q (codeletion increases survival especially in tumors harboring oligodendroglial component), IDH1 and IDH2 (most common mutation in grade II and III gliomas; better prognosis), p53, TERT (most common mutation in GBM; worse prognosis), EGFR (overexpression of EGFR is either an unfavorable predictor or inconclusive prognostic factor), PDGFR, PTEN
Preoperative MRI parameters	Tumor-enhancing volume and eloquent location negatively affect survival. Size of edema/invasion (on FLAIR sequence) over 85,000 mm^3 significantly increases mortality
Volume of cases	Improves survival for all brain cancer patients in general. Not specifically studied for glioblastoma

Table 2 Therapies for glioblastoma and their impact on survival

Treatment	Impact on survival
Palliative treatment (including corticosteroids)	Weeks to a few months, depending on the size, location and mass effect of the tumor. Toxicity of long-term therapy with corticosteroids may affect survival and quality of life by interfering with the immune system
Surgical resection	Six to ten months on average. Surgery per se prolongs life by reducing mass effect. Surgical adjuncts (especially navigation, new MRI sequences, fluorescence and intraoperative MRI guided resections and awake craniotomy) help neurosurgeons achieve higher rates of gross total resections, which seem to be associated to longer progression-free and probably overall survivals. Also useful in the elderly. At the time of recurrence, only surgery slightly prolongs life expectancy
Radiotherapy	Postoperative radiotherapy extends survival to 12 months on average. Also useful in the elderly. No clinical benefit for doses over 60 Gy. Efficacy demonstrated for whole brain and field-involved radiotherapy, but not for radiosurgery or interstitial brachytherapy. Proton therapy is not well studied yet
Chemotherapy	Concomitant to radiotherapy extends survival to slightly over 14 months on average. Temozolomide is the agent of choice for adjuvant therapy. Duration of chemotherapy debatable
Inhibition of angiogenesis	At the time of recurrence, bevacizumab (Avastin®) provides a few weeks gain in progression-free survival but does not affect overall survival. Usefulness in newly diagnosed GBM still unclear
TTF therapy	At the time of recurrence, TTF therapy is at least as efficacious as bevacizumab (prolongs progression-free survival weeks to a few months) and possibly less toxic. Combined therapy with bevacizumab under investigation
Interstitial chemotherapy (carmustine wafer)	Does not seem to influence survival or the effect is only marginal. Common adverse effects, occasionally severe
Molecularly targeted therapies, immunotherapy, gene therapy, nanoparticles.	Currently under investigation. Promising results in preclinical studies. No evidence of benefit on overall survival yet

because of the infiltrative nature of the tumor. Even when apparently large free-margin resections are performed, the vast majority of GBM recur locally or proximally, usually within 2 cm of the resection margins [26]. Surgery, either biopsy or resection, is a priori indicated in all GBM patients except for the very elderly, debilitated or those with poor performance status [1].

The purpose of surgery is the so-called *maximum safe resection*. That means resection of all the contrast-enhancing mass (gross total resection), trying not to provoke neurological deterioration. This can be achieved only in a percentage of the patients depending on tumor location. However, just tumor debulking can be beneficial by reducing intracranial pressure [27]. Resection of deep bulky lesions in eloquent areas is more likely to result in postoperative deficits. It has been classically reported that surgical resection alone results in a median survival gain of 6 months approximately [19]. However, the true value of surgery itself in prolonging survival remains controversial because no well-designed prospective studies specifically address the matter. Data from multivariate analysis show that extensive resections provide at least modest gains in overall survival [19] and progression-free survival [28]. Interestingly, a recursive partitioning analysis of 500 consecutive GBM patients showed that surgery improved overall survival, even when subtotal resections were performed [29]. The extent of resection (with a minimum threshold of 70 % resection) and the residual tumor (of less than 5 cm^3) influences survival positively, as concluded in a 250-patient retrospective review by Chaichana et al. [30]. This has been corroborated by another study in which an extent of resection greater than 90 % was associated with a significantly greater survival rate at 1 year [31]. More recently, it has been reported that a contrast-enhancing residual tumor volume after surgery of less than 2 cm^3 is also associated with higher overall survival rates [32]. In the multivariate analysis over 416 patients by Lacroix et al., the benefit of cytoreduction showed a 4.2-month survival advantage in patients with at least 98 % resection versus those with less than that [19]. Both the extent of resection and the amount of contrast-enhancing residual tumor seem to be strong predictors of survival in GBM [32] although further studies are needed to explain the true effect of these factors independently.

The impact of extent of resection of recurrent GBM is not well established. Bloch et al. reported an increased overall survival associated with higher extents of resection [33], findings also applicable to the elderly [34]. However, significantly higher postoperative permanent deficits are expected after reoperations in which at least 80 % of the mass is excised [35]. Interestingly, when gross total

resection is achieved at initial surgery, the extent of resection at the repeat operation does not seem to influence overall survival. However, after initial subtotal resections, a second gross total resection significantly improves overall survival, as concluded in a multivariate analysis [33].

Impact of surgical adjuncts

Some technological advances help neurosurgeons to optimize maximal safe resections. Adjuncts to surgery include functional and diffusion tensor MRI, intraoperative MRI, cortical and sub-cortical mapping, navigation guidance and fluorescence-guided resection. Additionally, the implantation of carmustine wafers inside the resection cavity results in a modest survival gain of about 8 weeks for recurrent GBM [36]. However, since complications associated to the use of this type of wafers commonly occur, this treatment method is not routinely recommended or used.

Following a volumetric analysis of specific tumor components, it has recently been suggested that some preoperative MRI parameters, such as contrast enhancement, necrosis and edema/invasion, play a significant role in survival prediction [37]. Tumor-enhancing volume and eloquent brain involvement seem to be independent prognostic indicators of overall survival, and an edema/invasion volume of more than 85,000 mm^3 and the proportion of enhancing tumor are significantly correlated with higher mortality [37].

Intraoperative navigation for GBM resection is useful for craniotomy planning and for evaluating the extent of resection [6], although its impact on overall survival has not been studied prospectively. Neurophysiological cerebral monitoring with cortex and sub-cortical mapping has made surgical resection safer and has demonstrated its efficacy in optimizing resection [38]. Data from a recent prospective study of 70 eloquently located high-grade gliomas show that these patients might also benefit from preoperative navigated transcranial magnetic stimulation mapping [39]. Brain functional MR images and diffusion tensor imaging tractography also help the neurosurgeon to achieve better and safer resections [40]. Although the combination of functional and diffusion tensor MR images permits the identification of eloquent areas and white matter involvement during GBM surgery [41, 42], a certain degree of brain shift is always expected to occur after dural opening.

Brain shift during glioma surgery is a problem inherent to neuronavigation that can be partially compensated for with the use of intraoperative MRI, which is considered to be the gold standard of real time intraoperative imaging. It is performed with a portable device (low or high magnetic field) inside the operating room. It helps the neurosurgeon to achieve higher rates of complete resection [43], which might lead to a better quality of life and increased survival rates [44]. In a recent prospective, randomized, triple-blind, controlled trial, a significant higher rate of gross total removal was achieved with the aid of 3.0 Tesla intraoperative MRI compared to standard navigated resection (86.36 versus 53.49 %) [45]. The use of this device increases surgical time by at least 1 or 2 h and requires MRI compatible surgical instruments. Moreover, adequate positioning of the patient is not always feasible and, although the quality of the images is acceptable, a 6–14 % rate of false positives is to be expected [46]. Low-field intraoperative MRI devices (which use a magnetic field ten times smaller than regular MRI scanners) are reported to warrant continuation of GBM resection in about 30 % (range 10–70 %) of cases [47]. However, to consider intraoperative MRI a technical standard for glioma surgery, a definite survival gain must be confirmed in further prospective studies.

5-Amino-levulinic acid (5-ALA) is a natural precursor of hemoglobin that induces the formation of protoporfirin IX at a significantly higher concentration within the malignant tumor compared to normal brain tissue. Under blue light (400–410 nm) operative microscope visualization, protoporfirin IX emits bright red fluorescence from solid tumor masses and pink fluorescence from infiltrative areas, whereas normal brain tissue remains blue. This differentiation helps the neurosurgeon to achieve more extensive resections. Patients undergoing 5-ALA fluorescence-guided resections are more likely to obtain gross total resections and to be progression-free at 6 months [48], although overall survival gain has not been definitely proved [49]. The cost of 5-ALA for malignant glioma resection is moderately increased over regular surgery (980€ per 1.5 g of Gliolan®) with a favorable cost-effectiveness ratio, according to data from a Spanish multicenter retrospective study (VISIONA study) of 251 cases [50]. In a recent meta-analysis on the efficacy of 5-ALA fluorescence image guided resection of GBM [51], the authors report a mean gross total resection rate of 75.4 % (95 % CI 67.4–83.5, $p < 0.001$), a mean time to tumor progression of 8.1 months (95 % CI 4.7–12, $p < 0.001$), but an ambiguous mean overall survival gain of 6.2 months (95 % CI −1 to 13, $p < 0.001$).

In the study by Coburger et al., the use of 5-ALA plus intraoperative MRI compared to intraoperative MRI alone significantly increased the extent of resection [52]. Maximizing resection in eloquent areas did not lead to an increased rate of complications or deficits if neurophysiological monitoring was performed. However, the benefits of a greater extent of resection could not be related to patients' progression-free survival (6 months in both

groups) or overall survival (18 months, CI 95 % 15.2–20.8 months, versus 17 months, CI 95 % 7.6–26.4 months, $p < 0.7$) [52].

Awake craniotomy is a well-known surgical technique which assists the neurosurgeon in the location of eloquent areas in the cortex to choose the best surgical approach to the tumor and to minimize intraoperative neurological morbidity, especially that affecting speech. It is performed under local anesthesia and sedation with the aid of a neurologist. The main limitation of awake craniotomy is the need for full cooperation by the patient [53], who ideally should be able to answer questions and perform certain movements on request, while remaining calm with their head fixed and their skull open until the cortical mapping is finished and the resection is completed. No prospective trial has tested its efficacy in comparison to standard craniotomy in terms of overall survival for GBM. However, it is likely that, by improving the extent of resection and decreasing the neurological morbidity, it would reasonably impact on survival and quality of life.

The efficacy of carmustine wafers implanted inside the tumor cavity after resection is controversial. Systematic reviews on the matter report either slightly longer median survival (even though progression-free survival was not significantly improved) or a marginal increase in survival (16.2 compared to 14 months) and local control in newly diagnosed GBM [54]. However, complication rates have been reported to be as high as a 42.7 % [55].

In recurrent GBM, it has been recently reported [56, 57] that dexamethasone (in doses over 4.1 mg per day) exerts a marked immunologic interference on the efficacy of treatment, resulting in a significant reduction of overall survival, both in patients undergoing TTF therapy (4.8 vs 11.0 months, $p < 0.0001$) or chemotherapy (6.0 vs 8.9 months, $p < 0.0015$). These authors conclude that future clinical trials for recurrent GBM should take into account the influence of dexamethasone use on therapeutic outcome due to its immune suppressive effect [56, 57]. They also suggest that a combination of NovoTTF-100A and rescue chemotherapy (or continuation of bevacizumab) may decrease the need for dexamethasone use in progressive GBM [57].

Impact of radiation therapy

Data from studies conducted in the 1970s provide strong evidence for survival gain after whole brain radiation therapy (WBRT) in GBM [58]. Involved-field radiotherapy at doses of 50–60 Gy in 2 Gy per fraction significantly increases survival (it almost doubled compared to lower doses or surgery alone), regardless of the extent of resection [59]. However, doses over 60 Gy did not provide further benefit [60]. Since most recurrences develop within 2 cm of the resection margins, radiation therapy has evolved towards 3D conformal schemes to minimize excess irradiation of normal brain. However, these techniques, including intensity-modulated radiotherapy, have not demonstrated significant benefit in terms of survival compared to WBRT [61, 62].

Data provided from the well-known study by Stupp et al. in 2005, confirm that the addition of radiotherapy to surgical resection increases survival in a range from 3 to 12 months depending on the case, and that the two-year survival rate increases to 26.5 % with radiotherapy plus temozolomide instead of 10.4 % with radiotherapy alone [20]. The efficacy of radiotherapy on survival is rather modest for the elderly (over 70 years of age) with a median survival of 29 weeks, compared to 17 weeks in those who only received supportive care [63]. Previous brain irradiation is a known risk factor for developing both benign and malignant brain tumors over time. Reirradiation at therapeutic doses for glioma increases 1- and 2-year survival rates, and it is considered a safe and feasible option if a 5-year interval between radiation exposures is observed [64], a situation very rarely applicable to GBM.

A RTOG phase III trial conducted in 2004 failed to demonstrate a significant benefit of stereotactic radiosurgery over involved-field radiotherapy followed by carmustine for newly diagnosed GBM (median survival of 13 months in both arms) [65]. Likewise, interstitial brachytherapy with radioisotope iodine-125 has shown marginal or absent benefit on median survival (68 versus 59 weeks) [66]. Charged heavy particles, such as helium and neon ions, have been used alone or as a boost to conventional photon radiotherapy, without significant benefit on survival [67]. Data on the utility of proton therapy for malignant gliomas is very limited. In the study by Fitzek et al. of 23 patients treated with a dose equivalent of 90 Gy, the median survival obtained was 20 months following surgical resection and proton therapy, at the expense of an increased rate of tissue necrosis [68].

Impact of systemic chemotherapy

After pathological confirmation of GBM, current standard therapy consists of external beam, involved-field cranial radiation therapy plus concomitant daily temozolomide, followed by six cycles of adjuvant temozolomide [4]. This well-known protocol provides the best outcome in terms of overall survival: 27.2 % at 2 years, 16.0 % at 3 years, 12.1 % at 4 years, and 9.8 % at 5 years with temozolomide, versus 10.9, 4.4, 3.0 and 1.9 % with radiotherapy alone (hazard ratio 0.6, 95 % CI 0.5–0.7; $p < 0.0001$). Median survival is moderately increased from 12.1 months

with radiotherapy alone to 14.6 months with radiotherapy plus temozolomide [4]. This benefit is also extended to patients aged 60–70 years. Methylation of the MGMT promoter is the strongest predictor of outcome and benefit for temozolomide chemotherapy: 2-year survival rates are 49 and 24 % for combination therapy and radiotherapy alone in methylated patients, compared to 15 and 2 %, respectively, for patients without the methylation [20]. Importantly, these survival gains were achieved with no negative impact on quality of life [20]. These results were later corroborated by another smaller phase II trial [69]. However, moderate to severe hematologic toxicity (mostly thrombocytopenia) is expected in 10–20 % of patients receiving temozolomide, which precludes continuation of concomitant chemoradiotherapy in a percentage of cases [70]. A dose-intensive temozolomide scheme (75–100 mg/m^2 days 1 to 21 repeated every 4 weeks), failed to improve survival compared to the standard schedule (150–200 mg/m^2 daily for 5 days a week, every 28 days) [71]. Whether to extend temozolomide therapy beyond six cycles or not remains controversial but it is not uncommon practice to maintain treatment in patients who tolerate it well, until disease progression ensues.

Bevacizumab given as part of the primary treatment in newly diagnosed GBM is under study. It is reported to prolong progression-free survival but not overall survival [72]. It also seems to positively influence quality of life by improving or preserving neurocognitive functions [72]. Still, no clinical or molecular data predict which subpopulations of GBM patients could benefit the most from bevacizumab treatment.

Impact of therapies for recurrent glioblastoma

At the time of recurrence, GBM patients keeping acceptable KPS (70 or higher) are eligible for re-intervention or participation in clinical trials. Those considered ineligible, may be offered single-agent bevacizumab (Food and Drug Administration (FDA) approval in 2009) or novel TTF therapy. Bevacizumab was associated with a radiological response (the so-called pseudo-response) in 30-40 % of the cases in single arm studies associated with irinotecan [73, 74]. However, the median overall survival after bevacizumab failure, using salvage chemotherapy, is limited to 5.2 months and progression-free survival to 2.0 months [75].

In April 2011, the FDA-approved NovoTTF-100A as a new locoregional technique for treating recurrent GBM. It uses electromagnetic energy (200 kHz alternating electric fields delivered by insulated transducer arrays applied onto the shaved scalp) to disrupt tumor cells in the mitotic stage by interfering with the formation of the mitotic spindle and to affect polar molecules at telophase, thus preventing cell division [25]. The electric field distribution in the brain seems to be highly non-uniform and depends on the tissue geometry and dielectric properties [76], which could explain variability in outcomes. Field strength, conditioned by the position of the arrays according to each patient's images, may also play a role in the appearance of recurrences [77]. About 20 % of patients treated with TTF develop dermatologic adverse events because of the continuous contact between the array components and the shaved scalp [78].

A phase III trial demonstrated that TTF had equivalent efficacy to chemotherapy without the typical and dangerous side effects of cyto-toxicity and that it permitted better quality of life [25]. Since bevacizumab is the other only FDA-approved therapy for recurrent GBM, it has been suggested that the combination of the two would eventually increase overall survival [79], which is still unproven for each of the treatments separately.

Prognostic factors affecting survival

Prognostic factors involved in high-grade glioma survival include: age (better for younger patients), tumor grade (better for anaplastic type versus glioblastoma), Karnofsky performance status (better for higher scores), and probably the extent of resection and several molecular genetic alterations [19, 80]. A recursive partitioning analysis revealed distinct survival rates according to subgroups based on four factors: age at presentation, tumor location, KPS and extent of surgery [24]. This was also applicable to patients over 70 years of age [5].

Molecular alterations which carry prognostic significance in gliomas include: MGMT promotor methylation, 1p19q codeletion (it is a predictive factor for improved survival and responsiveness to therapy in oligodendroglial tumors) and mutations in IDH1 and IDH2. MGMT promotor methylation is a confirmed prognostic factor of improved survival and may also be predictive of chemotherapy responsiveness in GBM patients [10, 81], including the elderly [82]. Mutations of IDH1 are found in more than 80 % of secondary GBM but in less than 5 % of primary GBM. They predict improved overall survival, independently of other prognostic factors [83], and they are more prevalent in long-term survivors [84]. Contrarily, mutations of the promotor TERT gene are present in 50–80 % of primary GBM and are independently associated with lower survival [85].

The EGFR is overexpressed in at least 60 % of glioblastomas, and the most common EGFR mutant, EGFRvIII, is expressed in 24–67 % of the cases [13]. In the study by Heimberger et al., neither the overexpressed wild-

type EGFR nor EGFRvIII were independent predictors of median overall survival gain in the cohort of patients who underwent extensive tumor resection. However, in patients surviving at least 1 year, the expression of EGFRvIII was an independent negative prognostic indicator [86]. Likewise, Shinojima et al. found EGFR amplification to be an independent, unfavorable predictor for overall survival [87].

GBM patients surviving over 36 months are referred to as long-term survivors. Reports on long-term survivors are commonly found in the literature. In the largest series, published by Krex et al. [9, 55], primary GBM were followed for a median of 7 years. Patients lived a median of 4.6 years, ranging from 3 to 15.3 years. Although the authors failed to identify unequivocal clinical factors associated with longer survival, MGMT hypermethylation was significantly more prevalent among long-term survivors (74 %) as compared to controls (43 %). In addition, long-term survival seemed to be favored by the combination of young age and female gender [9].

Future perspectives: emerging therapies

A detailed description of other therapies under research, like molecularly targeted therapies, immunotherapy and gene therapy, is beyond the scope of this review, and has been thoroughly addressed elsewhere [13]. Inappropriate activation of certain signal pathways (mainly membrane growth-factor receptors) drives tumor growth, survival, invasion into normal brain and secretion of angiogenic factors. Inhibition of these pathways and their downstream intracellular signaling is the purpose of molecularly targeted approaches, which use small molecule inhibitors (like gefitinib and erlotinib, inhibitors of tyrosine kinase pathways, which have failed to provide clinical benefit in clinical trials) and monoclonal antibodies (cetuximab, blocker of EGFR, and imatinib, blocker of PDGFR, which did not improve outcomes in clinical trials either) [13].

Since GBM is a greatly vascularized tumor, inhibition of angiogenesis by bevacizumab, a monoclonal antibody that binds and neutralizes the VEGF ligand, has been clinically tested for recurrent GBM. It proved to be beneficial in terms of progression-free survival as an adjuvant to radiotherapy and temozolomide [4]. Its effects in newly diagnosed GBM are currently being tested in ongoing trials, but there is some evidence that it does not improve overall survival, and may cause higher rates of toxicity [88]. Other angiogenic inhibitors (cedarinib, sunitinib, vatalanib, cilengitide) and some intracellular signaling pathway inhibitors (perfosine, rapamycin, sirolimus, tipifarnil, sorafenib) are currently under investigation although preliminary results are discouraging [13].

Immunotherapy attempts to influence the immune system to destroy tumor cells both passively (antibodies, immune cells like lymphocyte-activated killers and cytotoxic T lymphocytes) or actively (with the so-called cancer vaccines like rindopepimut, based on the EGFRvIII variant). Neither of them has demonstrated a definite impact on survival [13]. Finally, gene therapy involves the delivery of genetic material (cytotoxic genes, immuno-stimulatory genes, oncolytic viruses) into tumor cells via a specific vector (viral and non-viral) for therapeutic purposes. As with molecularly targeted therapies and immunotherapy, preclinical trials often provided promising results but the limited clinical experience has not confirmed their efficacy in prolonging survival of GBM patients, partly due to the low transfection efficiency of vectors.

In the interesting review by Carlsson et al. [89]. on the emergent strategies for GBM, the authors conclude that early detection of specific molecular mutations, diagnosed via blood microvesicle screening, would be useful for preoperative GBM sub-typing, and could eventually guide the application of targeted therapies, which could improve survival. Another therapy under research is the application of nanoparticles, based on their specific ability to conjugate with surface markers of tumor cells, to deliver anti-cancer agents across the blood brain barrier to the tumor area, thus reducing toxicity of healthy tissues. The impact of nanoparticle-based therapy on GBM survival is being tested and, currently, no prospective clinical trial supports its use [90].

Conclusions

The natural history of GBM remains poor despite advances in basic science and clinical research. Currently, maximum safe resection plus adjuvant chemoradiotherapy is the mainstay of GBM management, leading to a modest 14-month overall survival. Although important advances in the molecular pathways related to GBM formation and differentiation have permitted sub-typing GBM in several categories with prognostic implications, no realistic adjuvant therapy is yet available for curing this disease.

The complex molecular biology of GBM has led to the development of many novel therapies. Unfortunately, only a marginal gain in overall survival has been achieved throughout the last decades. However, these new and promising strategies, currently undergoing research, suggest a change in our understanding of this disease and in its prognosis. These new approaches would ultimately need confirmation by further basic and clinical investigations.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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