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TOPIC REVIEW

Trends in glioblastoma: outcomes over time and type of intervention: a systematic evidence based analysis

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Abstract

Introduction Despite aggressive treatment with chemoradiotherapy and maximum surgical resection, survival in patients with glioblastoma (GBM) remains poor. Ongoing efforts are aiming to prolong the lifespan of these patients; however, disparities exist in reported survival values with lack of clear evidence that objectively examines GBM survival trends. We aim to describe the current status and advances in the survival of patients with GBM, by analyzing median overall survival through time and between treatment modalities.

Methods A systematic review was conducted according to PRISMA guidelines to identify articles of newly diagnosed glioblastoma from 1978 to 2018. Full-text glioblastoma papers with human subjects, ≥ 18 years old, and n ≥ 25, were included for evaluation.

Results The central tendency of median overall survival (MOS) was 13.5 months (2.3–29.6) and cumulative 5-year survival was 5.8% (0.01%–29.1%), with a significant difference in survival between studies that predate versus postdate the implementation of temozolomide and radiation, [12.5 (2.3–28) vs 15.6 (3.8–29.6) months, $P < 0.001$]. In clinical trials, bevacizumab [18.2 (10.6–23.0) months], tumor treating fields (TTF) [20.7 (20.5–20.9) months], and vaccines [19.2 (15.3–26.0) months] reported the highest central measure of median survival.

Conclusion Coadministration with radiotherapy and temozolomide provided a statistically significant increase in survival for patients suffering from glioblastoma. However, the natural history for GBM remains poor. Therapies including TTF pooled values of MOS and provide means of prolonging the survival of GBM patients.

Keywords Glioblastoma · Trends · Epidemiology · Treatment · Therapy · Neoplasms · Glioma · Analysis · survival · Geographic location

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Why is it important to do this review?

Glioblastoma is the most common and aggressive primary brain tumor. With an incidence rate of 3.19 per 100,000 a year carrying a grim prognosis. Today, the median overall survival is estimated to be ~ 15 months, a value that was originally reported by the landmark Stupp trial which stablished the current standard of care of radiotherapy and temozolomide for GBM. This happened over a decade ago and since then, new treatment strategies have become available or are underway in an effort to prolong the lifespan of GBM patients. Currently, there is no source that critically analyzes the progress in increasing the median overall survival for GBM or the differences between the survival times of available treatment modalities reported in the literature. Hence, it is essential to perform a comprehensive review and critical appraisal of the current published data. To our knowledge, this is the largest systematic review to provide pooled cumulative data on the overall survival status of GBM. Our work in elucidating the most effective therapies as well as global survival disparities helps to direct future research and investment into potential areas of improvement.

Introduction

Glioblastoma (GBM) is the most common and aggressive primary malignant tumor of the central nervous system (CNS) and carries a bleak prognosis. GBM has historically been associated with relatively high mortality rates where the median survival rates range from 5 to 15 months and the 5-year survival rates range from 0 to 5% in several studies [1–7]. To date, there are no curative options for GBM, and the standard of care consists of cytoreductive surgery followed by adjuvant chemoradiotherapy [8]. The current favored treatment regimen was established over a decade ago by Stupp et al. in 2005, where they noted a significant difference in survival for patients receiving temozolomide (TMZ) with concomitant radiotherapy as compared to alone [9]. It remains unclear if any developments in regard to surgical therapy, radiation paradigms, and chemotherapeutic regimens have resulted in improved outcomes since the administration of this regimen [10–12].

The literature on GBM is constantly expanding with many basic science, translational research, and clinical studies being published each year, but the overall survival status of GBM patients remains poor [13]. Basic science studies continue to report new molecular pathways and potential therapeutic targets [14–16]. Translational and clinical trials studies are being conducted for safety and efficacy evaluating different surgical tools, therapeutic regimens, and various drugs to treat GBM [8]. Despite this ongoing research, the outcomes for patients with GBM remain disparate, with survival times ranging from months to a few years [17–19]. It therefore, remains unclear if substantial progress has been made in lengthening the survival of these patients. In order to adequately describe the current status of survival for patients with GBM, we conducted a systematic review of the existing literature characterizing how the length of median overall survival for patients diagnosed with GBM varied across time, treatment type and geographical distribution.

Methods

Systematic review

A systematic review was conducted in accordance with PRISMA guidelines and recommendations to identify all articles on newly diagnosed GBM from 1978 to 2018. Using the advanced search in PubMed/Medline with terms "glioblastoma OR GBM" and "Survival" for the "title" and "abstract" fields, 9162 number of total articles published between January of 1978 and January of 2018 were found in April of 2018. Two independent reviewers then screened each title and abstract for eligibility. Inclusion criteria involved full-text GBM papers with at least 25 human subjects, ≥ 18 years old with newly diagnosed GBM, and explicitly reported their MOS data. Clinical trials analyzed consisted of adult (age ≥ 18) newly diagnosed, histopathologically confirmed GBM with a Karnofsky Performance Score (KSP) ≥ 50. Case reports, reviews, meta-analyses, animal models/in-vitro experiments, studies with mixed survival data involving other glioma/brain tumors, or studies in languages other than English or Spanish were excluded. Reviews of established databases such as the SEER or TCGA were excluded due to potential repetition of data. Disagreement between observers regarding inclusion or exclusion of publications was resolved by discussion or adjudication by a third observer.

Data extraction

Median overall survival (MOS), 5-year probability of survival, geographic location, treatment types, and time period were extracted from each study. If MOS values were unavailable from text, they were approximated from provided Kaplan–Meier curves using a pixel-coordinate method where the axes of interest were mapped to mathematically calculate the percentages. Data was collected by members of the study team (L.M.H, O.W, P.S.M, D.M, C.J, K.O, C.P, M.H).

Evidence grading

All articles were independently graded using the Oxford Centre for Evidence-based Medicine levels of Evidence by two team members (L.M.H and P.S.M) [20]. Each article was assigned a grade from I to V, where I was indicative of the most robust evidence and V was indicative of the weakest evidence. Disagreements were resolved by discussion or the decision of a third observer.

Data analysis

Due to the exploratory nature of this review, all collected end points per regimen within each study were analyzed as independent observations. MOS (months), 5-year cumulative percentage of survival, mean age of patients (years), and proportion of males from each regimen were summarized with median and range. Number of regimens observed per continent, per country, and per patient population exclusively over 65 years old were summarized with frequency and percent. The Kruskal–Wallis Rank sum test was used to assess group-wise differences in MOS between studies conducted before and after the Stupp protocol (2005), continents, and clinical trial treatment types. Due to the low frequency of studies with recorded or used utilized treatment, observed outcomes from regimens that used more than one treatment type (bevacizumab, vaccines, etc.) were analyzed as part of each treatment group. All tests were two-sided, and p-values less than 0.05 were considered statistically significant. All analysis was performed using R Statistical Software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Literature search

The search strategy yielded 9,162 articles. Following the removal of non-relevant publications, a total of 1,725 full-text articles were assessed for eligibility (Fig. 1). 438 articles that were published from 1979 to 2017 were included for further analysis, where 308 were observational, 92 were one-arm clinical trials, and 38 were two or more arms clinical trials.

Level of evidence

Our review identified 308 level 3 and 4 studies. In randomized clinical trials (RCT), 12 level 1 studies and 28 level 2 studies were identified. 92 non-randomized clinical trials were identified as level 2 studies (Online Resource 1).

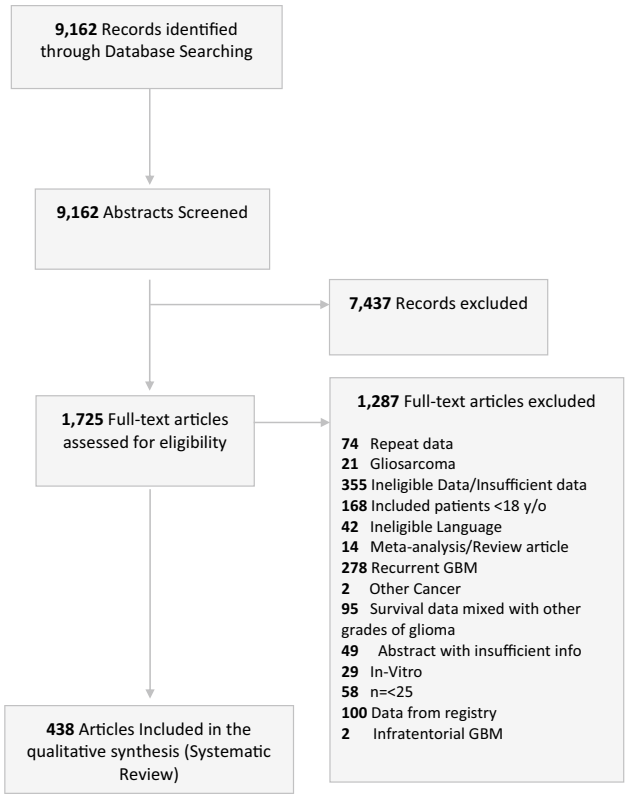
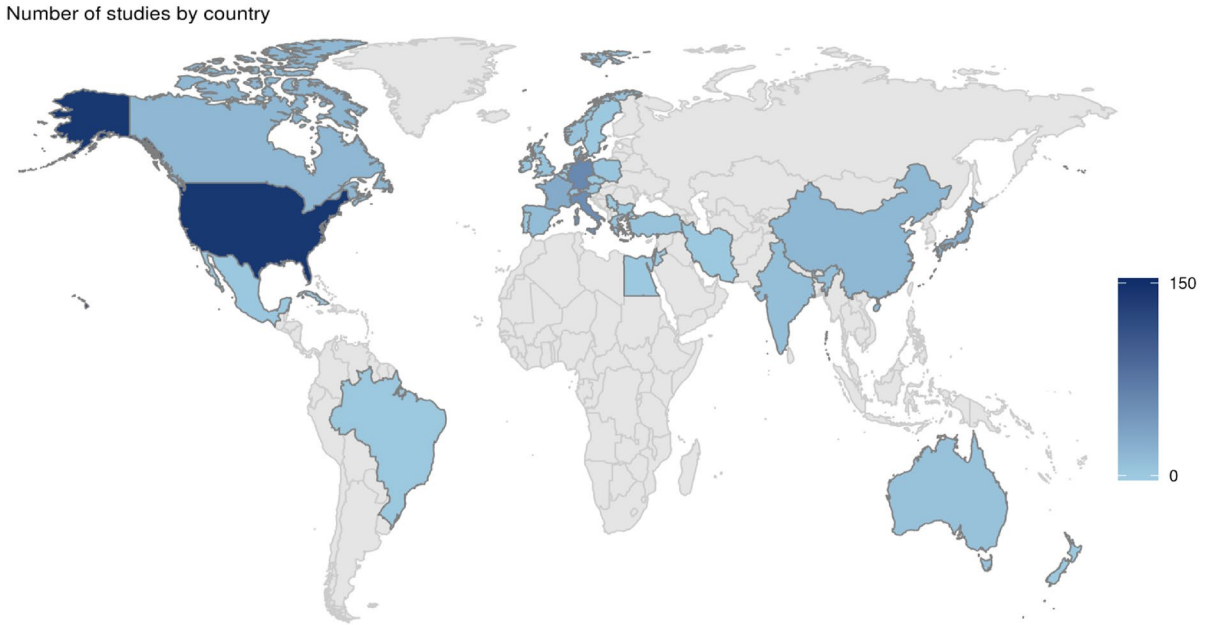


Fig. 1 Preferred reporting items for systematic review and meta-analysis (PRISMA) search strategy. *GBM* Glioblastoma

Current status of GBM

In this review a total of 438 studies from 1979–2017 were analyzed, where 308 (70.3%) survival outcomes were from observational, 92 (21%) from one arm clinical trials, and 38 (8.6%) from two arm clinical trials. Studies included a total of 56,626 patients with a median of 70 patients per study (range 133–1229 patients). The median of all recorded average ages was 57 (range 32–83) years, and the median proportion of males was 60% (range 26–91%). Forty-five (9.4%) studies had patient populations consisting exclusively of elderly patients. The overall median MOS estimate was 13.5 (range 2.3–29.6) months, where 338 (71%) studies had observed MOS between 11 to 20 months. Ninety-one (19%) had information regarding 5 year-survival, where the median 5-year survival percentage was 5.8% (range 0.01%–29.1%).

Overall, 476 data points for MOS were collected. From these, 204 (42.9%) were conducted in Europe, 165 (34.6%) in the Americas, 71 (14.9%) in Asia, and 8 (1.7%) in Africa and Oceania. The United States had the largest proportion of GBM reports (29.6%), followed by Germany (12.0%), Italy (11.3%), France (5.9%) and Japan (4.8%) (Fig. 2). There



Number of Studies by Continent

Continent	N	Median (Range)
Africa & Oceania	8	12.15 (6.7, 18)
Americas	165	13.12 (2.3, 29.6)
Asia	71	15.2 (7.9, 28.8)
Europe	204	13.355 (3.8, 28)

Median Overall Survival by Continent (Pre/Post Stupp Protocol)

	Pre-Stupp Protocol (N=260)	Post-Stupp Protocol (N=136)	Total (N=396)	P value
Africa & Oceania				
N	0	8	8	
Median (Range)	NA	12.15 (6.70, 18.00)	12.15 (6.70,18.00)	NA
Americas				
N	102	42	144	
Median (Range)	11.63 (2.30, 24.00)	16.15 (6.50, 29.60)	12.98 (2.30, 29.60)	**<0.001**
Asia				
N	32	32	64	
Median (Range)	13.70 (9.00, 22.60)	15.75 (7.90, 28.80)	15.00 (7.90, 28.80)	0.25
Europe				
N	126	54	180	
Median (Range)	12.50 (3.88, 28.00)	14.77 (3.80, 22.00)	13.00 (3.80,28.00)	0.056

Fig. 2 Global distribution of Survival by Country and Continent

were 28 (5.9%) studies that took place internationally on more than one continent. Overall there was an observed difference in median MOS between continents ($P \leq 0.002$) where Asia had the longest observed median MOS [15.2 (range 7.9–28.8)] months, followed by Europe [13.36 (range 3.8–28)] months, Americas [13.12 (range 2.3–29.6] months, and Africa and Oceania [12.15 (range 6.7–18] months (Fig. 3c). There was a statistically significant increase in survival for studies from the Americas after 2005 [16.2 months (range 6.5–29.6 months) vs. 11.63 months (range 2.3–24 months)] ($P < 0.001$). The Americas showed the highest central tendency in MOS of all continents post-dating implementation of TMZ with radiotherapy. (Fig. 2).

Within the observational studies, there were significant differences amongst treatments. Those that included bevacizumab (BVZ) had the longest median MOS [16.4 (range 10.5–22.6)] months, followed by TMZ [13.9 (range 2.3–28.8)] months, carmustine wafers [12.7 (range 2.3–20.0)] months and other types of chemotherapy [12.6 (range 2.3–28.0)] months (Fig. 3d).

There were 130 clinical trials included in this analysis. Eight phase I trials, 9 phase I/II trials, 96 phase II trials, 1 phase II/III trials and 16 phase III trials that fulfilled our inclusion criteria. Within clinical trials, the highest MOS involved tumor treating fields (TTF) with 20.7 (range 20.5–20.9) months, followed by vaccine immunotherapy with 19.2 (15.3–26) months, BVZ therapy with 18.2 (range 10.6–23) months, localized therapy with 16.6 (range 15.42–20.5) months, TMZ with 14.6 (range 6.1–22.3) months, antibody immunotherapy with 14.55 (range 8.4–18.27) months, carmustine wafers with 13.3 (11.51–17.8) months, and radiotherapy with 12.89 (6.69–28) months ($P = 0.047$) (Fig. 4).

Within clinical trials the treatment with the highest tendency in survival was TTF. The evidence originated from a large randomized phase III trial including 466 treated with TTF (20.9 months TTF-TMZ vs 16.0 months in the TMZ group; $P < 0.001$) [21, 22]. Regarding BZV, initial phase II studies favored its addition to radiotherapy and TMZ [23, 24]. However, phase III trials failed to show a

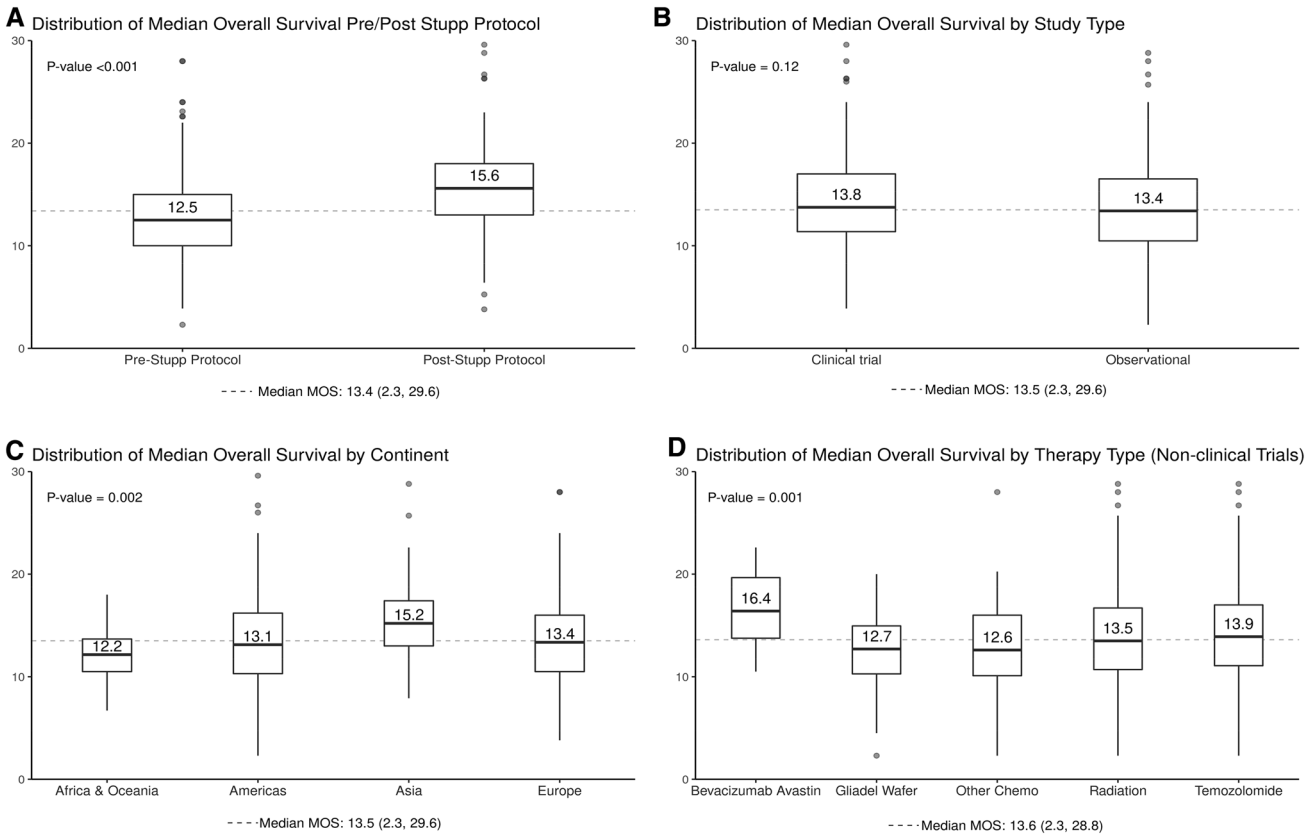


Fig. 3 Distribution of Median Overall Survival A. Pooled median overall survival for studies that predate and postdate Stupp Protocol 2005 B. Differences in pooled MOS between clinical trials vs observational studies. C. Median Overall Survival by continent D. Median Overall Survival by therapy type in observational studies. Overall studies in the Stupp era had higher cumulative survival values, with Asia having the largest central tendency of all studies analyzed regardless of time period. *Circles indicate observed data points. The box plot lines correspond from bottom of box to top: 25th percentile, median percentile, 75th percentile. The whiskers extend to the minimum and maximum value

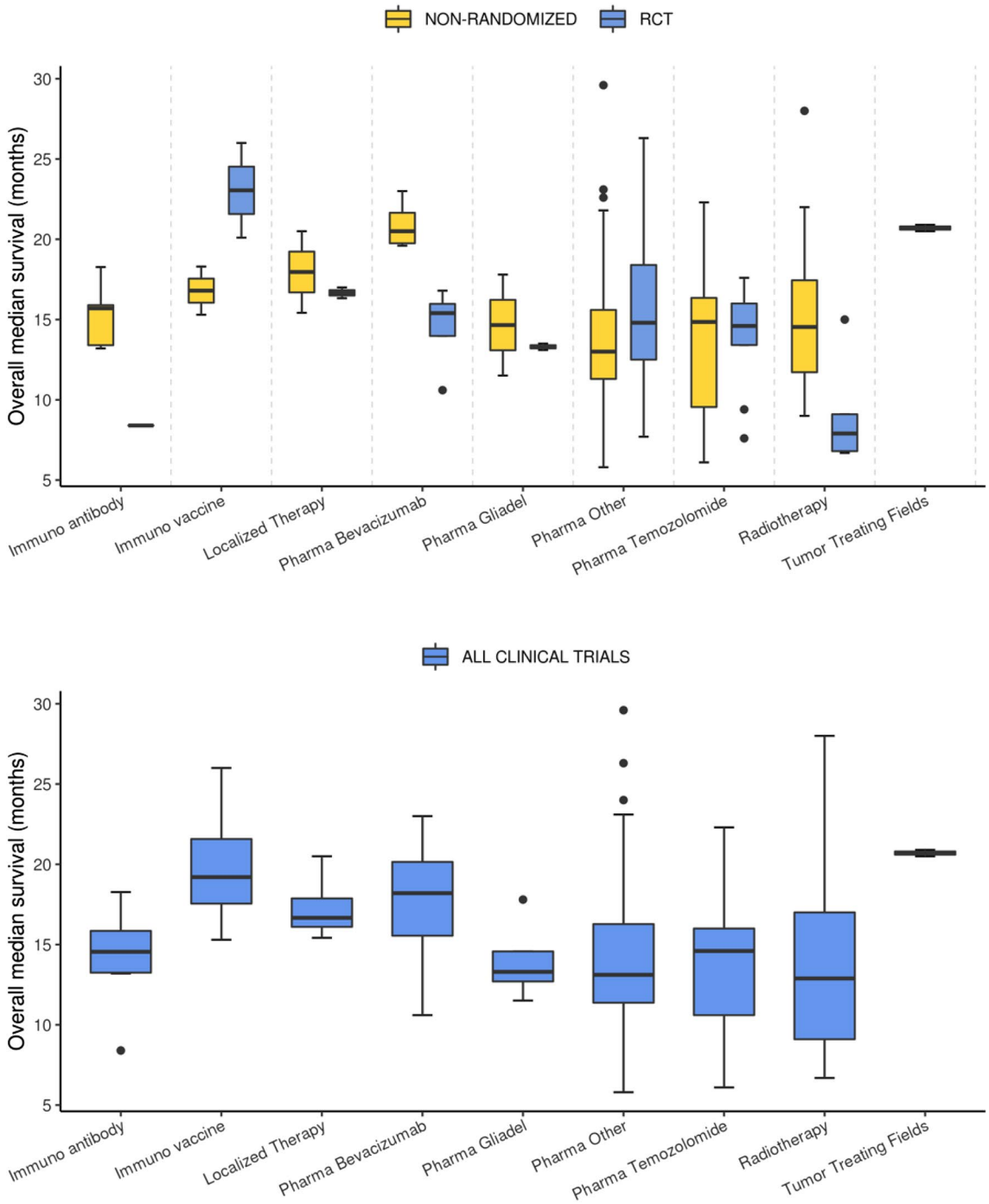


Fig. 4 Pooled median overall survival for different treatment modalities in A. Randomized and non-randomized clinical trials. B. Pooled median overall survival for all clinical trials. Overall, therapy that favored a higher pooled MOS included TTF, vaccines and bevacizumab

benefit in prolonging survival [25, 26]. Additional antibodies against GBM largely targeted EGFRvIII. An early non-randomized phase II trial evaluated the use of intravenous anti- EGRF i-425 monoclonal antibodies with radiotherapy in 46 patients diagnosed with GBM, reporting survival of 13.2 months [27]. Subsequent trials that targeted EGFRvIII had mixed results; In a small cohort of 30 patients, there was no observed survival benefit with the use of nitozumab [28]. In contrast, a randomized phase II trial concluded that the addition of nitozumab to RT and TMZ increased survival for GBM patients [29].

Vaccine therapy included EGFRvIII-targeted, multipeptide and dendritic cell vaccination [30–33]. Initial phase II trials evaluated the addition of rindopepimut (CDX11) to

standard of care, revealing an MOS of 21.8 months [30]. These results lead to ACT IV, a double blind phase III RCT examining 371 patients who underwent vaccination in addition to standard treatment; The trial was terminated after a preplanned interim analysis determined no statistically significant increase in survival with the addition of rindopepimut (20.1 months rindopepimut vs 20.0 months control; P = 0.93) [31]. Multipeptide and dendritic cell vaccination reported MOS of 15.3 months and 18.3 months respectively, however the non-comparative nature of these Phase I/ I-II trials limit their interpretation until RCTs are conducted [32, 33]. Lastly, localized therapy involved intralesional Lymphokine Activated Killer (LAK) cells, adenovirus gene therapy, immunostimulating cytosine-guanosine motives (CpG ODN) [34–36]. The results of a phase II trial assessing the efficacy of intralesional LAK cells were encouraging with MOS of 20.5 months from diagnosis [34]. Other phase II trials evaluating intracerebral injections of CpG ODN and a phase III ASPECT trial testing HSVtk gene therapy plus ganciclovir did not reach statistical significance at increasing survival for GBM patients [35, 36].

Impact of temozolomide with concurrent radiation therapy protocol (2005)

Overall, there were 269/426 (63.15%) studies conducted prior to initiation of the TMZ/radiation protocol and 157/426 (36.85%) conducted after its establishment in 2005. Fifty studies were excluded from this analysis due to missing years from when patient data was collected. Estimates of the median survival were significantly different between the two eras ($P < 0.001$, Fig. 3a) where post-TMZ/radiation studies had longer estimates of median survival (median: 15.6 months, range 3.8–29.6) as compared to pre-TMZ/radiation studies [15.6 (range 3.8–29.6) vs 12.5 (range 2.3–28)] months. Stupp *et al.* reported a MOS of 14.6 months (95% CI 13.2–16.8 months) in the first large RCT that proved the efficacy of radiotherapy and TMZ at prolonging survival. In this review, studies following 2005 had a central tendency of MOS of 15.6 months. Being that the survival values of studies postdating 2005 fall within the 95% CI of MOS reported by Stupp, there was no statistically significant difference between these two values. Further analysis of 9 studies consisting of 1353 patients, where data was collected after 2010, revealed a central tendency of MOS of 15 months (range 12–20.1 months).

Discussion

Despite decades of research, GBM remains the deadliest and most challenging primary brain tumor to treat [37–39]. Approximately 219.8 billion dollars are dedicated to brain tumor research, constituting only ~ 1% of funds awarded by the NIH in 2018 for neuroscience research [40]. Intrinsic characteristics of GBM, such as intratumoral heterogeneity and plasticity hinder the ability to target it with a single pharmacological agent [37, 40]. Currently, there is a lack of consensus on survival outcomes, as they vary drastically in the literature from months to years [41–45]. In an attempt to understand the current progress in prolonging the MOS of patients with GBM, we conducted a systematic review of the literature to identify the trends in improving survival for GBM patients over time and different treatment modalities. To our knowledge, this report is the largest systematic review to provide pooled cumulative data on the overall survival status of GBM reported in the literature.

Our analysis demonstrates a cumulative survival of 13.5 months for published works regarding newly diagnosed, adult GBM patients with an increase in the median survival to 15.6 months since the administration of TMZ and radiotherapy. The most relevant study for GBM treatment was the design of the well-known Stupp trial conducted in 2005 [9]. This study, consisted of the administration of radiation with concomitant and adjuvant TMZ, reporting an increase of MOS from 12.1 to 14.6 months, thus becoming the current gold standard treatment for newly diagnosed GBM [9]. Consistent with those numbers, we observed a statistically significant difference in the survival estimates between studies that predate and postdate this protocol ($P < 0.001$). Publications in the TMZ era reported a median survival of 15.6 months, similar to the values stated in the literature [46]. The 5-year cumulative survival rate for our analysis was 5.8%. The cumulative percentage of 5-year survivors identified in this study did not differ from the 2011 to 2014 Central Brain Tumor Registry of the United States (CBTRUS), which indicated a relative 5-year survival of 5.5% [1].

Examination of clinical trials for GBM revealed that TTF, BVZ, and vaccine-based immunotherapy reported the longest survival times within studies. BVZ, an anti-angiogenic drug, was approved in 2017 for the treatment of recurrent GBM, nonetheless, the role of BVZ in newly diagnosed GBM remains controversial [25, 26, 47, 48]. Our analysis found that BVZ could have a positive impact on survival. Although our data suggest BVZ-containing regimens to have longer survival estimates, two phase III RCTs reported that BVZ lengthened progression-free survival without a significant effect on MOS in either study [25, 26]. Vaccines also granted an overall increase in survival; however, further stratification showed that results varied according to the type of vaccination. Vaccines included tumor associated peptide, dendritic, and Epidermal Growth Factor Receptor (EGFR) targeted vaccinations [31–33, 49]. With EGFR targeted vaccines, there was an observed benefit within small cohorts, while larger RCTs did not reveal a statistically significant

survival benefit [31, 49]. Peptide associated vaccines did not significantly lengthen survival when compared to standard of care, and a marginal benefit with dendritic vaccines was observed [32, 33]. Treatment Therapy with TTF, a non-invasive antimitotic therapy that selectively disrupts cell division, increased MOS [50]. After the completion of trials conducted by Kirson et al. in 2007 and by Stupp et al. in 2012, this therapy received FDA approval in 2015 to be used in combination with radiochemotherapy for the treatment of newly diagnosed GBM [51, 52]. In our analysis, TTF provided the longest median survival estimate of 20.7 months. These results originated from a large RCT conducted by Stupp et al. that evaluated 695 randomized patients with newly diagnosed GBM comparing TMZ/radiation vs TMZ/radiation plus TTF [21, 22].

Among continents, Asian studies reported the highest central tendency of survival followed by Europe, America, Africa, and Oceania ($P < 0.002$). Despite having the highest survival measure, these were fewer in number ($n = 32$) than studies from America ($n = 106$) and Europe ($n = 106$). After 2005, North America possessed the highest values of survival. Due to possible confounders we do not propose using continent as a prognostic factor. However, these preliminary results could call for an assessment of GBM survival on a global scale, which to date has not been conducted [53].

The increase in survival following the adaptation of TMZ and RT as standard of care is encouraging. However, a closer analysis reveals similar 95% confidence intervals between the two eras, which begs the question- have we changed outcomes for patients with GBM? Overall, studies conducted in recent years report longer survival values for GBM patients, additionally over the last decade novel therapies have shown favorable results by providing a modest increase in MOS for patients with GBM; TTF being the most promising and recently adopted treatment modality. Selected immune therapy-based regimes seem to confer some benefit but more robust evidence in the form of RCT is required to come to an adequate conclusion. Currently, GBM remains an incurable disease, as we approach the era of precision medicine, treatment strategies tailored to individual tumor characteristics could hold the key to redirecting the natural history of GBM.

Strengths and limitations

This is the first and largest systematic review of the literature to provide pooled cumulative data and characterize the overall survival status of newly diagnosed GBM patients. Here we provide valuable information by examining the progress of survival through the years, and disparities in MOS according to available treatment modalities. In its synthesis, this review adhered to PRISMA guidelines and recommendations. The information contained in this work could help guide decision making in GBM patients and orient the design of future experimental clinical studies. Due to the large number of articles on GBM, this systematic review was carried out by evaluating only one database.

As GBM diagnosis becomes more established, the identification of prognostic mutations such as IDH-1 and MGMT emerged as key factors in estimating survival, incorporated as part of regular clinical practice within the last decade. Due to its relative novelty, the present analysis could not take prognostic mutations into consideration, as most studies did not conduct molecular testing or only performed testing in selected patients. Other variables including neurological status, academic versus non-academic setting, and tumor location could not be assessed. These have been known to affect outcomes, but this study was not able to achieve this granularity of detail. Due to their retrospective and descriptive nature, most observational studies did not control for KPS scores. It is also biased by what has been reported in the literature, as only studies that have been published were reflected in this analysis.

Conclusion

Based on the published literature, this systematic review demonstrated a statistically significant increase in survival following the adoption of the TMZ/radiation protocol as the standard of care in 2005, with TTF being the only additional treatment to be approved by the FDA since 2015 to treat patients with newly diagnosed GBM. The amount of clinical, research and surgical advancements have provided a modest benefit in survival for GBM patients throughout the years. However, GBM remains largely refractory to treatment. Currently, great efforts are underway to find novel therapies that target GBM. Emerging therapies such as immunotherapy and personalized therapy are promising alternatives for GBM patients that could hold the key to prolonging survival.

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Compliance with ethical standards

Conflict of interest The authors report no funding sources or conflict of interests concerning the materials or methods used in the study or the findings specified in this paper.

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