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RESEARCH

Limited survival benefit in patients diagnosed with glioblastoma post-2016: a SEER population based registry analysis

Shaurya Dhingra[1] · **Matthew Koshy**[1] · **Mark Korpics**[1]

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Abstract

Background The EF14 clinical trial reported an improvement in median overall survival (OS) from 16.0 months to 20.9 months in patients with glioblastoma (GBM) who received treatment with tumor treating fields (TTFs). This study evaluates overall survival in a large population-based cohort of patients with GBM before and after FDA approval of TTFs in 2015.

Methods A total of 27,534 patients from the Surveillance, Epidemiology and End Results (SEER) database with GBM who underwent surgery and post-operative radiotherapy were grouped into three diagnosis periods: those diagnosed pre-temozolomide (2000–2004), those diagnosed post-temozolomide (2005–2015), and those diagnosed post-TTFs (2016–2020). Overall survival (OS) was calculated using the Kaplan–Meier method, and multivariate Cox regression models were employed to estimate hazard ratios (HR).

Results GBM diagnosis in the post-TTFs period was associated with a median OS of 15 months (95% CI 14–15 months) compared to a median OS of 14 months (95% CI 14–14 months, $p < 0.001$) for GBM diagnosis in the post-temozolomide/pre-TTFs period. 24-months OS was 25.6% (95% CI 24.5–26.8%) in the post-TTFs period and 24.7% (95% CI 24.0–25.4%) in the post-temozolomide/pre-TTFs period. In a multivariate model accounting for clinical characteristics, diagnosis in the post-TTFs period as compared to the post-temozolomide/pre-TTFs period was significantly associated with OS (HR: 0.941, 95% CI 0.912–0.972, $p < 0.001$).

Conclusion This population-based cohort demonstrated minimal change in survival for patients diagnosed with GBM before and after FDA approval of TTFs in 2015.

Keywords "Tumor treating fields" (TTFs) · "Glioblastoma" (GBM) · "Radiation" · "Temozolomide" · "Surveillance · Epidemiology · And end results" (SEER)

Introduction

Glioblastoma (GBM) is a highly malignant brain tumor associated with an extremely poor prognosis (Brown et al. 2022; Rong et al. 2022; Carlsson et al. 2014; Sales et al. 2022). Surgical resection with adjuvant radiotherapy remained the mainstay of treatment for GBM until 2005, when a landmark clinical trial demonstrated that combined adjuvant radiotherapy and temozolomide provided survival benefit over radiotherapy alone (Sales et al. 2022; Stupp et al. 2005). Surgery with combined adjuvant radiotherapy and temozolomide was adopted as the new standard of care. Patients diagnosed with GBM during 2005–2006 showed improved survival in large population-based cohorts (Poon et al. 2020; Koshy et al. 2011).

The development of Tumor Treating Fields (TTFs) represented the next and now most-recent major development in the treatment of GBM. TTFs interfere with mitotic spindle formation and interrupt cell division via alternating electric fields of low-intensity and intermediate frequency (Kirson et al. 2009). In patients with recurrent GBM, a phase 3 trial associated TTFs with improved quality of life compared to chemotherapy but failed to demonstrate improved survival (Stupp et al. 1990). However, improved survival was demonstrated in a subsequent pivotal phase 3 trial where TTFs were added to maintenance temozolomide therapy, following

✉ Mark Korpics
korpics1@uic.edu

[1] Department of Radiation Oncology, University of Illinois Hospital and Health Sciences System, 1801 West Taylor Street, OCC C400, Chicago, IL 60612, USA

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completion of surgery and radiotherapy (Stupp et al. 2015; Stupp et al. 2017). In late 2015, TTFs were FDA approved for newly diagnosed GBM.

In this study, we examine the survival of patients diagnosed with GBM pre-temozolomide (2000–2004), post-temozolomide/pre-TTFs (2005–2015), and post-TTFs (2016–2020). We use a large population-based cohort from the Surveillance, Epidemiology, and End Results (SEER) database to evaluate whether a GBM diagnosis after FDA approval of TTFs is associated with improved overall survival (OS).

Methods

Data and study population

Incidence and survival data was obtained from the SEER database containing information on primary tumor site, age, sex, histology, stage at diagnosis, first course of treatment, and overall survival from 17 population-based cancer registries. Data on use of TTFs was not available in the SEER database. Patients selected for inclusion in this study were aged 20 years and older and had a microscopically-confirmed first primary of glioblastoma (International Classification of Diseases for Oncology, Version 3 histology codes 9440–9442, and 9445) diagnosed during 2000–2020. All selected patients underwent either surgical resection or biopsy followed by post-operative radiation therapy. The final sample size included 27,534 patients.

Statistical analysis

Survival was calculated using the Kaplan–Meier method. For overall survival (OS) analysis, 23,948 patients were followed until time of death, and the remaining were censored at their last point of follow up. Survival curves were compared using the log-rank test and the proportional hazards assumption was verified graphically using a plot of the log cumulative hazard. Univariable and multivariable analyses, including calculation of hazard ratios (HR) and the 95% confidence intervals (CI), were performed using Cox proportional hazards regression models. Variables included in the multivariable model were either important patient characteristics such as age, sex, and race, or were significantly different between groups in the chi-square test. The exact age for patients 90 years and older was not available in the SEER database, thus such patients were excluded from the multivariable analyses in which age was used as a continuous variable ($n = 37$). Significance was defined as $p < 0.05$ for all tests. All statistical analyses were carried out in R version 4.1.2 using the 'survival' and 'survminer' packages. Survival figures were created using GraphPad PRISM version 10.3.0.

Ethics

This study utilized data that is available upon request from the SEER database and no individually identifying information was used. Therefore, institutional review board (IRB) approval was not required in accordance with the University of Illinois at Chicago College of Medicine's policy.

Results

Study demographics

A total of 27,534 patients newly diagnosed with GBM were included in the study (Table 1). 4909 (17.84%) patients were diagnosed between 2000 and 2004, 14,554 (52.86%) were diagnosed between 2005 and 2015, and the remaining 8071 (29.31%) were diagnosed in 2016 or later. Gross total resection had been performed on 11,973 (43.48%), while subtotal resection was performed on the remaining patients. A total of 4383 (15.92%) patients either did not receive chemotherapy or had an undetermined chemotherapy status.

Over the 21-year period examined, the number of patients for which data was available increased steadily, from 915 patients diagnosed in 2000 to 1650 patients diagnosed in 2020 (Supplementary Table 1). The median follow-up time remained relatively stable, ranging between 10 and 15 months, with a slight increase observed in later years, except for patients diagnosed in 2020 for whom median follow-up time was 4 months. As expected, the maximum follow-up time decreased consistently over the years examined, going from a maximum of 249 months of follow-up for patients diagnosed in 2000 to 11 months for those diagnosed in 2020.

Overall survival

Kaplan–Meier analysis demonstrated a statistically significant increase in OS for patients diagnosed with GBM in both the post-temozolomide period ($p < 0.001$) and the post-TTFs period ($p < 0.001$) compared to those diagnosed in the pre-temozolomide period. A statistically significant increase in OS was also observed for patients diagnosed with GBM in the post-TTFs period versus the post-temozolomide period ($p = 0.011$). Median OS was 11 months (95% CI 11–11 months) for patients diagnosed in the pre-temozolomide period, 14 months (95% CI 14–14 months) for those diagnosed in the post-temozolomide period, and 15 months (95% CI 14–15 months) for those diagnosed in the post TTFs period (Fig. 1). Two-year overall survival for

Table 1 Cohort demographics

	Total (n = 27,534)	2000–2004 (n = 4909)	2005–2015 (n = 14,554)	2016–2020 (8071)	p-value
Gender					
Male	16,359 (59.41%)	2972 (60.54%)	8603 (59.11%)	4784 (59.27%)	0.201
Female	11,175 (40.59%)	1937 (39.46%)	5951 (40.89%)	3287 (40.73%)	
Age					
20–34 years	974 (3.54%)	197 (4.01%)	474 (3.26%)	303 (3.75%)	<0.001
35–44 years	1992 (7.23%)	502 (10.23%)	980 (6.73%)	510 (6.32%)	
45–54 years	5432 (19.73%)	1090 (22.20%)	3046 (20.93%)	1296 (16.00%)	
55–64 years	8776 (31.87%)	1382 (28.15%)	4779 (32.84%)	2615 (32.40%)	
65–74 years	7226 (26.24%)	1159 (23.61%)	3674 (25.24%)	2393 (29.65%)	
75 + years	3134 (11.38%)	579 (11.79%)	1601 (11.00%)	1601 (19.80%)	
Race					
White	24,522 (89.06%)	4482 (91.30%)	13,022 (89.47%)	7018 (86.95%)	< 0.001
Black	1463 (5.31%)	215 (4.38%)	773 (5.31%)	475 (5.89%)	
Other	1549 (5.63%)	212 (4.32%)	759 (5.22%)	578 (7.16%)	
Ethnicity					
Hispanic	2995 (10.88%)	428 (8.72%)	1505 (10.34%)	1062 (13.16%)	< 0.001
Non-hispanic	24,539 (89.12%)	4481 (91.28%)	13,049 (89.66%)	7009 (86.84%)	
Extent of surgery					
Gross total	11,973 (43.48%)	2072 (42.21%)	6092 (41.86%)	3809 (47.19%)	< 0.001
Subtotal	15,561 (56.52%)	2837 (57.79%)	8462 (58.14%)	4262 (52.81%)	
Chemotherapy					
No/unknown	4383 (15.92%)	2275 (46.34%)	1520 (10.44%)	588 (7.29%)	< 0.001
Yes	23,151 (84.08%)	2634 (53.66%)	13,034 (89.56%)	7483 (92.71%)	

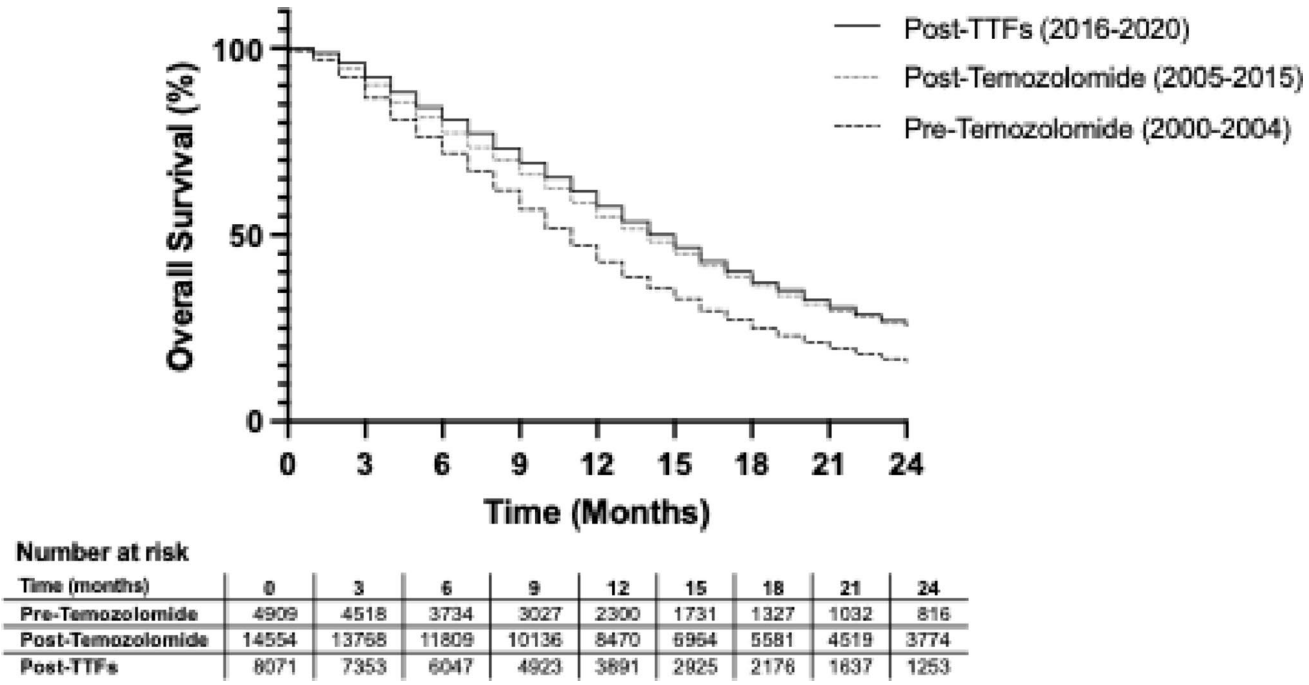

Fig. 1 Kaplan–Meier survival analysis showing overall survival

the same cohorts were 16.0% (95% CI 15.0–17.0%), 24.7% (95% CI 24.0–25.4%), and 25.6% (95% CI 24.5–26.8%), respectively. When examining temporal trends within each of the three diagnosis periods, a gradual increase in Kaplan–Meier median OS was observed during the pre-temozolomide period, however, no trends were observed in the post-temozolomide periods and the post-TTFs periods (Supplementary Fig. 1).

Multivariate analysis

In a multivariate Cox proportional hazards model, accounting for clinical characteristics including age, race, sex, ethnicity, extent of surgery, and chemotherapy usage (Table 2), patients diagnosed with GBM in the post-temozolomide period demonstrated a statistically significant association with OS (HR: 0.863, 95% CI: 0.833–0.895, $p < 0.001$), as did patients diagnosed in the post-TTFs period (HR: 0.813, 95% CI 0.779–0.848, $p < 0.001$), when compared to those diagnosed in the pre-temozolomide period. In the same model, when using diagnosis in the post-temozolomide/pre-TTFs period as the reference, diagnosis in the post-TTFs period demonstrated a statistically significant association with OS when compared to the post-temozolomide/pre-TTFs period (HR: 0.941, 95% CI 0.912–0.972, $p < 0.001$). Gross total resection and chemotherapy use was associated with improved survival outcomes, as was being Hispanic, or a race other than white or black. Male sex and age both had a negative association with survival. In an alternate model where age was evaluated as a stratified variable comparing patients under 70 to those aged 70 or older, those aged 70 or older were found to have worse survival outcomes (Supplementary Table 2).

To address potential confounding from the higher use of chemotherapy in the post-temozolomide and post-TTFs periods, we performed a sensitivity analysis excluding chemotherapy as a covariate (Supplementary Table 3), which yielded results consistent with the primary analysis. Additionally, to further isolate the effects of TTFs, we performed an additional analysis of only patients confirmed to have received chemotherapy treatment, considering the high likelihood that patients receiving TTFs therapy would have also received temozolomide treatment (Supplementary Table 4). These findings once again aligned with previous results.

Table 2 Overall survival cox proportional hazard analysis (n = 27,497)

	Hazard Ratio	95% CI	p-value
Gender			
Female	Ref	–	–
Male	1.120	1.091 – 1.150	< 0.001
Age	1.032	1.031 – 1.033	< 0.001
Race			
White	Ref	–	–
Black	1.025	0.968 – 1.086	0.392
Other	0.852	0.804 – 0.902	< 0.001
Ethnicity			
Non-Hispanic	Ref	–	–
Hispanic	0.950	0.910 – 0.991	0.017
Extent of Surgery			
Subtotal	Ref	–	–
Gross Total	0.751	0.732 – 0.770	< 0.001
Diagnosis Period			
2000–2004	Ref	–	–
2005–2015	0.863	0.833 – 0.895	< 0.001
2016–2020	0.813	0.779 – 0.848	< 0.001
2000–2004	1.158	1.117 – 1.201	< 0.001
2005–2015	Ref	–	–
2016–2020	0.941	0.912 – 0.972	< 0.001
Chemotherapy			
No/Unknown	Ref	–	–
Yes	0.588	0.567 – 0.611	< 0.001

Discussion

In this SEER population-based cohort of individuals from across the nation, we examined patients newly diagnosed with GBM who underwent both surgery and post-operative radiation therapy. Our findings redemonstrate the previously seen survival benefit observed after FDA approval of temozolomide. However, diagnosis GBM in the period following the FDA approval of tumor-treating fields (TTFs) is associated with only a limited survival benefit compared to diagnosis in the period immediately prior to the approval of TTFs.

Although SEER does not account for the type of chemotherapy administered, nor the receipt of TTFs, we observed that GBM diagnosis after the publication of EORTC/NCIC 22981/2698 trial establishing temozolomide as standard of care (2005), and GBM diagnosis after the FDA approval of TTFs (2016) were both associated with improved median OS of 14 months and 15 months, respectively, compared to 11 months for GBM diagnosis pre-temozolomide (prior to the publication of EORTC/NCIC 22981/2698). Two-year OS was 16.0% pre-temozolomide, 24.7% post-temozolomide, and 25.6% post-TTFs ($p < 0.001$). After adjusting for patient characteristics, the multivariable proportional hazards model in this study demonstrated that increased OS was associated with GBM diagnosis in the post-TTFs period versus the pre-temozolomide period (HR: 0.813, 95% CI 0.779–0.848, $p < 0.001$) as well as in the post-temozolomide/pre-TTFs period versus the pre-temozolomide period (HR: 0.863, 95% CI 0.833–0.895, $p < 0.001$). When adjusting the same model

to compare GBM diagnosis in the post-TTFs period to the post-temozolomide period, the observed survival increase in the post-TTFs period was limited (HR: 0.941, 95% CI 0.912–0.972, $p < 0.001$). Associations with OS remained consistent in a sensitivity analysis where chemotherapy use was excluded as a covariate, and another where only patients with confirmed receipt of chemotherapy were studied.

These results suggest that the OS benefit from TTFs observed in the EF14 clinical trial was not apparent in this population-based cohort after FDA approval of TTFs in 2015. The modest statistically significant OS increase associated with diagnosis in the post-TTFs period may be attributable to some TTFs uptake, improved accessibility of temozolomide, or advances in other treatment modalities including improved neurosurgical techniques. The observed results may also reflect the potentially limited efficacy of TTFs, particularly given criticisms raised about the EF-14 trial design such as the lack of a sham control device, randomization only after receiving radiotherapy, and offering TTFs to control participants at the study's interim analysis point, all of which may have led to an overestimation of the treatment's true effectiveness (Mehta et al. 2017). Patients selected in the EF-14 trial required a Karnofsky performance score (KPS) of 70 or higher following surgical resection, radiotherapy, and temozolomide chemotherapy. In contrast, our population-based cohort encompassed all individuals who underwent surgical resection and subsequent radiotherapy. Due to limitations in the SEER database, we were unable to identify the type of chemotherapy administered to participants, and definitive use of chemotherapy was not established for 15.9% of patients.

These results may also indicate a potential underutilization of TTFs in the clinical setting, which may be attributable to factors including accessibility and patient compliance. 75% of individuals in the EF-14 study achieved a compliance of 75%, or 18 h TTFs treatment daily. This was associated with an overall survival improvement of more than three months (Stupp et al. 2017). A 2022 study found that 35% of patients with newly diagnosed GBM declined treatment with TTFs, and 68% of patients who utilized TTFs had a compliance of less than 75% (Ballo et al. 2022). The utilization of TTFs in newly diagnosed cases has been reported to be as low as 3% (Lassman et al. 2020). In cohorts of individuals utilizing TTFs, a compliance of greater than 75% is observed in only 18–60% of individuals (Nishikawa et al. 2023; Pandey et al. 2022). Other barriers affecting the utilization of TTFs may include socio-economic disparities preventing access to therapy, limited adoption by medical practices due technical or logistical challenges, as well as personal preferences regarding lifestyle disruption, limitations in mobility, and required hair shaving. Further study is required to clarify the utilization and compliance rates of TTFs in the general population.

Additional limitations of this study arise from the limited availability of some data in the SEER database. Glioblastoma patients with mutations in the isocitrate dehydrogenase 1 or 2 (IDH1/2) genes are known to have a positive association with OS; however, information on IDH mutation status was unavailable in the SEER database and thus not included in this analysis (Sanson et al. 2009; Zou et al. 2013). Information on methylation of the O^6-methylguanine DNA methyltransferase (MGMT) promoter, which has been found to correlate with an improved response to temozolomide, was also unavailable (Hegi et al. 2024). Additionally, data on KPS, a measure of functional independence known to be a significant prognostic factor in glioblastoma, was not available in the database (Carson et al. 2007; Laws et al. 2024). Data on the utilization and compliance of TTFs, radiotherapy technique, and type of chemotherapy were also unavailable. Patients diagnosed in 2020 had limited follow up time because they were diagnosed more recently, which may have further impacted results (Supplementary Table 1). This study is also unable to assess the impact of changes in other treatment modalities, including improvements in neurosurgical techniques, and the development of anti-angiogenic therapies like bevacizumab.

Conclusion

This population-based cohort demonstrated minimal change in survival for patients diagnosed with GBM before and after FDA approval of TTFs in 2015. The largest and most significant increase in OS was observed in patients diagnosed in 2005 or later, which is attributed to the incorporation of temozolomide into standard of care. These results are concerning for underutilization of TTFs, which may in part be due to limited accessibility or compliance of the technology, a topic that requires further study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-025-06171-4.

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Data availability Data from the SEER database is available upon request to the National Institutes of Health. Data generated during analysis will be available upon request, in accordance with SEER policies.

Declarations

Conflict of interest The authors declare no competing interests.

References

Ballo MT, Qualls KW, Michael LM et al (2022) Determinants of tumor treating field usage in patients with primary glioblastoma: a single institutional experience. Neuro-Oncol Adv. https://doi.org/10.1093/noajnl/vdac150

Brown NF, Ottaviani D, Tazare J et al (2022) Survival outcomes and prognostic factors in glioblastoma. Cancers. https://doi.org/10.3390/cancers14133161

Carlsson SK, Brothers SP, Wahlestedt C (2014) Emerging treatment strategies for glioblastoma multiforme. EMBO Mol Med 6(11):1359. https://doi.org/10.15252/emmm.201302627

Carson KA, Grossman SA, Fisher JD, Shaw EG (2007) Prognostic factors for survival in adult patients with recurrent glioma enrolled onto the new approaches to brain tumor therapy CNS consortium phase I and II clinical trials. JCO 25(18):2601. https://doi.org/10.1200/jco.2006.08.1661

Hegi ME, Diserens A, Gorlia T, et al (2005) MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Kirson ED, Schneiderman RS, Dbalý V et al (2009) Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). BMC Med Phys 9(1):1. https://doi.org/10.1186/1756-6649-9-1

Koshy M, Villano JL, Dolecek TA et al (2011) Improved survival time trends for glioblastoma using the SEER 17 population-based registries. J Neurooncol 107(1):207. https://doi.org/10.1007/s11060-011-0738-7

Lassman AB, Joanta-Gomez AE, Pan PC, Wick W (2020) Current usage of tumor treating fields for glioblastoma. Neuro-Oncol Adv. https://doi.org/10.1093/noajnl/vdaa069

Laws ER, Parney IF, Huang W, et al (2003) Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project

Mehta M, Wen P, Nishikawa R, Reardon D, Peters K (2017) Critical review of the addition of tumor treating fields (TTFields) to the existing standard of care for newly diagnosed glioblastoma patients. Crit Rev Oncol Hematol. https://doi.org/10.1016/j.critrevonc.2017.01.005

Nishikawa R, Yamasaki F, Arakawa Y et al (2023) Safety and efficacy of tumour-treating fields (TTFields) therapy for newly diagnosed glioblastoma in Japanese patients using the Novo-TTF System: a prospective post-approval study. Jpn J Clin Oncol 53(5):371. https://doi.org/10.1093/jjco/hyad001

Pandey M, Xiu J, Mittal S et al (2022) Molecular alterations associated with improved outcome in patients with glioblastoma treated with tumor-treating fields. Neuro-Oncol Adv. https://doi.org/10.1093/noajnl/vdac096

Poon MTC, Sudlow CLM, Figueroa JD, Brennan PM (2020) Longer-term (≥ 2 years) survival in patients with glioblastoma in population-based studies pre- and post-2005: a systematic review and meta-analysis. Sci Rep. https://doi.org/10.1038/s41598-020-68011-4

Rong L, Li N, Zhang Z (2022) Emerging therapies for glioblastoma: current state and future directions. J Exp Clin Cancer Res. https://doi.org/10.1186/s13046-022-02349-7

Sales AHA, Beck J, Schnell O, Fung C, Meyer B, Gempt J (2022) Surgical treatment of glioblastoma: state-of-the-art and future trends. JCM. https://doi.org/10.3390/jcm11185354

Sanson M, Marie Y, Paris S et al (2009) Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. JCO 27(25):4150. https://doi.org/10.1200/jco.2009.21.9832

Stupp R, Wong ET, Kanner AA et al (1990) 2012 NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer 48(14):2192–2202. https://doi.org/10.1016/j.ejca.2012.04.011

Stupp R, Mason WP, van den Bent MJ et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352(10):987–996. https://doi.org/10.1056/NEJMoa043330

Stupp R, Taillibert S, Kanner AA et al (2015) Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma. JAMA. https://doi.org/10.1001/jama.2015.16669

Stupp R, Taillibert S, Kanner A et al (2017) Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA: J Am Med Assoc 318(23):2306–2316. https://doi.org/10.1001/jama.2017.18718

Zou P, Xu H, Chen P et al (2013) IDH1/IDH2 mutations define the prognosis and molecular profiles of patients with gliomas: a meta-analysis. PLoS ONE. https://doi.org/10.1371/journal.pone.0068782