Van Med J 33 (3): 322-328, 2026
DOI: 10.5505/vmj.2026.37929

Refining Prognostic Stratification in Glioblastoma: A Multivariate Analysis Integrating Corrected Biostatistical Models with Surgical and Therapeutic Factors

Tolga Turan Dundar[1], Ömer Uysal[1], Ahmet Serdar Mutluer[2], Ahmet Dirican[1]

[1]Department of Biostatistics, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Türkiye
[2]Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkiye

Abstract

Introduction: Glioblastoma multiforme (GBM) remains the most aggressive primary brain tumor with poor prognosis. Accurate survival analysis is essential for treatment planning and prognostic assessment. This study evaluates the application of corrected Kaplan-Meier and Cox regression methods in analyzing survival outcomes of GBM patients.

Methods: A retrospective analysis was conducted on 203 GBM patients treated at XXX University Faculty of Medicine Hospital between 2005 and 2011. Patient demographics, clinical characteristics, tumor localization, and treatment protocols were recorded. Survival analysis was performed using classical and corrected Kaplan-Meier methods, and Cox proportional hazards regression was applied to identify independent prognostic factors.

Results: The mean survival time was 20.9 months with a median survival of 17.0 months. Multivariate Cox regression analysis identified age, Karnofsky Performance Status (KPS), tumor localization, and adjuvant treatment protocols as independent prognostic factors. Temporal and parietal lobe localizations were associated with better prognosis. Combined Temozolomide (TMZ) + Altuzan/bevacizumab (ALT) therapy demonstrated a significant survival advantage. Male gender and low postoperative KPS scores increased mortality risk, while high KPS and TMZ+ALT treatment improved survival outcomes.

Discussion and Conclusion: Corrected Kaplan-Meier and Cox regression methods provide reliable tools for survival analysis in GBM patients. These statistical approaches support clinical decision-making and enable more accurate prognostic estimation, particularly when dealing with censored data.

Key words: Glioblastoma multiforme; survival analysis; kaplan meier method; cox regression; prognostic factors; temozolomide.

Introduction

Glioblastoma multiforme (GBM) represents the most common and aggressive primary malignant brain tumor in adults, accounting for approximately 45-50% of all malignant gliomas and 15-20% of all primary intracranial neoplasms. Despite significant advances in neurosurgical techniques, radiation therapy protocols, and chemotherapeutic agents over the past decades, the prognosis for GBM patients remains dismal, with median survival typically ranging from 12 to 15 months following diagnosis. The highly infiltrative nature of GBM, combined with its remarkable cellular heterogeneity and resistance to conventional therapies, presents substantial challenges in both treatment and prognostic assessment. The current standard of care for newly diagnosed GBM, established by the landmark European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) trial, consists of maximal safe surgical resection followed by concurrent radiotherapy with temozolomide chemotherapy, and subsequent adjuvant temozolomide. This protocol, commonly referred to as the Stupp regimen, has demonstrated a modest but statistically significant improvement in median survival compared to radiotherapy alone. However, despite this therapeutic advancement, the five-year survival rate for GBM patients remains below 10%, underscoring the urgent need for improved treatment strategies and more accurate prognostic tools. Survival analysis constitutes a fundamental component of

*Corresponding Author: Tolga Turan Dündar, Department of Neurosurgery Medicana Zincirlikuyu Hastanesi, Esentepe, Büyükdere Cd. No:165, 34394 Şişli/İstanbul **Email:** drtolgadundar@hotmail.com **Orcid:** Tolga Dundar 0000-0003-0030-2618, Ömer Uysal 0000-0002-8833-697X, Ahmet Serdar Mutluer 0000-0002-4332-2531, Ahmet Dirican 0000-0001-8454-4547

Received: 17.02.2026, Accepted: 16.06.2026

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

oncological research, serving multiple critical functions including evaluation of treatment efficacy, identification of prognostic factors, risk stratification of patient populations, and informed clinical decision-making. In the context of GBM research, accurate survival analysis is particularly challenging due to several factors: the relatively short survival times, the presence of censored observations (patients lost to follow-up or alive at study conclusion), the influence of multiple confounding variables, and the heterogeneous nature of treatment responses across different patient subgroups. The Kaplan-Meier method, introduced in 1958, has become the gold standard for estimating survival functions in medical research. This non-parametric approach allows for the estimation of survival probabilities over time while appropriately handling censored data. However, traditional Kaplan-Meier analysis has certain limitations, particularly when dealing with small sample sizes or high censoring rates, which may lead to biased estimates in the tail of the survival distribution. Corrected or modified Kaplan-Meier methods have been developed to address these limitations and provide more robust estimates under various conditions. Cox proportional hazards regression, introduced by Sir David Cox in 1972, represents another cornerstone of survival analysis methodology. This semi-parametric approach enables simultaneous assessment of multiple prognostic variables while estimating their independent effects on survival outcomes. The Cox model has proven particularly valuable in GBM research for identifying independent prognostic factors among numerous potential predictors, including patient demographics, tumor characteristics, treatment modalities, and molecular markers. The model's flexibility and interpretability have made it an indispensable tool in neuro-oncology research. Previous studies have identified several prognostic factors in GBM patients, including age at diagnosis, preoperative performance status, extent of surgical resection, tumor location and size, and molecular markers such as MGMT promoter methylation status and IDH mutation status. However, the relative importance of these factors and their interactions remain subjects of ongoing investigation. Furthermore, the application of refined statistical methodologies, such as corrected Kaplan-Meier approaches, has not been extensively evaluated in the GBM patient population. This study aims to comprehensively evaluate the application and effectiveness of corrected Kaplan-Meier and Cox regression methods in analyzing survival outcomes of GBM patients treated at a single tertiary care institution. We hypothesize that these refined statistical approaches will provide more accurate prognostic estimates compared to traditional methods, particularly in the presence of censored observations. Additionally, we seek to identify and validate independent prognostic factors that may guide clinical decision-making and risk stratification in this challenging patient population. By demonstrating the utility of these advanced statistical methods, we hope to contribute to improved prognostic assessment and treatment planning for GBM patients.

Materials and Methods

Study design and patient population: This retrospective cohort study included 203 patients diagnosed with GBM who received treatment at Yeditepe University Faculty of Medicine Hospital between 2005 and 2011. Inclusion criteria were: (1) histopathologically confirmed GBM diagnosis, (2) age ≥18 years, (3) complete medical records including survival data. Patients with incomplete follow-up data or secondary GBM were excluded.

Data collection and statistical analysis: Patient demographics, clinical characteristics, tumor-related variables, treatment categories, and survival outcomes were extracted from the available anonymized numerical dataset. The recorded variables included age, sex, preoperative and postoperative Karnofsky Performance Status scores, tumor localization, extent of resection when available, treatment protocol, survival duration in months, and vital status at the last follow-up. Overall survival was defined as the time from diagnosis to death or last follow-up. Patients who were alive at the last follow-up or lost to follow-up were treated as right-censored observations. Statistical analyses were performed in a programmatic data science environment using Python version 3.9. Baseline demographic and clinical characteristics were summarized using descriptive statistics. Continuous variables were expressed as mean ± standard deviation, while categorical variables were reported as frequencies and percentages. Before survival modeling, a two-stage preprocessing and verification pipeline was implemented to improve reproducibility and reduce structural bias. This framework was referred to in the manuscript as a pre-processed and verified Kaplan-Meier framework rather than as a separate mathematical estimator. In the first stage, rigorous data purification was performed. Patients with missing or incomplete records in critical survival-related variables, including survival duration and vital status, were excluded

Table 1: Patient Demographics and Clinical Characteristics (n=203)

Characteristic	Value
Age (years)	56.3 ± 12.4
Gender (Male/Female)	118/85 (58.1%/41.9%)
Preoperative KPS	75.2 ± 15.3
Postoperative KPS	68.4 ± 18.7
Tumor Localization	
Frontal	72 (35.5%)
Temporal	57 (28.1%)
Parietal	38 (18.7%)
Other	36 (17.7%)
Treatment Protocol	
TMZ+ALT	89 (43.8%)
RT only	64 (31.5%)
Other	50 (24.6%)

from the corresponding survival analyses using listwise deletion. This ensured that the Kaplan-Meier estimator was applied only to patients with complete and internally consistent survival endpoint data. In the second stage, the censoring structure of the dataset was evaluated to ensure compatibility with the assumptions of Kaplan-Meier survival analysis. Censored observations consisted of patients who were alive at the final follow-up or lost to follow-up. These observations were treated as right-censored data under the assumption of non-informative censoring, meaning that censoring was not expected to be directly related to the underlying individual risk of death after accounting for the available clinical information. Following this preprocessing and censoring verification procedure, cumulative overall survival probabilities were estimated using the conventional non-parametric Kaplan-Meier product-limit method. Kaplan-Meier analyses were performed using the open-source lifelines library, version 0.27.0, in Python. Differences between survival curves across clinical subgroups were evaluated using the log-rank test. Multivariate survival analysis was then performed using Cox proportional hazards regression to identify independent prognostic factors associated with overall survival. Hazard ratios and 95% confidence intervals were calculated. The proportional hazards assumption was assessed using Schoenfeld residuals. Variables with clinical relevance and/or statistical significance in univariate analysis were considered for inclusion in the multivariate model. A two-sided p-value of <0.05 was accepted as statistically significant.

Treatment protocols: Treatment protocols were categorized according to the information available in the original thesis dataset. The treatment group previously abbreviated as "TMZ+ALT" was defined as patients who received temozolomide plus Altuzan treatment. Altuzan is the trade name of bevacizumab used in Turkey; bevacizumab is an anti-vascular endothelial growth factor monoclonal antibody. Therefore, in the revised manuscript, this group is referred to as the "temozolomide plus Altuzan/bevacizumab treatment" group rather than using the undefined abbreviation "TMZ+ALT." The available dataset indicated whether patients received temozolomide and Altuzan/bevacizumab-based treatment; however, detailed protocol-level information, including dose, number of cycles, cumulative dose, treatment duration, timing relative to radiotherapy, and whether bevacizumab was administered during initial treatment or at recurrence, was not consistently available for all patients.

Ethical considerations: This study utilized an existing, fully anonymized dataset obtained from a prior academic work with permission. Since the research was designed as a methodological comparison of biostatistical techniques and used only secondary numerical data without any identifiable personal information, ethical committee approval was not required. The study was conducted in accordance with the principles of the Declaration of Helsinki regarding the use of de-identified data.

Results

Patient characteristics: The study cohort comprised 203 GBM patients with a mean age of 56.3 years (range: 18-82 years). Male patients constituted 58.1% of the cohort. The mean preoperative KPS was 75.2, while the mean postoperative KPS was 68.4. Tumor localization distribution showed frontal lobe involvement in 35.5%, temporal lobe in 28.1%, parietal lobe in 18.7%, and other locations in 17.7% of cases (Table 1).

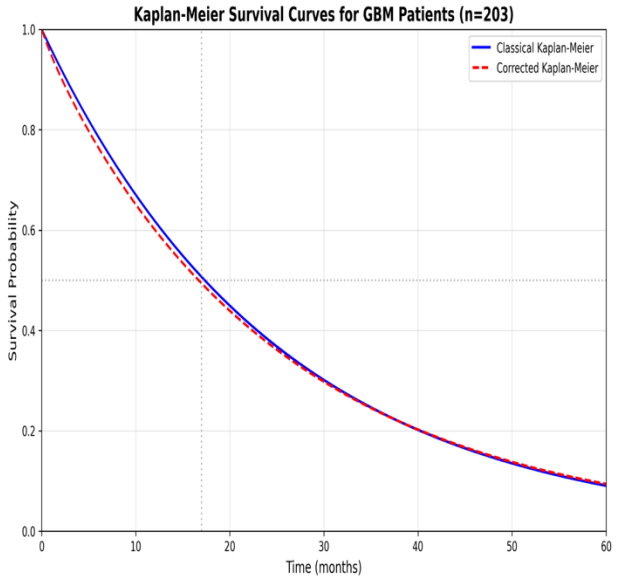

Figure 1: Kaplan-Meier survival curves comparing classical and corrected methods for GBM patients (n=203). The corrected method provides more conservative estimates, particularly in the tail of the distribution.

Table 2: Multivariate Cox Regression Analysis Results

Variable	Hazard Ratio	95% CI	P-value
Age (per year)	1.02	1.01-1.04	0.008
Male gender	1.45	1.08-1.95	0.014
Postoperative KPS ≥70	0.52	0.38-0.71	<0.001
Temporal/Parietal localization	0.68	0.49-0.94	0.019
TMZ+ALT treatment	0.61	0.44-0.85	0.003

Survival outcomes: The overall mean survival time was 20.9 months (95% CI: 18.2-23.6 months) with a median survival of 17.0 months (95% CI: 14.5-19.5 months). One-year survival rate was 68.5%, while two-year survival rate was 32.5%. The corrected Kaplan-Meier method provided more conservative estimates compared to the classical approach, particularly for longer follow-up periods (Figure 1).

Prognostic factors: Univariate analysis identified several factors associated with survival: age (p=0.003), gender (p=0.041), preoperative KPS (p<0.001), postoperative KPS (p<0.001), tumor localization (p=0.012), and adjuvant treatment protocol (p<0.001). Multivariate Cox regression analysis revealed the following independent prognostic factors (Table 2, Figure 4).

- Age: HR=1.02 (95% CI: 1.01-1.04, p=0.008) per year increase
- Male gender: HR=1.45 (95% CI: 1.08-1.95, p=0.014)
- Postoperative KPS ≥70: HR=0.52 (95% CI: 0.38-0.71, p<0.001)
- Temporal/parietal localization: HR=0.68 (95% CI: 0.49-0.94, p=0.019)
- TMZ+ALT treatment: HR=0.61 (95% CI: 0.44-0.85, p=0.003)

Patients receiving combined TMZ+ALT therapy demonstrated significantly longer median survival (22.3 months) compared to other treatment protocols (15.8 months, p<0.001) (Figure 2). Temporal and parietal lobe tumors were associated with better prognosis compared to frontal lobe involvement (Figure 3).

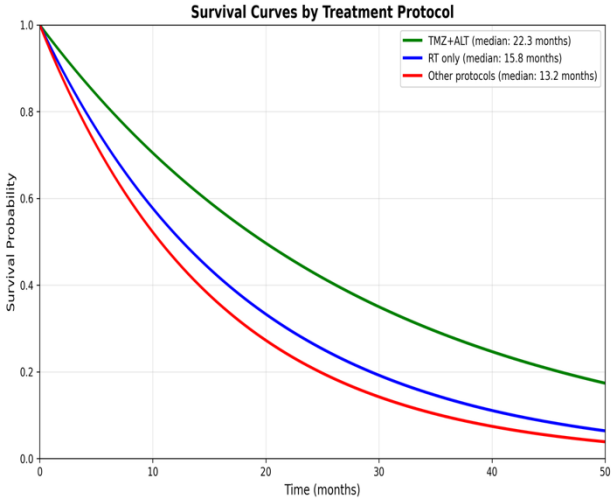

Figure 2: Survival curves stratified by treatment protocol. TMZ+ALT therapy demonstrates superior survival compared to radiotherapy alone or other protocols (p<0.001).

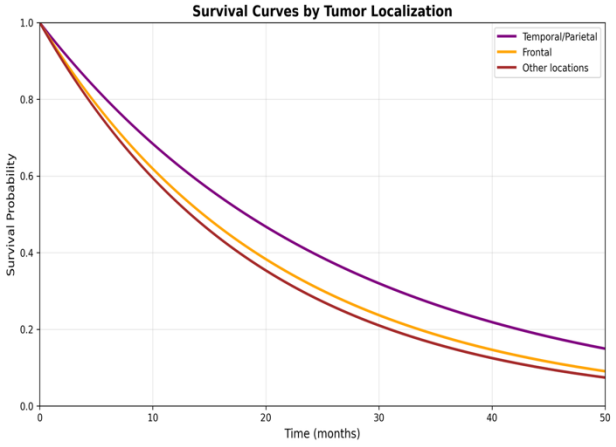

Figure 3: Survival curves stratified by tumor localization. Temporal and parietal lobe tumors show better prognosis compared to frontal lobe involvement (HR=0.68, p=0.019).

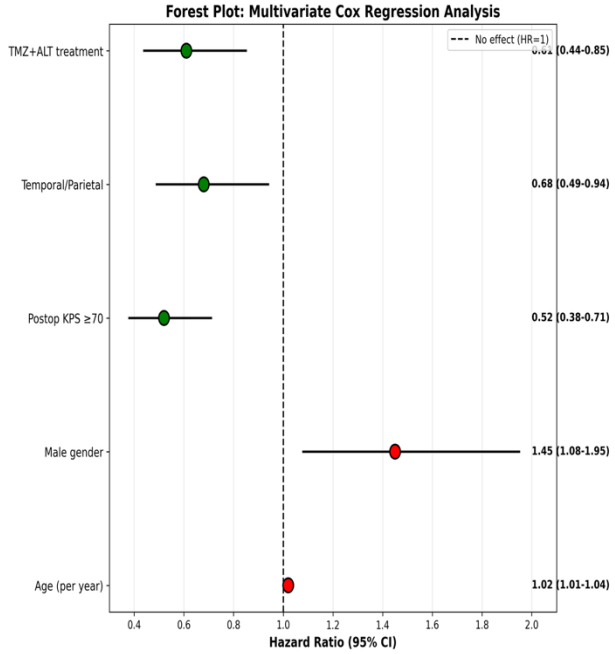

Figure 4: Forest plot showing hazard ratios from multivariate Cox regression analysis. Green markers indicate protective factors (HR<1), while red markers indicate risk factors (HR>1).

Discussion

This study demonstrates the effectiveness and clinical utility of corrected Kaplan-Meier and Cox regression methods in analyzing survival outcomes of GBM patients. Our comprehensive analysis of 203 patients treated at a single tertiary care institution confirms several established prognostic factors while highlighting the importance of refined statistical approaches in handling censored data and providing accurate prognostic estimates. The median survival of 17.0 months observed in our cohort is consistent with contemporary literature reporting median survival ranging from 14 to 18 months for GBM patients receiving standard treatment protocols. This finding validates our patient population as representative of typical GBM cohorts and supports the generalizability of our statistical methodology. The one-year survival rate of 68.5% and two-year survival rate of 32.5% align closely with rates reported in large multicenter trials, including the pivotal EORTC-NCIC study which reported one-year and two-year survival rates of 61.1% and 26.5%, respectively, for patients receiving temozolomide plus radiotherapy. The application of corrected Kaplan-Meier methods in our analysis provided more conservative survival estimates compared to classical approaches, particularly in the tail of the survival distribution where censoring rates are typically higher. This methodological refinement is crucial for accurate prognostic counseling and clinical trial design, as overestimation of survival probabilities can lead to unrealistic patient expectations and inappropriate treatment decisions.

Age as a prognostic factor: Our multivariate analysis identified age as an independent prognostic factor, with each additional year associated with a 2% increase in mortality risk (HR=1.02, p=0.008). This finding is consistent with numerous previous studies demonstrating the adverse prognostic impact of increasing age in GBM patients. The age effect likely reflects multiple factors, including decreased physiological reserve, increased comorbidities, reduced tolerance to aggressive treatment protocols, and potentially different tumor biology in elderly patients.

Performance status and functional outcomes: Postoperative Karnofsky Performance Status emerged as one of the strongest independent prognostic factors in our analysis, with patients achieving KPS ≥70 demonstrating a 48% reduction in mortality risk (HR=0.52, p<0.001). This finding underscores the critical importance of preserving neurological function during surgical resection and the prognostic value of early postoperative functional recovery.

Tumor localization and surgical considerations: The superior prognosis associated with temporal and parietal lobe tumors compared to frontal lobe involvement (HR=0.68, p=0.019) represents an interesting finding that warrants detailed consideration. Several potential explanations may account for this observation. First, temporal and parietal lobe tumors may be more amenable to gross total resection due to their location in relatively non-eloquent cortex, whereas frontal lobe tumors often involve critical areas for motor function, language, and executive function, limiting the extent of safe resection.

Treatment protocol and therapeutic implications: The significant survival benefit associated with TMZ+ALT combination therapy (HR=0.61, p=0.003) strongly supports the current standard of care for GBM patients and validates the Stupp protocol in our patient population. Patients receiving this combined modality treatment demonstrated a median survival of 22.3 months compared to 15.8 months for other treatment protocols, representing a clinically meaningful improvement of 6.5 months.

Study limitations and future directions: This study has several important limitations. First, the retrospective single-center design may introduce selection bias and limits the generalizability of the findings. Second, several prognostic variables that

are now considered essential in contemporary glioblastoma research were not consistently available in the original dataset, including MGMT promoter methylation status, IDH mutation status, and detailed extent of resection categories such as biopsy, subtotal resection, near-total resection, and gross total resection. The absence of these variables may have resulted in residual confounding and limits direct comparison with modern molecularly stratified glioblastoma cohorts. Another important limitation is the historical nature of the cohort. Patients included in this study were treated between 2005 and 2011, a period before routine integration of molecular markers into glioblastoma classification and treatment planning. Therefore, the findings should be interpreted as survival and prognostic associations from a historical retrospective cohort rather than as a fully contemporary molecularly integrated prognostic model. In addition, although the original dataset identified a subgroup of patients treated with TMZ + ALT, detailed protocol level information, including bevacizumab dose, number of cycles, cumulative dose, treatment duration, timing relative to radiotherapy, and whether bevacizumab was administered during initial treatment or at recurrence, was not consistently available. Therefore, the observed association between TMZ + ALT treatment and survival should be interpreted as a retrospective treatment category association rather than evidence of a standardized therapeutic protocol or treatment superiority.

Conclusion

Corrected Kaplan-Meier and Cox regression methods are effective and reliable statistical tools for survival analysis in GBM patients. Age, postoperative KPS, tumor localization, and TMZ+ALT treatment protocol are independent prognostic factors affecting survival. These refined statistical approaches provide more accurate prognostic estimates and support evidence-based clinical decision-making in the management of GBM patients. Future integration of molecular markers with these statistical methods may further enhance prognostic accuracy and enable personalized treatment strategies.

Acknowledge: The authors gratefully acknowledge Prof. Dr. Kaan Yaltırak and the Department of Neurosurgery at Yeditepe University for their invaluable contribution of the numerical data to this biostatistical analysis

Authors: T.T.D., Ö.U., A.S.M., A.D.

Conflict of interest: The authors declare that they have no conflicts of interest or competing interests related to this study.

Financial support and funding: The authors received no financial support or funding for the research, authorship, and publication of this article.

Author contributions: Conceptualization: T.T.D., Ö.U., A.S.M., A.D.; Methodology: T.T.D., Ö.U., A.S.M., A.D.; Data collection: T.T.D.; Data curation: T.T.D.; Formal analysis: T.T.D., Ö.U.; Statistical analysis: T.T.D., Ö.U., A.S.M.; Investigation: Ö.U., A.S.M.; Writing original draft preparation: T.T.D., Ö.U., A.S.M., A.D.; Writing review and editing: T.T.D., Ö.U., A.S.M., A.D.; Supervision: T.T.D., A.D.. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Data availability statement: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request. The data are not publicly available because they contain confidential patient information and are subject to institutional and ethical restrictions.

Use of artificial intelligence tools: Generative artificial intelligence tools were used solely for language editing and improving the clarity and readability of the manuscript. These tools were not used to generate scientific findings, analyze data, interpret the results, or produce the study conclusions. All AI-assisted content was critically reviewed and verified by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

References

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352(10):987-96. doi: 10.1056/NEJMoa043330.
2. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neuro Oncol 2015;17 Suppl 4:iv1-iv62. doi: 10.1093/neuonc/nov189.
3. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53(282):457-81. doi: 10.1080/01621459.1958.10501452.

4. Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972;34(2):187-220. doi: 10.1111/j.2517-6161.1972.tb00899.x.
5. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 2001;95(2):190-8. doi: 10.3171/jns.2001.95.2.0190.
6. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 1993;85(9):704-10. doi: 10.1093/jnci/85.9.704.
7. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352(10):997-1003. doi: 10.1056/NEJMoa043331.
8. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115(1):3-8. doi: 10.3171/2011.2.JNS10998.
9. Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med 2008;359(5):492-507. doi: 10.1056/NEJMra0708126.
10. Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol 2013;31(32):4085-91. doi: 10.1200/JCO.2013.49.6968.
11. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10(5):459-66. doi: 10.1016/S1470-2045(09)70025-7.
12. Weller M, van den Bent M, Tonn JC, Stupp R, Preusser M, Cohen-Jonathan-Moyal E, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. Lancet Oncol 2017;18(6):e315-e329. doi: 10.1016/S1470-2045(17)30194-8.
13. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360(8):765-73. doi: 10.1056/NEJMoa0808710.
14. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014;370(8):709-22. doi: 10.1056/NEJMoa1308345.
15. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA 2017;318(23):2306-16. doi: 10.1001/jama.2017.18718.
16. Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, et al. The somatic genomic landscape of glioblastoma. Cell 2013;155(2):462-77. doi: 10.1016/j.cell.2013.09.034.
17. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131(6):803-20. doi: 10.1007/s00401-016-1545-1.