AbdelFatah *et al.*
Egyptian Journal of Neurosurgery (2022) 37:3
https://doi.org/10.1186/s41984-022-00145-1

Egyptian Journal of Neurosurgery

REVIEW

Open Access

Impact of extent of resection of newly diagnosed glioblastomas on survival: a meta-analysis

Mohamed A. R. AbdelFatah[1*], Ali Kotb[1], Mohamed Ahmed Said[2] and Emad M. H. Abouelmaaty[1]

Abstract

Background: Because of the continuing practice variation regarding the extent of glioblastoma (GBM) resection, we sought to systematically examine the recent literature to evaluate the impact of the extent of resection of primary GBM on patients' survival.

Main body of the abstract: We examined all the published studies from January 2009 to January 2020 concerning primary glioblastoma resection and survival. The data synthesis was performed using the random-effects model in Review Manager (version 5.3; Cochrane Collaboration). Eight studies met our selection criteria. The included studies involved a total of 2249 patients. A total of **1247** patients underwent gross total resection (GTR) of the GBM, and **1002** experienced an incomplete resection. The mean progression-free survival for GTR versus incomplete resection was 10 versus 6.3 months, and the mean overall survival (GTR vs. incomplete resection) was 28.7 versus 13.5 months. Using the random-effects model, the outcome results revealed that GTR was insignificantly different than incomplete resection on survival among the included cases (*P* value: 0.47). The quality of evidence of the available studies was of low certainty.

Conclusion: The outcome results revealed that gross total resection was insignificantly different than incomplete resection on survival among the included cases (*P* value: 0.47). However, the quality of evidence of the available studies was of low certainty. Additionally, no data on patients' quality of life were reported across the included studies. Thus, prospective randomized controlled trials are required to investigate both the safety and the survival benefit of GTR of glioblastoma.

Keywords: Glioblastoma, Extent of resection, Survival, Gross total resection

Background

Glioblastoma (GBM) constitutes the most common primary malignant brain tumor in adults and continues to represent a great challenge for neurosurgeons [1].

The recent WHO Classification of Tumors of the central nervous system (CNS) diagnosed glioblastoma in the setting of an IDH-wildtype diffuse and astrocytic glioma in adults with microvascular proliferation or necrosis or TERT promoter mutation or EGFR gene amplification or +7/−10 chromosome copy number changes [2].

The clinical presentation of a patient with a newly diagnosed primary GBM is dependent on the size, location, and degree of infiltration of the tumor [3].

The current first-line treatment for newly diagnosed GBM is composed of maximal safe tumor resection, followed by combined radiotherapy and adjuvant temozolomide [4].

Moreover, it is thoroughly recognized that GBM is a diffusely infiltrating neoplasm that typically invades multiple lobes of the brain on diagnosis [5].

*Correspondence: mohamed_abdelrahman@med.asu.edu.eg
[1] Neurosurgery Department, Faculty of Medicine, Ain Shams University, Villa 204, Mohamed AlNasharty Street, area F, South of Police Academy, Fifth District, New Cairo 11835, Egypt
Full list of author information is available at the end of the article

There is no consensus on the definition of gross total resection of GBM, hence the widespread practice variation among neurosurgeons. In addition, the overall survival of patients with GBM varies significantly and there are long survivors in spite of incomplete resection [6].

Because of this continuing practice variation regarding the extent of GBM resection, we sought to systematically examine the recent literature to evaluate the impact of the extent of resection of primary GBM on patients' survival.

Main text

Methods

The present study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7].

Information sources and search strategy

The following electronic databases were searched on 1 February 2020: PubMed, Google Scholar, MEDLINE, Embase, and science Direct, using the keywords as glioblastoma; malignant glioma; survival; surgical outcome; prognosis; extent of resection; tumor excision; Debulking; GBM; malignant glioma; microsurgery.

Eligibility criteria

Types of studies All published studies from January 2009 to January 2020 concerning GBM resection and survival including randomized controlled studies, cohort studies, and case series.

Types of participants Adult patients with histopathologically confirmed GBM.

Types of interventions Surgical excision of newly diagnosed GBM.

Types of outcome measures Survival rate after GBM resection.

Exclusion criteria

Systematic reviews, technical notes, letters, and comments.

Studies not written in English.

Studies that selectively examined GBM in a non-eloquent area.

Studies discussing Recurrent or multiple GBM.

Studies that included other brain tumors.

Study selection

After removing duplicate records, all titles and abstracts were screened by two authors (MA and MS). The full texts of the studies that passed the initial screening underwent full eligibility assessment against the inclusion and exclusion criteria. Any uncertainties were resolved through discussion between the study team.

Data extraction

Studies that met the inclusion criteria were reviewed, and data were analysed. We assessed the participants, methods, and intervention effects of the included studies for heterogeneity. This enabled us to determine whether results can be pooled across studies.

Data items

We collected data on study characteristics including first author name, year of publication, study design, number of patients, median age, gender, and survival rates.

Evidence of publication bias

Publication bias was assessed with funnel plots.

Statistical considerations

The data synthesis was performed using the random-effects model in Review Manager (version 5.3; Cochrane Collaboration). Significance was established using CIs at the level of 95% or P value < 0.05.

We evaluated the overall body of evidence utilizing the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system. The GRADE rating scale assigns high, moderate, low, or very low-reliability categories to a body of evidence [8].

Results

Study selection

The flow diagram of the study selection processes is shown in Fig. 1.

The initial search from the electronic databases yielded 831 studies. By properly reading the titles and the abstracts, seven hundred and fifty-five reports were excluded as duplicates or for investigating irrelevant topics.

A total of 76 studies was retrieved for full-text evaluation, from which 68 were further excluded as they did not meet our selection criteria. There were no other eligible studies from the manual search of the reference lists of these studies. In the end, eight studies met our criteria and were selected for the final systematic review and meta-analysis.

Study characteristics

The year of publication and the type of the included studies are demonstrated in Table 1. Eight studies were included; five were retrospective and three were prospective studies [9–16].

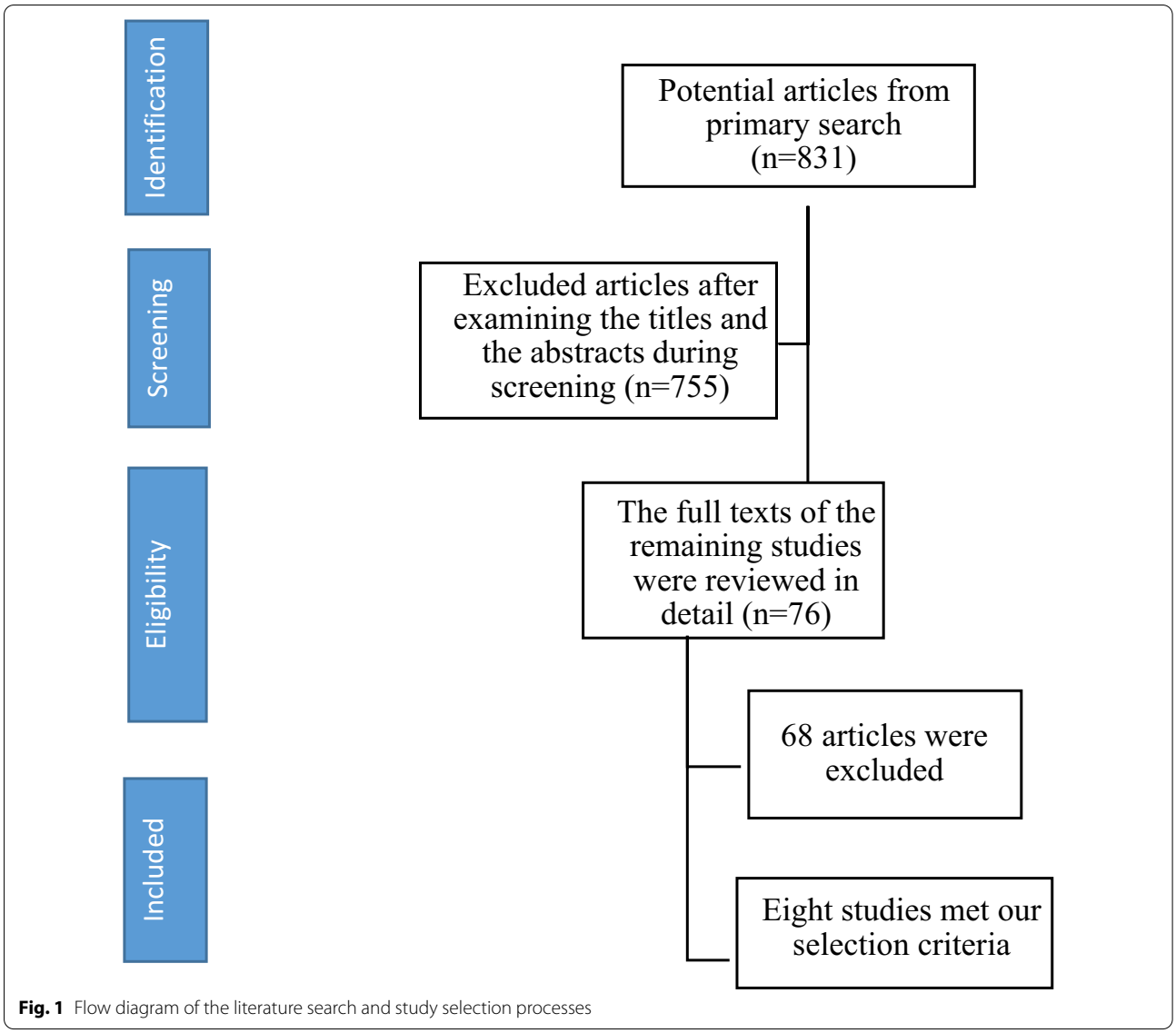

Fig. 1 Flow diagram of the literature search and study selection processes

Table 1 Types of the included studies:

No.	Studies	Year of publication	Type of the study
1	Byun et al. [9]	2019	Retrospective
2	Esquenazi et al. [10]	2017	Retrospective
3	Pessina et al. [11]	2017	Retrospective
4	Hamada and Abou-Zeid [12]	2016	Prospective
5	Li et al. [13]	2016	Retrospective
6	Kreth et al. [14]	2013	Prospective
7	Ewelt et al. [15]	2011	Retrospective
8	Allahdini et al. [16]	2010	Prospective

Patients' characteristics of the included studies

As shown in Table 2, a total of **2249** cases was included with a mean age of 56.6 years. **1388** patients were males.

Tumor characteristics

The tumor locations mentioned in the included studies in descending order were Frontal, Parietal, Temporal, Occipital, Insular, and thalamic.

For all the included cases, the mean preoperative tumor volume was 41.8 cm^3 and the mean postoperative tumor volume was 22.15cm^3.

Table 2 Patients characteristics:

No.	Studies	Year of publication	Number of patients	Mean age	Males
1	Byun et al. [9]	2019	110	57	68
2	Esquenazi et al. [10]	2017	86	56	57
3	Pessina et al. [11]	2017	282	61	177
4	Hamada and Abou-Zeid [12]	2016	59	48.57	43
5	Li et al. [13]	2016	1229	55.7	758
6	Kreth et al. [14]	2013	345	61	209
7	Ewelt et al. [15]	2011	103	65	52
8	Allahdini et al. [16]	2010	35	49.3	24

Table 3 Extent of resection

No.	Studies	Year of publication	Gross total resection (%)	Incomplete resection (%)
1	Byun et al. [9]	2019	29.09	70.91
2	Esquenazi et al. [10]	2017	29.06	70.94
3	Pessina et al. [11]	2017	18.79	81.21
4	Hamada et al. [12]	2016	67.79	32.21
5	Li et al. [13]	2016	71.27	28.73
6	Kreth et al. [14]	2013	45.79	54.21
7	Ewelt et al. [15]	2011	45.10	54.90
8	Allahdini et al. [16]	2010	48.57	51.43

Surgical characteristics

The extent of resection in each study is demonstrated in Table 3. Altogether, 55.44% (1247 patients) of all the included cases underwent gross total resection, while 44.55% sustained incomplete resection.

Outcome measures

Altogether, the mean progression-free survival (PFS) for GTR versus incomplete resection was 10 versus 6.3 months, and the mean overall survival (OAS) for GTR versus incomplete resection was 28.7 versus 13.5 months.

Studies heterogeneity

There is significant heterogeneity among the included studies (I^2 99%) which is a consequence of clinical and methodological diversity among the studies. Subgroup analysis indicated that the number of cases in each study, the publication year, the Country of the study, and the study quality might affect the therapeutic effects of the extent of resection on survival. In addition, meta-regression was not considered due to the limited number of the included studies and the small number of patients in each study.

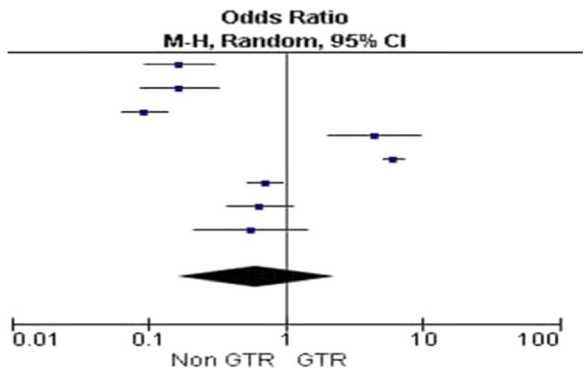

Fig. 2 Forest plot for gross total resection (GTR)

Publication bias

The Forest plot for the included studies is revealed in Fig. 2 and Table 4.

A funnel plot was constructed and compared GTR to incomplete resection in the included studies and is shown in Fig. 3.

Using the random-effects model, the outcome results revealed that GTR was insignificantly different than incomplete resection in survival among the included cases (*P* value: 0.47). The quality of evidence of the present studies was of low certainty.

Discussion

The overall survival of patients with GBM varies significantly, and there are long survivors with incomplete resection [6]. So, we sought to systematically examine the literature to detect the impact of the extent of resection of primary GBM on survival.

Eight studies met our selection criteria with a total of **2249** patients. Gross total tumor resection was applied for 1247 patients (55.44%), and **1002** patients underwent

Table 4 Forest plot for gross total resection

Studies	Total cases in each study	Gross total resection	Incomplete resection	Weight (%)	Odds ratio random effects, 95%CI
Byun et al. [9]	110	32	78	12.5	0.17 [0.09, 0.30]
Esquenazi et al. [10]	86	25	61	12.4	0.17 [0.09, 0.32]
Pessina et al. [11]	282	53	229	12.7	0.09 [0.06, 0.14]
Hamada and Abou-Zeid [12]	59	40	19	12.3	4.43 [2.05, 9.59]
Li et al. [13]	1229	876	353	12.8	6.16 [5.17, 7.33]
Kreth et al. [14]	345	158	187	12.7	0.71 [0.53, 0.96]
Ewelt et al. [15]	103	46	57	12.5	0.65 [0.38, 1.13]
Allahdini et al. [16]	35	17	18	12.1	0.56 [0.22, 1.45]
Total (95% CI)	2249 cases			100	0.61 [0.16, 2.32]

CI confidence interval

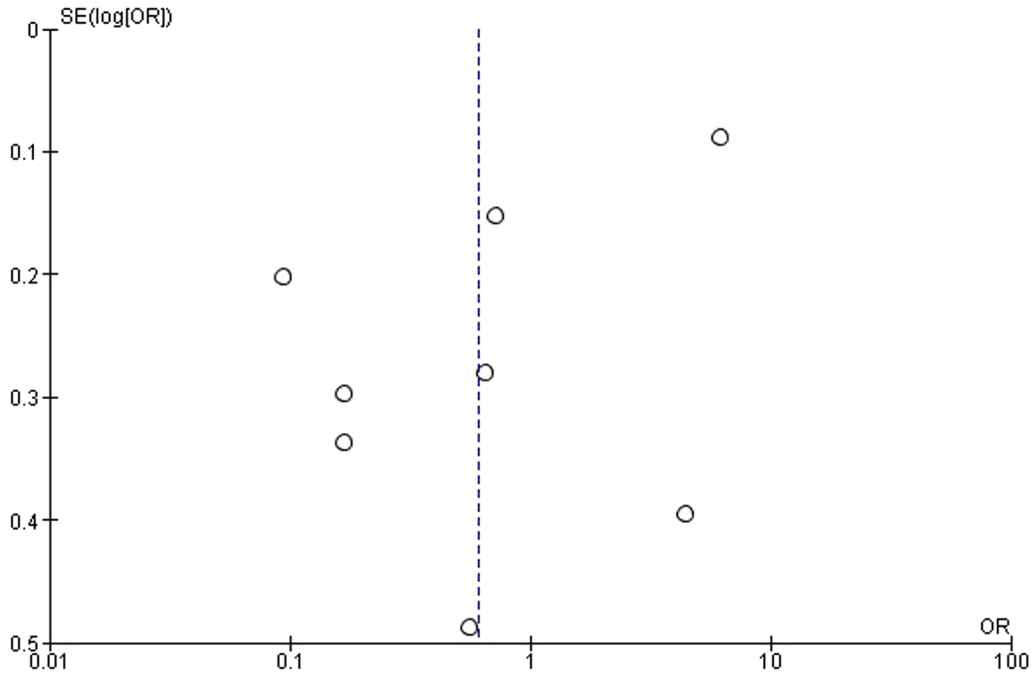

Fig. 3 Funnel plot for gross total resection (GTR)

incomplete resection. Mean PFS (GTR vs. incomplete resection) was 10 months versus 6.3 months and mean OAS (GTR vs. incomplete resection) was 28.7 versus 13.5 months.

Using the random-effects model, the outcome results revealed that GTR was insignificantly different than incomplete resection in survival among the included cases (*P* value: 0.47). However, the quality of evidence of the available studies was of low certainty. Therefore, it remains unclear whether GTR of glioblastoma actually improves survival than incomplete resection.

GBM location near the eloquent areas is critical in clinical decision-making; hence, it remains a crucial prognostic factor. However, no clear comparison with GBMs located in the eloquent areas is available. GBMs located in the non-eloquent areas such as the frontal or temporal poles could possibly undergo safe GTR [17].

GTR should not be attempted at any cost. The aim of GBM surgery should be to maximize the extent of resection without causing new neurological deficits and maintaining a good quality of life for patients.

Li et al. [13] performed the first study that presented the effect of T2 fluid-attenuated inversion recovery (FLAIR) resection of GBM to improve the survival of patients.

There is no consensus on the definition of gross total resection of GBM. Gross total resection can be defined as the removal of all the tumor, as detected by magnetic resonance imaging whether on T2WI or FLAIR [18].

Extending the tumor resection could be considered by performing awake craniotomies with additional imaging adjuncts like the intraoperative MRI, ultrasound, and 5-ALA guidance [19].

However, despite these intraoperative technologies that allow real-time visualization of tumor borders, a clear differentiation between the normal brain and the residual tumor continues to be a major challenge. Hopefully, by combining multiple technologies, we may achieve a safe and nearly total tumor resection [20].

We found in our review that the incidence of the postoperative new neurological deficit was deficient in most of the included studies and was reported only descriptively, without the use of validated tests and quantitative outcome measures. Additionally, no data on patients' quality of life were reported across the included studies. The safety of the GTR, therefore, could not be confirmed.

Overall, the results of our analysis should be interpreted with caution because of several limitations. *First*, the heterogeneity across the analyzed studies, which possibly arose from several factors, like the differences in defining GTR and the non-randomized treatment assignment. The definitions of GTR across the studies varied from additional resection of fluorescing tumor tissue to total resection of T2-weighted or FLAIR hyperintensity. The lack of a consensus in defining GTR made it challenging to draw clear conclusions that would benefit the clinical practice of neurosurgeons. *Second*, because the safety of resecting T2 weighted or FLAIR hyperintense regions remains unclear, GTR was likely performed for a selected group of patients and not for tumors located in eloquent brain areas. *Third*, the exact characteristics of tumor grade, molecular status, and the exact tumor location were not available in most studies, restricting further stratified analyses. *Forth*, the adjusted factors differed across the included studies, and such factors might perform a critical role in the prognosis of GBM. These prognostic factors include age, Karnofsky Performance Status Scale (KPS) score, tumor volume, and tumor location. With consideration of these limitations, we employed a random-effects model to provide an interpretation of the treatment effect of GTR.

Future directions

Prospective randomized controlled trials are required to investigate both the safety and the survival benefit of GTR of GBM. These trials should clearly standardize the definition of GTR. Such a standardized definition of GTR would be expected to improve comparability between studies and improve the quality of evidence of the new-coming studies.

Ultimately, validated measures for postoperative neurological outcomes and quality of life assessments should be used to study the benefit of GTR of glioblastoma on patients' survival and safety.

Conclusions

The outcome results revealed that GTR was insignificantly different than incomplete resection in survival among the included cases. The quality of evidence of the available studies was of low certainty. Additionally, no data on patients' quality of life were reported across the included studies. Therefore, it remains unclear whether GTR is safe and actually improves the survival of patients with GBM. Prospective randomized controlled trials are required to investigate both the safety and the survival benefit of GTR of glioblastoma.

Abbreviations

5-ALA: 5-Aminolevulinic acid; CI: Confidence interval; CNS: Central nervous system; EGFR: Epidermal growth factor receptor; EOR: Extent of resection; FLAIR: Fluid-attenuated inversion recovery; GBM: Glioblastoma; GRADE: Grading of recommendations, assessment, development and evaluations; GTR : Gross total resection; IDH: Isocitrate dehydrogenase; KPS: Karnofsky performance status scale; MRI: Magnetic resonance imaging; n: Number of studies; OAS: Mean overall survival; PFS: Progression-free survival; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; TERT: Telomerase reverse transcriptase; WHO: World Health Organization.

Acknowledgements

Not applicable.

Authors' contributions

MA and MS performed the search. MA and MS analyzed and interpreted the patients' data in each study. MA and MS wrote the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable (No funding was received for this research).

Availability of data and material

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee, Faculty of Medicine, Ain Shams University (FWA 000017585).

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Neurosurgery Department, Faculty of Medicine, Ain Shams University, Villa 204, Mohamed AlNasharty Street, area F, South of Police Academy, Fifth District, New Cairo 11835, Egypt. [2]Neurosurgery Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

Received: 17 November 2021 Accepted: 10 January 2022
Published online: 01 February 2022

References

1. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee ShU. Glioblastoma multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment. Asian Pac J Cancer Prev. 2017;18:3–9.
2. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23(8):1231–51.
3. Davis ME. Glioblastoma: overview of disease and treatment. Clin J Oncol Nurs. 2016;20(5 Suppl):S2–8.
4. 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;352:987–96.
5. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. JAMA Oncol. 2016;2(11):1460–9.
6. Çoban G, Mohan S, Kural F, Wang S, O'Rourke DM, Poptani H. Prognostic value of dynamic susceptibility contrast-enhanced and diffusion-weighted MR imaging in patients with glioblastomas. AJNR Am J Neuroradiol. 2015;36(7):1247–52.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
8. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
9. Byun J, Kim YH, Nam SJ, Park JE, Cho YH, Kim HS, et al. Comparison of survival outcomes between partial resection and biopsy for primary glioblastoma: a propensity score-matched study. World Neurosurg. 2019;121:e858–66.
10. Esquenazi Y, Friedman E, Liu Z, Zhu JJ, Hsu S, Tandon N. The survival advantage of "Supratotal" resection of glioblastoma using selective cortical mapping and the subpial technique. Neurosurgery. 2017;81(2):275–88.
11. Pessina F, Navarria P, Cozzi L, Ascolese AM, Simonelli M, Santoro A, et al. Maximize surgical resection beyond contrast-enhancing boundaries in newly diagnosed glioblastoma multiforme: is it useful and safe? A single institution retrospective experience. J Neurooncol. 2017;135(1):129–39.
12. Hamada SM, Abou-Zeid AH. Anatomical resection in glioblastoma: extent of resection and its impact on duration of survival. Egypt J Neurol Psychiatry Neurosurg. 2016;53(3):135–45.
13. Li YM, Suki D, Hess K, Sawaya R. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: can we do better than gross-total resection? J Neurosurg. 2016;124(4):977–88.
14. Kreth FW, Thon N, Simon M, Westphal M, Schackert G, Nikkhah G, et al. Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. Ann Oncol. 2013;24(12):3117–23.
15. Ewelt C, Goeppert M, Rapp M, Steiger HJ, Stummer W, Sabel M. Glioblastoma multiforme of the elderly: the prognostic effect of resection on survival. J Neurooncol. 2011;103(3):611–8.
16. Allahdini F, Amirjamshidi A, Reza-Zarei M, Abdollahi M. Evaluating the prognostic factors effective on the outcome of patients with glioblastoma multiformis: does maximal resection of the tumor lengthen the median survival? World Neurosurg. 2010;73(2):128–34.
17. Roh TH, Kang SG, Moon JH, Sung KS, Park HH, Kim SH, et al. Survival benefit of lobectomy over gross-total resection without lobectomy in cases of glioblastoma in the noneloquent area: a retrospective study. J Neurosurg. 2019;132(3):895–901.
18. 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.
19. Moliterno JA, Patel TR, Piepmeier JM. Neurosurgical approach. Cancer J. 2012;18(1):20–5.
20. Kuhnt D, Becker A, Ganslandt O, Bauer M, Buchfelder M, Nimsky C. Correlation of the extent of tumor volume resection and patient survival in surgery of glioblastoma multiforme with high-field intraoperative MRI guidance. Neuro Oncol. 2011;13(12):1339–48.

Publisher's Note