Chaulagain *et al.*
Egyptian Journal of Neurosurgery (2022) 37:19
https://doi.org/10.1186/s41984-022-00161-1

Egyptian Journal of Neurosurgery

REVIEW Open Access

The role of extent of resection on the prognosis of low-grade astrocytoma: a systematic review and meta-analysis

Dipak Chaulagain[1*], Volodymyr Smolanka[1], Andriy Smolanka[1], Sunil Munakomi[2] and Taras Havryliv[1]

Abstract

Purpose: To investigate the predictor factors of mortality describing the prognosis of primary surgical resection of low-grade astrocytoma.

Materials and methods: A systemic search was conducted from electronic databases (PubMed/Medline, Cochrane Library, and Google Scholar) from inception to November 14, 2021. All statistical analysis was conducted in Review Manager 5.4.1. Studies meeting inclusion criteria were selected. A random-effect model was used when heterogeneity was seen to pool the studies, and the result were reported in the hazards ratio (HR) and corresponding 95% confidence interval.

Result: Five cohort studies were selected for meta-analysis. There was statistically significant effect of total resection on increase mortality after surgery in low-grade astrocytoma patients (HR = 0.70 [0.52, 0.94]; $p = 0.02$; I^2 = Not applicable). On the other hand, there was statistically nonsignificant effect of patient's age (HR = 1.27 [0.95, 1.68]; $p = 0.11$; $I^2 = 83\%$), tumor size (HR = 1.13 [0.94, 1.35]; $p = 0.19$; $I^2 = 73\%$), and increasing KPS (HR = 0.59 [0.20, 1.77]; $p = 0.35$; $I^2 = 86\%$) on prognosis of low-grade astrocytoma after surgery.

Conclusion: The results of meta-analysis showed significant relationship of extent of resection and mortality, while factors such age, KPS score, and tumor size were nonsignificant to determine mortality in patient diagnosed with low-grade astrocytoma. The gross total resection surgery should be preferred over subtotal resection since the incidence of malignant formation is low in gross total resection.

Keywords: Extent of resection, Low-grade astrocytoma, Gross total resection

Introduction

Low-grade astrocytoma (LGA) is responsible for 15% of all primary brain tumors, including grade I and grade II astrocytoma, primarily affecting young adults [1]. Pilocytic astrocytoma (WHO grade I) is a typically well-circumcised tumor, with low growth, and can regress spontaneously, primarily tend to arise in the cerebellum and chiasmatic or hypothalamic region, but can involve the cerebral hemisphere, brain stem, or spinal cord [2]. The 10-year overall survival rate in pediatric patients is more than 90%; however, the survival rate decreases with increase in age, 70% overall survival rate by the age of 40 years [3]. World health organization defines diffuse astrocytoma (WHO grade II) as diffusely infiltrating astrocytoma with a characteristic mutation in the IDH1 or IDH2 gene. The tumor is composed of cells with pleomorphism of moderate extent, advanced astrocytic differentiation, and a prolonged growth period [4]. The grade II astrocytoma has a 5-year overall survival and

*Correspondence: neurodipak@gmail.com

[1] Neurosurgery Department, Uzhhorod Regional Clinical Center of Neurosurgery and Neurology, Uzhhorod National University, Uzhhorod, Ukraine
Full list of author information is available at the end of the article

progression-free survival ranges from 58 to 72% and 37% to 55%, respectively [5].

The preferred treatment for grade I astrocytoma is complete resection of the tumor. The rate of recurrence occurs in less than 5% of patients, with a 10-year survival rate of nearly 100%. After subtotal resection, a portion of the tumor can slowly progress or undergoes arrested growth or regress spontaneously [6]. In post-resection progression, surgery is the treatment of choice; however, when the tumor is not amenable to surgery, chemotherapy is often preferred before radiation therapy [7]. Similar beneficial effects for surgery were reported in the treatment of grade II astrocytoma; gross total resection is the preferred treatment, associated with a lower frequency of seizures, than subtotal tumor resection [8].

In this systematic review and meta-analysis, we evaluated the factors that predict the mortality in patients with LGA, underwent surgical resection of the tumor. No previously published meta-analysis and systematic review have analyzed the factors responsible for predicting post-surgical mortality. We assessed the relation of age, tumor size, extent of resection, and Karnofsky Performance Status (KPS) Scale to predict mortality.

Method

Data sources and search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines [9]. An electronic search from PubMed/Medline, Cochrane Library, and Google Scholar was conducted from their inception to November 14, 2021 (detailed strategy provided in Additional file 1: Table S1), with only English language-based literature, using the search string: (low-grade astrocytoma OR grade I astrocytoma) AND (resection OR surgical process OR operation) AND (extent). In addition, we manually screened the cited articles of previous meta-analyses, cohort studies, and review articles to identify any relevant studies.

Study selection

All studies were included if they met the following eligibility criteria which can be described as PICOS: (1) *P* (Patients): Low-grade astrocytoma (Grade I or II); (2) *I* (Intervention): Any type of surgical resection in low-grade astrocytoma; (3) *C* (Control): None; (4) *O* (Outcome): Predictive factors of mortality using multivariate analysis of patient's age, tumor size, total resection, and increasing KPS; (5) *S* (Studies): Cross-sectional studies, cohort studies and human-based randomized controlled trials published in English only.

Data extraction and quality assessment of studies

Two reviewers independently searched electronic databases. Studies searched were exported to the EndNote Reference Library software version 20.0.1 (Clarivate Analytics), and duplicates were screened and removed.

Data extraction and quality assessment of included studies was done simultaneously and independently by two reviewers. Newcastle–Ottawa Scale (NOS) was used to assess the quality of the cross-sectional studies. NOS score 1–5 was considered high risk for bias, 6–7 was moderate, and score > 7 was considered low risk of bias (details of scoring provided in Additional file 1: Table S2).

Statistical analysis

Review Manager (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020) was used for all statistical analyses. The data from studies were pooled using a random-effects model. Analysis of results was done by Hazards Ratio (HR) with respective 95% confidence intervals (CI). The Chi-square test was performed to assess any differences between the subgroups. Sensitivity analysis was done to see if any individual study was driving the results and to implore reasons of high heterogeneity. As per Higgins et al. scale for heterogeneity was considered as follows: $I^2 = 25–60\%$—moderate; 50–90%—substantial; 75–100%—considerable heterogeneity, and $p < 0.1$ indicated significant heterogeneity [10]. A $p < 0.05$ was considered significant for all analyses.

Results

Literature search results

The initial search of the three electronic databases yielded 1256 potential studies. After exclusions based on titles and abstracts, the full texts of 371 studies were read for possible inclusion. A total of 5 studies remained for quantitative analysis. Figure 1 summarizes the results of our literature search.

Study characteristics

Table 1 provides the basic characteristics of included studies [11–15]. Our analysis included 5 published studies. All are cohort studies. A total of 853 patients were included in this analysis. Two studies are from South Korea [15]; 1 is from Germany [11], Brazil [12], USA [13], and Norway [14]. Average age from these studies was 42.9 years.

Publication bias and quality assessment

There are less than 10 studies so publication bias cannot be assessed.

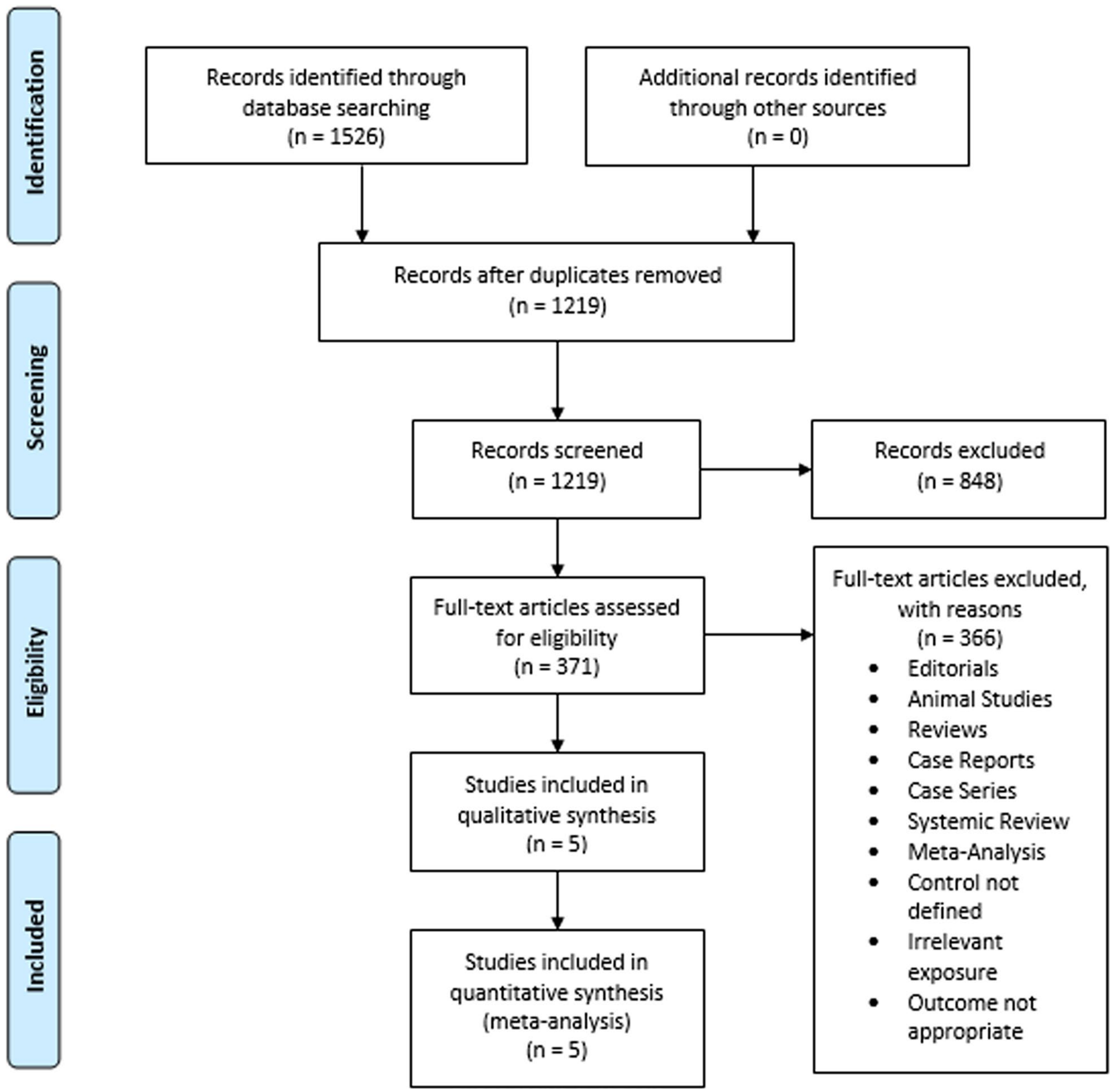

Fig. 1 Prisma flowchart

Table 1 Basic characteristics of selected articles

Study	Study design	Duration	Country	Total no. of patients (*n*)	Male (%)	Mean age (years)	Factors present	Risk of bias
Juratli et al. [11]	Cohort	1993–2007	Germany	71	N/A*	43.5	Age	Low risk
Bianco et al. [12]	Cohort	1999–2008	Brazil	82	57	41.3	KPS	Low risk
Babu et al. [13]	Cohort	N/A*	USA	500	55.4	40.1	Age, size, and resection	Low risk
Jakola et al. [14]	Cohort	1998–2009	Norway	117	58	44	Age, KPS, and size	Low risk
Choi et al. [15]	Cohort	2003–2015	South Korea	153	56	45.6	Size	Low risk

N/A* = Not available

All studies have low risk of bias.

Results of meta-analysis

Detailed forest plot outlining the effect size of predictors of mortality in low-grade astrocytoma (Fig. 2) is provided in the manuscript. We assessed 4 factors: patient's age, tumor size, total resection and increasing KPS.

Our analysis was based on subgroups, which assessed five studies. Three studies were used to analyze patient's age [11, 13, 14] and tumor size [14, 16] while one study was pooled to analyze total resection [13] and increasing KPS [12, 14]. Pooled result showed only total resection as statistically significant predictor of mortality (HR = 0.70 [0.52, 0.94]; $p=0.02$; $I^2=$ Not applicable). Analysis showed statically nonsignificant results in patient's age (HR = 1.27 [0.95, 1.68]; $p=0.11$; $I^2=83\%$), tumor size (HR = 1.13 [0.94, 1.35]; $p=0.19$; $I^2=73\%$), and increasing KPS (HR = 0.59 [0.20, 1.77]; $p=0.35$; $I^2=86\%$).

Sensitivity analysis

A sensitivity analysis was conducted to assess the influence of each study on the overall effect by excluding one study at a time, followed by the generation of pooled Hazard Ratio (HR) for the rest of the studies. No significant change was observed after the exclusion of any individual study, suggesting that the results were robust.

Discussion

In this study, we presented the assessment of evidence from 6 cohort studies to evaluate the factor responsible for the prediction of mortality in LGA, in patients who underwent tumor resection surgery. The results of the analysis showed nonsignificant relation of patient's age, the size of the tumor, and increased preoperative Karnofsky Performance Status (KPS) Scale with mortality. Significant results were obtained for the extent of resection (EOR) only.

The EOR has emerged as a significant prognostic factor in patients with LGA. The greater EOR has been shown to improve overall and progression-free survival, and the time to malignant transformation (16). The primary goal of surgery is to maximize the EOR, avoiding a postoperative neurological deficit. For the maximum safe resection, several advanced surgical techniques have been

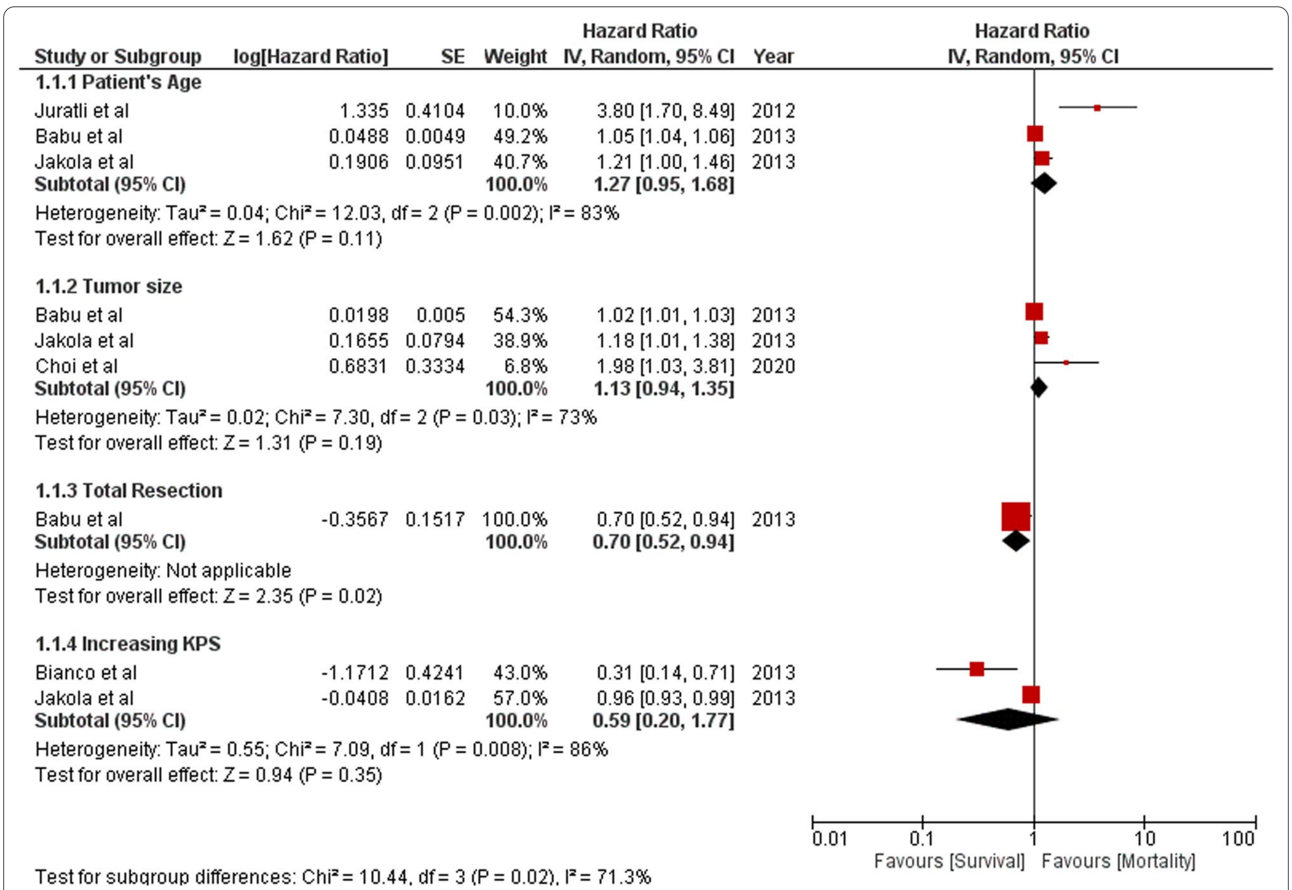

Fig. 2 Forest plot showing effect size of predictor factors of mortality in low-grade astrocytoma

employed [17]. Intraoperative magnetic resonance imaging, intraoperative functional pathway mapping, fluorescence-guided surgery, and neuro-navigation are common techniques in glioma surgery [18]. Bond et al. published a systematic review and meta-analysis to evaluate the relationship of the extent of tumor resection and recurrence, in patients diagnosed with adult-pilocytic astrocytoma (WHO grade I). They found that the tumor reoccurred in 31% of patients, primarily after subtotal resection (73%), less prevalent after gross total resection (27%). Therefore, they concluded that the goal of surgery should be gross total resection rather than subtotal resection when feasible [19]. Another systematic review and meta-analysis evaluated the role of surgical tumor resection in pediatric spinal cord astrocytoma. It was found that the gross total resection showed better 5-year overall survival than subtotal resection [20].

The results suggested that the extent of resection is a significant factor for predicting mortality in LGA. Babu et al. in the multivariant found that the increasing age, large tumor, and tumor resection as individual predicting factors for survival. They found that the patients who underwent resection had more than twice the survival than the patients who underwent biopsy only. The result of the analysis favors the results of Babu et al., and therefore, the extent of resection can be used to predict the mortality in LGA. Nonetheless, because of a smaller number of included studies, the available data is not large enough to predict a strong result. The less than gross total resection has a potential for malignant transformation, therefore impacting the survival by 50%, which could be the reason for the significance of EOR for survival [21].

Malignant transformation can be defined as the progression of an LGA to a WHO grade III and IV tumor [22]. The incidence ranges from 23 to 72%, with the median time ranging from 2.7 to 5.4 years. The histology of astrocytoma, less than gross total resection, and tumor size greater than 3 cm are important prognostic factors [23]. Murphy et al. [24] concluded that the older age, male sex, multiple tumor locations, residual disease, and chemotherapy alone can contribute to malignant transformation.

The results of the analysis suggested a nonsignificant role of age, size of the tumor, and KPS score (the KPS score is a commonly used system to distinguish the patient prognosis and to determine the appropriate management in astrocytoma). Bianco et al. found malignant degeneration in 57% of patients, in a median time of 2 years. Thirty percent of detected patients survive. The malignant transformation plays an important role in postsurgical mortality; therefore, factors such as EOR, which potentially affects malignant transformation, contribute significantly to determining survival and mortality [25]. Therefore, the gross total resection surgery should be implemented, if possible, to minimize the risk of mortality. The age, KPS score, and tumor size are less significant postoperative contributing factors of malignant transformation, therefore, less effective in predicting mortality.

Limitation

Our study is limited in several ways. Firstly, our analysis was based on few studies with minimal patient population which might not cover all the aspect. Secondly, all studies were cohort, and no randomized controlled trials were used in the analysis. Finally, high heterogeneity was observed in all nonsignificant factors (patient's age, tumor size, and increasing KPS). These studies were pivotal in forming analysis, but more studies should be conducted.

Conclusion

The results of meta-analysis showed significant relationship of extent of resection and mortality. While factors such age, KPS score, and tumor size were nonsignificant to determine mortality in patient diagnosed with low-grade astrocytoma. The gross total resection surgery should be preferred over subtotal resection since the incidence of malignant formation is low in gross total resection. The age, preoperative KPS score, and tumor size were found unrelated to malignant formation. However, the available data and published studies were not sufficient to predict a strong result. New studies evaluating the factor responsible for malignant transformation and determining mortality in low-grade astrocytoma are needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41984-022-00161-1.

Additional file 1: Table S1 Search string. **Table S2** Quality assessment of cohorts using new Ottawa scale

Acknowledgements
Not applicable.

Author contributions
VS and AS were involved in study supervision; DC helped in conception and design; DC contributed to statistical analysis; DC was involved in first draft of manuscript; AS, TH, and SM helped in critical revision of the first draft; all authors revised submitted version; all authors read and approved the final manuscript.

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

Availability of data and materials
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, Neurosurgery Department, Uzhhorod National University.

Consent for publication
Not applicable.

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

Author details
[1]Neurosurgery Department, Uzhhorod Regional Clinical Center of Neurosurgery and Neurology, Uzhhorod National University, Uzhhorod, Ukraine. [2]Neurosurgery Department, College of Medical Science, Teaching Hospital, Bharatpur, Nepal.

Received: 23 April 2022 Accepted: 13 May 2022
Published online: 04 July 2022

References

1. Pedersen CL, Romner B. Current treatment of low grade astrocytoma: a review. Clin Neurol Neurosurg. 2013;115(1):1–8. https://doi.org/10.1016/j.clineuro.2012.07.002.
2. Bornhorst M, Frappaz D, Packer RJ. Pilocytic astrocytomas. Handb Clin Neurol. 2016;134:329–44. https://doi.org/10.1016/B978-0-12-802997-8.00020-7.
3. Ostrom QT, de Blank PM, Kruchko C, Petersen CM, Liao P, Finlay JL, Stearns DS, Wolff JE, Wolinsky Y, Letterio JJ, Barnholtz-Sloan JS. Alex's lemonade stand foundation infant and childhood primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro Oncol. 2015;16 Suppl((Suppl 10)):x1–36. https://doi.org/10.1093/neuonc/nou327.
4. International agency for research on cancer: WHO classification of tumours of the central nervous system, 4 edn Vol. 1 (ed by D. N. Louis, H. Ohgaki, O. D. Wiestler, W. K. Cavenee) (WHO/IARC, 2016)
5. Buckner J, Giannini C, Eckel-Passow J, Lachance D, Parney I, Laack N, Jenkins R. Management of diffuse low-grade gliomas in adults - use of molecular diagnostics. Nat Rev Neurol. 2017;13(6):340–51. https://doi.org/10.1038/nrneurol.2017.54.
6. Ogiwara H, Bowman RM, Tomita T. Long-term follow-up of pediatric benign cerebellar astrocytomas. Neurosurgery. 2012;70(1):40–8. https://doi.org/10.1227/NEU.0b013e31822ff0ed.
7. Di Maio S, Gul SM, Cochrane DD, Hendson G, Sargent MA, Steinbok P. Clinical, radiologic and pathologic features and outcome following surgery for cervicomedullary gliomas in children. Child's Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg. 2009;25(11):1401–10. https://doi.org/10.1007/s00381-009-0956-x.
8. Hasselblatt M, Jaber M, Reuss D, Grauer O, Bibo A, Terwey S, Schick U, Ebel H, Niederstadt T, Stummer W, von Deimling A, Paulus W. Diffuse astrocytoma, IDH-wildtype: a dissolving diagnosis. J Neuropathol Exp Neurol. 2018;77(6):422–5. https://doi.org/10.1093/jnen/nly012.
9. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84. https://doi.org/10.7326/M14-2385.
10. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557.
11. Juratli TA, Kirsch M, Robel K, et al. IDH mutations as an early and consistent marker in low-grade astrocytomas WHO grade II and their consecutive secondary high-grade gliomas. J Neurooncol. 2012;108(3):403–10. https://doi.org/10.1007/s11060-012-0844-1(3).
12. Bianco Ade M, Miura FK, Clara C, et al. Low-grade astrocytoma: surgical outcomes in eloquent versus non-eloquent brain areas. Arq Neuropsiquiatr. 2013;71(1):31–4. https://doi.org/10.1590/s0004-282x20120050000174.
13. Babu R, Bagley JH, Park JG, Friedman AH, Adamson C. Low-grade astrocytomas: the prognostic value of fibrillary, gemistocytic, and protoplasmic tumor histology. J Neurosurg. 2013;119(2):434–41. https://doi.org/10.3171/2013.4.JNS1223295.
14. Jakola AS, Unsgård G, Myrmel KS, et al. Surgical strategy in grade II astrocytoma: a population-based analysis of survival and morbidity with a strategy of early resection as compared to watchful waiting. Acta Neurochir (Wien). 2013;155(12):2227–35. https://doi.org/10.1007/s00701-013-1869-86.
15. Choi J, Kim SH, Ahn SS, et al. Extent of resection and molecular pathologic subtype are potent prognostic factors of adult WHO grade II glioma. Sci Rep. 2020;10(1):2086. https://doi.org/10.1038/s41598-020-59089-x8.
16. Claus EB, Horlacher A, Hsu L, Schwartz RB, Dello-Iacono D, Talos F, Jolesz FA, Black PM. Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. Cancer. 2005;103(6):1227–33. https://doi.org/10.1002/cncr.20867.
17. Jakola AS, Myrmel KS, Kloster R, Torp SH, Lindal S, Unsgård G, Solheim O. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. JAMA. 2012;308(18):1881–8. https://doi.org/10.1001/jama.2012.12807.
18. Hollon T, Hervey-Jumper SL, Sagher O, Orringer DA. Advances in the surgical management of low-grade glioma. Semin Radiat Oncol. 2015;25(3):181–8. https://doi.org/10.1016/j.semradonc.2015.02.007.
19. Bond KM, Hughes JD, Porter AL, Orina J, Fang S, Parney IF. Adult pilocytic astrocytoma: an institutional series and systematic literature review for extent of resection and recurrence. World Neurosurg. 2018;110:276–83. https://doi.org/10.1016/j.wneu.2017.11.102.
20. Azad TD, Pendharkar AV, Pan J, Huang Y, Li A, Esparza R, Mehta S, Connolly ID, Veeravagu A, Campen CJ, Cheshier SH, Edwards M, Fisher PG, Grant GA. Surgical outcomes of pediatric spinal cord astrocytomas: systematic review and meta-analysis. J Neurosurg Pediatr. 2018;22(4):404–10. https://doi.org/10.3171/2018.4.PEDS17587.
21. Vertosick FT Jr, Selker RG, Arena VC. Survival of patients with well-differentiated astrocytomas diagnosed in the era of computed tomography. Neurosurgery. 1991;28(4):496–501. https://doi.org/10.1097/00006123-199104000-00002.
22. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, Tihan T, Vandenberg S, McDermott MW, Berger MS. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol Off J Am Soc Clin Oncol. 2008;26(8):1338–45. https://doi.org/10.1200/JCO.2007.13.9337.
23. Chaichana KL, McGirt MJ, Laterra J, Olivi A, Quiñones-Hinojosa A. Recurrence and malignant degeneration after resection of adult hemispheric low-grade gliomas. J Neurosurg. 2010;112(1):10–7. https://doi.org/10.3171/2008.10.JNS08608.
24. Murphy ES, Leyrer CM, Parsons M, Suh JH, Chao ST, Yu JS, Kotecha R, Jia X, Peereboom DM, Prayson RA, Stevens G, Barnett GH, Vogelbaum MA, Ahluwalia MS. Risk factors for malignant transformation of low-grade glioma. Int J Radiat Oncol Biol Phys. 2018;100(4):965–71. https://doi.org/10.1016/j.ijrobp.2017.12.258.
25. McGirt MJ, Chaichana KL, Attenello FJ, Weingart JD, Than K, Burger PC, Olivi A, Brem H, Quinoñes-Hinojosa A. Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas. Neurosurgery. 2008;63(4):700–8. https://doi.org/10.1227/01.NEU.0000325729.41085.73.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.