RESEARCH ARTICLE

Editorial Process: Submission:01/17/2025 Acceptance:07/07/2025

The Association between *p53* Expression and Histopathology Grade of Astrocytoma

Thea Saphira Mugiarto[1,2], Rusdy Ghazali Malueka[2,3], Rita Cempaka[1,2], Rachmat Andi Hartanto[2,4], Ery Kus Dwianingsih[1,2]*

Abstract

Background: The *p53* gene is vital in gliomagenesis. As a tumor suppressor, mutations in TP53 lead to disruptions in apoptosis, cellular senescence, and cell cycle arrest. Ongoing research presents conflicting results about the significance of TP53 mutations in gliomas, particularly in astrocytomas. Histopathologic grade is crucial for assessing tumor aggressiveness, prognosis, and therapy selection. Recent studies and the updated WHO classification emphasize molecular profiling as a key factor in astrocytic glial tumor classification. Furthermore, the high occurrence of *p53* mutations in astrocytoma makes it a promising target for therapy in this type of tumor. This study investigates the association between *p53* mutations and histopathologic grade in astrocytoma. **Methods:** The research subjects were patients diagnosed with astrocytoma of all grades in formalin-fixed paraffin-embedded form between 2017 and 2022 at Dr. Sardjito Hospital in Yogyakarta, Indonesia. Immunohistochemistry was used to determine the p53 mutation status. A 10% cut-off is applied to determine *p53* immunopositivity. Statistical analysis assessed the correlation of *p53* mutation with glioma grade. **Results:** Our study includes 140 patients with astrocytoma, including 10 patients with grade 1, 21 patients with grade 2, 10 patients with grade 3, and 99 patients with grade 4. Our study found a significant correlation between TP53 mutations and histopathological grades in astrocytoma (p=0.001). We present analysis results using Spearman's correlation for bivariate relationships and ordinal regression for multivariate analysis. **Conclusion:** *p53* mutations are associated with histopathologic grade in Astrocytoma. These findings underscore the importance of *p53* in astrocytoma prognosis and therapy. Further research is necessary to support their role in advancing astrocytoma management and treatment.

Keywords: Astrocytoma- immunohistochemistry- *p53*- histopathologic grade

Asian Pac J Cancer Prev, **26 (7)**, 2521-2526

Introduction

Astrocytoma is a type of tumor in the central nervous system (CNS) originating from astrocytes and accounts for 60% of brain tumors [1]. A previous Taiwan Cancer Registry study reported that astrocytoma comprised 58.4% of all malignant CNS tumors between 2002 and 2010 [2]. Another study in Korea reported astrocytoma consisted of 53.95% of all tumors of neuroepithelial tissue between 2007-2016 [3]. Astrocytoma consists of 4 grades; its highest grade, grade 4 glioma, is the most severe, with 70-75% of gliomas falling into this category, having a five-year overall survival rate of 5-10%, with a median overall survival of 14-17 months. Recent research indicates that molecular profiles have significant implications as prognostic markers, therapy indicators, and histopathologic grade. Therefore, the latest WHO grading system for astrocytoma also includes molecular markers [4-6].

The *TP53* gene is known to be the most frequently mutated gene in astrocytoma. This gene can play various roles in complex cellular processes by regulating the expression of target genes. Known as the "Guardian of the Genome," *p53* integrates stress signals and regulates cell cycle and apoptosis to prevent damaged cells from proliferating. Alterations in the *TP53* gene lead to changes in tumor suppressor activity, primarily by altering the expression of many genes involved in cell cycle regulation and apoptosis. These changes typically occur as a response to DNA damage, genotoxicity, oncogene activation, abnormal growth signals, and hypoxia, all of which can arise in carcinogenesis [6]. *p53* mutations involved in the pathogenesis and development of astrocytoma may serve as indicators for determining the grade. The *p53* protein

*[1]Anatomical Pathology Department, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia. [2]Department of Neurology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia. [3]Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.[4]Sardjito General Hospital, Indonesia. *For Correspondence: ery_malueka@ugm.ac.id*

significantly influences the development of pilocytic astrocytoma (PA). Although *TP53* gene mutations are less frequently observed than high-grade astrocytoma, such as glioblastoma, some studies have identified a role for *p53* in PA. This includes interactions with molecular pathways such as *MAPK* and *PI3K/AKT/mTOR*. These findings suggest that *p53* can be a prognostic biomarker [7-10].

A meta-analysis by Jin et al. [11] showed a significant relationship between *p53* expression and astrocytoma, while a meta-analysis by Levidou et al. [12] showed contrary results. Other research indicates that *TP53* gene mutations can accelerate cell proliferation and promote cancer cell metastasis [13]. Although there are sources explaining theories about the relationship between *p53* mutations and astrocytoma grade, inconsistencies remain across various journals, including meta-analyses [11, 12]. Thus, the relationship between them has not yet been proven.

Materials and Methods

This retrospective study involved patients diagnosed with astrocytoma of all grades (grades 1-4) based on the WHO Classification of Tumours of the Central Nervous System (2021 edition) from December 2017 to the end of December 2022 at Dr. Sardjito General Hospital. Ethical clearance was obtained from the ethical committee (KE/FK/1110/EC/2024). The research samples comprised Formalin-Fixed Paraffin-Embedded (FFPE) for Hematoxylin-Eosin (HE) and immunohistochemical staining with Anti-*p53* mutant (M00001-3, Boster, Pleasanton, CA, USA). Positive control was performed on normal brain tissue; negative control was not used in this study. The inclusion criteria required astrocytoma patients with tumor samples in FFPE and complete medical records, including age, gender, and histologic grade data. Samples with poor pre-analytic procedures were excluded.

The status of the *p53* mutation was determined through an immunohistochemistry examination. A strong, diffuse nuclear immunopositivity of 10% was considered positive [14]. Two pathologists used the eyeballing technique to analyze the *p53* mutation status, and the interrater reliability was measured using Cohen's kappa level of agreement. The association between *p53* mutation and astrocytoma histologic grade was analyzed using Spearman's Correlation Test. Additionally, the relationship between *p53* mutation and age, gender, and IDH mutation will be examined using a multivariate ordinal regression test.

Results

Patient characteristics

Among 140 patients, 85 (60.7%) were male, and 55 (39.3%) were female. The mean patient age was 45.5 years, the median was 47.5 years, the youngest was six years, and the oldest was 79. This study categorized age into two groups: before 50 and 50 years or older.

Tumor grade

The subjects of this study had astrocytoma grades categorized as grade 1, 2, 3, and 4. Our study includes 140 patients, including 10 patients with grade 1 (7.1%), 21 patients with grade 2 (15%), 10 patients with grade 3 (7.1%), and 99 patients with grade 4 (70.7%). Glioblastoma and Astrocytoma grade 4, NOS, was the most common diagnosis (64.3%). We also present the data on the tumor's location, morphology, and IDH status retrieved from the medical records. Most tumors were glioblastoma and astrocytoma grade 4, accounting for 90 patients (64.3%). The tumors in our sample were predominantly located in the parietal (50.7%) and frontal (42.1%) lobes; additionally, tumors in the parietal and temporal lobes were common, while less frequent occurrences were noted in the occipital lobe (7.9%), cerebellum (2.9%), and posterior fossa (2.9%) (Table 1). Characteristics of study subjects are presented in the Table 1.

p53 status with immunohistochemistry examination

The interobserver agreement in the IHC examination was analyzed using Cohen's kappa value measurement, yielding a value of 0.805. Ninety-eight samples (70%) showed *p53* mutant (positive immunostaining), and 42 samples (30%) showed *p53* wild-type (negative immunostaining) (Figure 1).

The association between p53 mutation status and astrocytoma grade

Out of 140 samples, 77 (70%) were interpreted as

Table 1. Characteristics of the Study Subjects

Variable	Frequency	Percentage
Age (years)		
Mean±SD 45.5±15.9		
<50 years old	74	52.90%
≥50 years old	66	47.10%
Sex		
Male	85	60.70%
Female	55	39.30%
Location		
Frontal	59	42.10%
Parietal	71	50.70%
Temporal	54	38.60%
Occipitalis	11	7.90%
Cerebellum	4	2.90%
IDH1		
Mutant	37	26.40%
Wild Type	91	65.00%
No data available	12	8.60%
p53		
Positive	98	70.00%
Negative	42	30.00%
WHO grade		
Grade 1	10	7.10%
Grade 2	21	15.00%
Grade 3	10	7.10%
Grade 4	99	70.70%

Table 2. The association between *p53* Mutation Status and Astrocytoma Grade

		WHO grade				r	p
		Grade 1	Grade 2	Grade 3	Grade 4		
p53	Negative	8 (19.0%)	6 (14.3%)	6 (14.3%)	22 (52.4%)	0.274	0.001*
	Positive	2 (2.0%)	15 (15.3%)	4 (4.1%)	77 (78.6%)		

Table 3. Bivariate Analysis of Age, Gender, Tumor Location, and IDH Status on Astrocytoma Grade

Variable	CNS WHO 2021									
	Grade 1		Grade 2		Grade 3		Grade 4		r	p
	n	%	n	%	n	%	n	%		
Age										
<50 years old	9	12.20%	13	17.60%	6	8.10%	46	62.20%	0.216	0.010*
≥50 years old	1	1.50%	8	12.10%	4	6.10%	53	80.30%		
Sex										
Male	5	5.90%	14	16.50%	4	4.70%	62	72.90%	-0.053	0.535
Female	5	9.10%	7	12.70%	6	10.90%	37	67.30%		
Location										
Frontal	1	1.70%	12	20.30%	4	6.80%	42	71.20%	0.029	0.73
Parietal	3	4.20%	9	12.70%	2	2.80%	57	80.30%	0.203	0.016*
Temporal	0	0.00%	10	18.50%	3	5.60%	41	75.90%	0.11	0.194
Occipital	0	0.00%	0	0.00%	1	9.10%	10	90.90%	0.14	0.099
Cerebellum	4	100.00%	0	0.00%	0	0.00%	0	0.00%	-0.344	0.001*
IDH1										
Mutant	0	0.00%	11	29.70%	6	16.20%	20	54.10%	0.316	0.001*
Wild-type	0	0.00%	10	11.00%	4	4.40%	77	84.60%		
p53										
Negative	8	19.00%	6	14.30%	6	14.30%	22	52.40%	0.274	0.001*
Positive	2	2.00%	15	15.30%	4	4.10%	77	78.60%		

immunopositive, of which 2 of them were grade 1 (2.0%), 15 of them were grade 2 (15.3%), 4 of them were grade 3 (4.1%), and 77 of them (78.6%) was grade 4. Most of the immunopositive samples (78.6%) were in grade 4. This study found a significant association between *p53* mutation and astrocytoma grade with $p < 0.05$ ($p=0.001$) (Table 2).

Bivariate analysis of age, gender, location, and IDH status on astrocytoma grade

A bivariate test analyzed the relationship between other factors toward astrocytoma grade. The result showed significant associations between astrocytoma grade with age and IDH mutation status. Age is positively correlated with astrocytoma grade ($r = 0.216$, $p = 0.010$), indicating that older patients are more likely to have higher-grade tumors, with 80.3% of patients aged 50 years or older having grade 4 astrocytoma. IDH mutation status is also significantly related to astrocytoma grade ($r = 0.316$, $p = 0.001$), suggesting that IDH wild-type tumors are more frequently high-grade (84.6% in Grade 4) than IDH mutant tumors. Other factors do not show significant associations with astrocytoma grade (Table 3).

Table 4. Multivariate Analysis of Age, Tumor Location, and *p53* Expression on Astrocytoma

Variable	Estimate	p	95% CI	
			Lower	Upper
p53 (Positive)	1.139	0.007*	0.305	1.973
Age (>50 years old)	0.96	0.023*	0.132	1.788
Histopathology type	-0.149	0.067	-0.308	0.011
Location (Parietal)	0.8	0.069	-0.063	1.662
Location (Temporal)	0.248	0.566	-0.598	1.093
Location (Occipitalis)	1.128	0.315	-1.072	3.327
Location (Cerebellum)	.	.	.	.

The multivariate analysis examined the relationships between age, tumor location, *p53* expression, and astrocytoma grade. The results revealed significant associations between astrocytoma grade, *p53* expression, and age (Table 4). Patients with positive *p53* expression who are over 50 years old are more likely to present with higher-grade astrocytoma.

Discussion

Out of 140 patients, 85 (60.7%) were male, which is higher than the 55 female patients (39.3%). This finding is consistent with prior studies, which showed similar

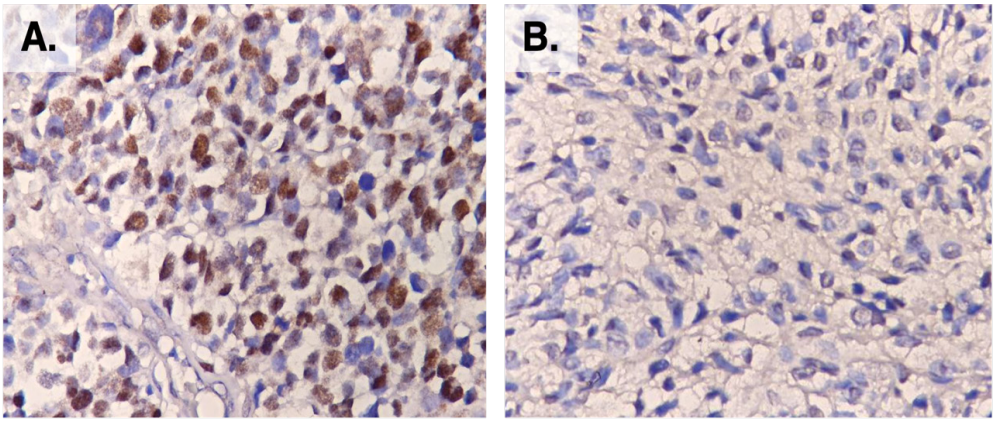

Figure 1. Immunohistochemistry Staining of *p53* Mutant (High Power View, Magnification 400x). (A). Intense nuclear staining in immunopositive in ³10% of tumor cells was interpreted as positive (*p53* mutant). (B). Weak nuclear staining was interpreted as negative as immunonegative *(p53* wild-type)

results [15, 11]. There were 74 patients (52.9%) under 50 and 66 patients aged 50 or older. Mean±SD was 45.5±15.9 with a median age of 47.5 years, consistent with previous research [16].

Overall, our study showed a significant association between *p53* mutation and astrocytoma grade, with p <0.05 (p=0.001), indicating a robust statistical significance (p <0.05). This finding is consistent with prior meta-analyses [11]. Most of the immunopositive samples (78.6%) were in grade 4. The data suggest interesting associations between *p53* mutation status, astrocytoma grades, and IDH mutation status. *p53* positivity is significantly associated with higher-grade astrocytoma, where 78.6% of immunopositive *p53* cases are at grade 4. The association between *p53* positivity and high-grade astrocytoma can be explained by its role in tumor progression and aggressiveness. *p53* mutations or overexpression are often seen in advanced astrocytomas. Mutant *p53* proteins cannot activate the negative feedback response through the MDM2 pathway, leading to the accumulation of mutant *p53*. This accumulation results in gain-of-function (GOF) mutations, which subsequently increase cell proliferation, migration, and invasion. These mutations are also associated with tumor progression to higher grades; these tumors were also more resistant to chemotherapy. This supports the notion that *p53* positivity is linked to more aggressive disease [17].

In addition, this research also showed that astrocytoma with an IDH mutant was associated with a lower grade (p=0.028), which is consistent with previous studies [18]. IDH-mutant astrocytomas are less aggressive and generally associated with lower tumor grades. This is particularly caused by the accumulation of 2-hydroxyglutarate (2-HG), which leads to DNA hypermethylation and contributes to the differentiation blockade, slowing down tumor growth. IDH mutations often come with additional mutations, such as ATRX loss or *TP53* mutations, to promote tumor progression [19].

The high percentage of IDH wild-type tumors (65.0%) was associated with higher-grade astrocytoma. IDH mutant tumors were more commonly associated with lower-grade astrocytoma, as IDH mutations are recognized in >80% of WHO grade 2 and 3 cases. This aligns with previous studies' findings suggesting that IDH mutations are often associated with a more favorable prognosis and lower-grade tumors [20-22].

In bivariate analysis, we found a statistically significant association between age and the histopathologic grade of astrocytoma. This finding is consistent with a prior study which mentioned that older age is associated with higher grades [23]. The tumor's location does not significantly impact the histopathologic grade, consistent with earlier studies that indicated no statistically significant differences in astrocytoma areas among major histologic subtypes [24, 25].

Variables with p<0.25 in the bivariate analysis were included in the multivariate analysis. A multivariate analysis was conducted for WHO grades (1-4) using Ordinal Regression Analysis (Table 4). The IDH1 variable was excluded from the multivariate analysis because all grade 1 samples lacked IDH1 mutation. The results of the multivariate analysis revealed a significant association between *p53* expression and WHO grade (p=0.007), with a positive regression coefficient of 1.139. This indicates that positive *p53* expression is associated with a 1.139-level higher increase in histopathological grade. Another factor showing a significant association with WHO grade was age (p=0.023), with a positive regression coefficient of 0.960, suggesting that individuals over 50 experience a 0.960-level higher increase in WHO grade.

The association between *p53* positivity and astrocytoma grade significantly impacts astrocytoma pathology. *p53* positivity is strongly linked to higher-grade astrocytoma, with tumors showing increased proliferation, migration, and invasion, contributing to progression to higher grades and resistance to chemotherapy. However, *p53* mutations can also be observed in lower-grade astrocytoma, which may still affect tumor behavior and progression [26, 27]. The novelty of this study lies in addressing contradictory findings reported in previous meta-analyses [26, 27]. By investigating a previously unexamined population, this study contributes to advancing research on astrocytoma.

In conclusion, our study highlights a significant correlation between *p53* positivity and astrocytoma grade. In multivariate analysis, IDH wild-type tumors are associated with higher astrocytoma grade. Further research

is needed for a more comprehensive view of astrocytoma behavior, treatment strategies, and patient outcomes.

Author Contribution Statement

EKD conceptualized and designed the study and was supported in executing the study by TM and RC. RGM and RAH led data collection and import. TM and EKD were responsible for cleaning, analyzing, and interpreting the data. RGM and RC prepared tables and figures. TM wrote the first draft of the manuscript. All authors contributed substantially to the manuscript's critical review, editing, and revision. All authors had full access to all data in the study, approved the final version of the manuscript, and had final responsibility for the decision to submit the manuscript for publication.

Acknowledgements

This manuscript is part of a research project conducted at the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada.

Fundings

The DAMAS Grant Program of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, partly supported this study.

Ethics approval

This study was approved by the Institutional Review Board of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia (KE/FK/1110/EC/2024).

Availability of data

The submission includes all data generated or analyzed during this study. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

1. Kapoor M, Gupta V. Astrocytoma. Statpearls. Treasure Island (FL): 2025.
2. Chien LN, Gittleman H, Ostrom QT, Hung KS, Sloan AE, Hsieh YC, et al. Comparative brain and central nervous system tumor incidence and survival between the united states and taiwan based on population-based registry. Front Public Health. 2016;4:151. https://doi.org/10.3389/fpubh.2016.00151.
3. Kang H, Song SW, Ha J, Won YJ, Park CK, Yoo H, et al. A nationwide, population-based epidemiology study of primary central nervous system tumors in korea, 2007-2016: A comparison with united states data. Cancer Res Treat. 2021;53(2):355-66. https://doi.org/10.4143/crt.2020.847.
4. Malueka RG, Hartanto RA, Alethea M, Sianipar CM, Wicaksono AS, Basuki E, et al. Associations among smoking, idh mutations, mgmt promoter methylation, and grading in glioma: A cross-sectional study. F1000Res. 2022;11. https://doi.org/10.12688/f1000research.110726.1.
5. Theresia E, Malueka RG, Pranacipta S, Kameswari B, Dananjoyo K, Asmedi A, et al. Association between ki-67 labeling index and histopathological grading of glioma in indonesian population. Asian Pac J Cancer Prev. 2020;21(4):1063-8. https://doi.org/10.31557/apjcp.2020.21.4.1063.
6. Zhang Y, Dube C, Gibert M, Cruickshanks N, Wang B, Coughlan M, et al. The *p53* pathway in glioblastoma. Cancers. 2018;10(9). https://doi.org/10.3390/cancers10090297.
7. Li X, Moreira DC, Bag AK, Qaddoumi I, Acharya S, Chiang J. The clinical and molecular characteristics of progressive hypothalamic/optic pathway pilocytic astrocytoma. Neuro Oncol. 2023;25(4):750-60. https://doi.org/10.1093/neuonc/noac241.
8. Sadighi Z, Slopis J. Pilocytic astrocytoma: A disease with evolving molecular heterogeneity. J Child Neurol. 2013;28(5):625-32. https://doi.org/10.1177/0883073813476141.
9. Mascelli S, Nozza P, Jones DT, Colin C, Pistorio A, Milanaccio C, et al. *Tp53 codon 72* polymorphism may predict early tumour progression in paediatric pilocytic astrocytoma. Oncotarget. 2016;7(30):47918-26. https://doi.org/10.18632/oncotarget.10295.
10. Wemmert S, Romeike BF, Ketter R, Steudel WI, Zang KD, Urbschat S. Intratumoral genetic heterogeneity in pilocytic astrocytomas revealed by cgh-analysis of microdissected tumor cells and fish on tumor tissue sections. Int J Oncol. 2006;28(2):353-60.
11. Jin Y, Xiao W, Song T, Feng G, Dai Z. Expression and prognostic significance of *p53* in glioma patients: A meta-analysis. Neurochem Res. 2016;41(7):1723-31. https://doi.org/10.1007/s11064-016-1888-y.
12. Levidou G, El-Habr E, Saetta AA, Bamias C, Katsougiannis K, Patsouris E, et al. P53 immunoexpression as a prognostic marker for human astrocytomas: A meta-analysis and review of the literature. J Neurooncol. 2010;100(3):363-71. https://doi.org/10.1007/s11060-010-0204-y.
13. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cbio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012;2(5):401-4. https://doi.org/10.1158/2159-8290.Cd-12-0095.
14. Cancer IAfRo. Central nervous system tumours, who classification of tumours series. 2021. Available from: https://tumourclassification.iarc.who.int/chapters/45. 2024.
15. Pellerino A, Caccese M, Padovan M, Cerretti G, Lombardi G. Epidemiology, risk factors, and prognostic factors of gliomas. Clin Transl Imaging. 2022;10(5):467-75. https://doi.org/10.1007/s40336-022-00489-6.
16. Ahrendsen JT. Gliomas, glioneuronal tumors and neuronal tumors. 2023. Available from: https://www.pathologyoutlines.com/topic/cnstumorgliomageneral.html. Accessed 20 December 2024.
17. Pellot Ortiz KI, Rechberger JS, Nonnenbroich LF, Daniels DJ, Sarkaria JN. Mdm2 inhibition in the treatment of glioblastoma: From concept to clinical investigation. Biomedicines. 2023;11(7). https://doi.org/10.3390/biomedicines11071879.
18. Network CGAR. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med. 2015;372(26):2481-98. https://doi.org/10.1056/NEJMoa1402121.
19. Bledea R, Vasudevaraja V, Patel S, Stafford J, Serrano J, Esposito G, et al. Functional and topographic effects on DNA methylation in idh1/2 mutant cancers. Sci Rep. 2019;9(1):16830. https://doi.org/10.1038/s41598-019-

53262-7.
20. Malueka RG, Dwianingsih EK, Bayuangga HF, Argo IW, Donurizki AD, Shaleh S, et al. Association of idh1 mutation with survival of glioma patients in indonesia. J Neurol Sci. 2019;405. https://doi.org/10.1016/j.jns.2019.10.408.
21. Mellinghoff IK, Chang SM, Jaeckle KA, van den Bent M. Isocitrate dehydrogenase mutant grade ii and iii glial neoplasms. Hematol Oncol Clin North Am. 2022;36(1):95-111. https://doi.org/10.1016/j.hoc.2021.08.008.
22. Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, et al. Idh mutation in glioma: Molecular mechanisms and potential therapeutic targets. Br J Cancer. 2020;122(11):1580-9. https://doi.org/10.1038/s41416-020-0814-x.
23. Krigers A, Demetz M, Thomé C, Freyschlag CF. Age is associated with unfavorable neuropathological and radiological features and poor outcome in patients with who grade 2 and 3 gliomas. Sci Rep. 2021;11(1). https://doi.org/10.1038/s41598-021-96832-4.
24. Larjavaara S, Mantyla R, Salminen T, Haapasalo H, Raitanen J, Jaaskelainen J, et al. Incidence of gliomas by anatomic location. Neuro Oncol. 2007;9(3):319-25. https://doi.org/10.1215/15228517-2007-016.
25. Anindita AS, Malueka RG, Hartanto RA, Krisnugraha YP, Cempaka R, Dwianingsih EK. The association of alpha-thalassemia x-linked intellectual disability mutation with histopathological grading in isocitrate- dehydrogenase-mutant glioma. Turk J Neurol. 2023;29(4):302-8. https://doi.org/10.4274/tnd.2023.17837.
26. Aiman W, Gasalberti DP, Rayi A. Low-grade gliomas. Statpearls. Treasure Island (FL): 2025.
27. Noor H, Briggs NE, McDonald KL, Holst J, Vittorio O. *Tp53* mutation is a prognostic factor in lower grade glioma and may influence chemotherapy efficacy. Cancers. 2021;13(21). https://doi.org/10.3390/cancers13215362