Low-Grade Gliomas in Children

Abstract
Low-grade gliomas (LGG) are primary tumors of the central nervous system, originating from malignant transformation of cells in the brain or spinal cord. They are distinct from metastatic cancers that spread to the CNS from other parts of the body. While low-grade gliomas can occur throughout the nervous system, they are most commonly found in the cerebellum and central regions of the cerebrum, including the optic pathway and hypothalamic-pituitary axis. The growth of low-grade gliomas varies, with some tumors growing slowly and remaining localized, while others may progress rapidly and aggressively. Due to the limited space within the skull, the growth of a tumor can potentially damage critical areas of the brain, posing a risk to the patient's life. Although the risk of metastasis through the cerebrospinal fluid is generally low, children diagnosed with optic pathway gliomas at a young age may have a slightly increased risk of developing metastases. Research focus on new targets to treat this rare group of brain cancer in childhood.

Key Words
Glioma-child-low grade-treatment

Introduction

Epidemiopathological aspects

"Low grade gliomas are typically diagnosed between the ages of five and seven, with a higher incidence in children aged two to five" (1-6). "Boys are slightly more affected than girls, with a gender ratio of 1.1-1.3 to 1" (1-3). The incidence of LGG is 6.5/100000 inhabitants per year (2,3). "In Germany, around 250 children and adolescents under 18 are diagnosed with low-grade glioma each year, with an incidence rate of 2 to 3 per 100,000 children" (3,35). "20 per cent of all patients with LGG have an association with neurofibromatosis 1" (7). "LGG include forms of sporadic cases and spontaneous regression" (8,9,10,11,12,13). "Low-grade gliomas are primary tumors of the central nervous system, originating from malignant transformation of cells in the brain or spinal cord. They are distinct from metastatic cancers that spread to the CNS from other parts of the body". (50) "While low-grade gliomas can occur throughout the nervous system, they are most commonly found in the cerebellum and central regions of the cerebrum, including the optic pathway and hypothalamic-pituitary axis" (45). The growth of low-grade gliomas varies, with some tumors growing slowly and remaining localized, while others may progress rapidly and aggressively. Due to the limited space within the skull, a growing tumor can pose a threat to vital brain functions and become life-threatening. The risk of metastasis through the cerebrospinal fluid is generally low, except for children with optic pathway gliomas diagnosed at a young age, who may have a slightly increased risk. The large group of low-grade gliomas consists of various types of tumors that can be distinguished by their appearance under the microscope and their biological behavior, especially molecular genetic characteristics. Metastases are rarely found. The 5 years survival rate is 85-90 per cent (14,15). LGG were found most often in the cerebellum, cerebral in 15 percent, deep midline structures in 10-15 percent, optic pathways 5 percent and as brain stem glioma in 2-4 percent (14,15).

Genetic aspects

The *causes* of LGG pathogenesis focus on genetic changes on chromosome 7 (2,3). In a few cases, duplications of the 7q34 region were present with higher BRAF-1 expression and activation of RAS/RAF/MEK signal pathway (16). In 5-10 percent of all cases TP-53 mutations and nidogen-1 expression were described (17-19,42-43). Moreover, mutations of isocitrate dehydrogenase (IDH) with gain-or loss of function were found, resulting in high levels of 2-hydroxyglutarat as a *driver* of gliomagenesis (20-23).

Histological features

"Low-grade gliomas develop from neuroglia that have become malignant. These cells provide support and protection for the brain's nerve cells" (25). "The exact cause of this transformation of glial cells into malignancy is not fully understood. It is known that children with certain inherited diseases, such as neurofibromatosis type 1 or tuberous sclerosis, have a higher risk of developing low-grade gliomas compared to healthy individuals. For example, up to 20% of patients with neurofibromatosis 1 develop a low-grade glioma within the first 20 years of life, often in the optic pathway or lower brain stem. Up to 15 percent of patients with tuberous sclerosis are diagnosed with subependymal giant cell astrocytoma, a specific subtype of low-grade glioma, before reaching adulthood. These genetic diseases that predispose individuals to cancer are known as cancer predisposition syndromes. Additionally, childhood brain radiotherapy, such as that received by patients with certain forms of leukemia or retinoblastoma, is linked to an increased risk of developing a CNS tumor later in life" (25).

Classification (WHO)

The World Health Organization classifies low-grade gliomas as WHO-grade I or WHO-grade II tumors. High-grade gliomas (WHO-grade III and IV tumors) are highly malignant and are discussed separately on this website. WHO-grade I tumors are considered benign gliomas with slow growth and well-defined margins. These tumors may compress adjacent tissue but typically do not invade it. WHO-grade II tumors tend to grow diffusely into surrounding structures and spread more rapidly throughout the central nervous system. Transformation of low-grade gliomas into high-grade tumors, as seen in adults, is rare in children. Low-grade gliomas also vary in their degree of malignancy, with differences in growth rate and aggressiveness. Grade I is localized more at the brain stem region, Grade II LGG are more infiltrative. LGG are found supratentorial, pontin or infratentorial. From histological aspects, astrocytic, oligodendroglial and mixed glial-neuronal prominent forms of LGG were described.

Symptoms of LGG

The symptoms of low-grade gliomas vary depending on the patient's age, tumor location, size, and spread within the CNS. General and specific symptoms may be typical. General symptoms are nonspecific and can mimic other diseases. These symptoms may include headaches, back pain, dizziness, loss of appetite, nausea, vomiting, weight loss, fatigue, difficulty concentrating, school issues, mood changes, and developmental delays. These symptoms are often caused by increased intracranial pressure due to the growing tumor within the skull or blockage of cerebrospinal fluid flow, leading to

hydrocephalus. In infants, elevated intracranial pressure may present as a bulging fontanelle or macrocephalus. Specific symptoms depend on the tumor location and affected CNS regions. For example, a low-grade glioma in the cerebellum can cause dizziness and gait problems, while a tumor in the hemispheres may lead to seizures or motor deficits. Spinal cord tumors can cause back pain, muscle weakness, and numbness. Vision, mental, and sleep issues may also indicate tumor location.

Therapeutical aspects

"There are currently no ongoing therapy optimization trials for children and adolescents with low-grade glioma in Germany. The last trial, SIOP-LGG 2004, closed for patient registration in early 2012, and a subsequent trial has not yet been initiated but is in the planning stages. From April 2012 to the end of 2018, children and adolescents with low-grade glioma were enrolled in the SIOP-LGG 2004 Registry. The LOGGIC Registry is an international registry available for patients with low-grade glioma in Germany (35). Since January 1, 2019, the LOGGIC Registry has been enrolling children and adolescents under 21 years of age in Europe who have newly diagnosed low-grade glioma" (35). "The LOGGIC Core Bio Clinical Data Bank, opened in April 2019, documents molecular tumor characteristics. The LOGGIC Registry and LOGGIC Core aim to collect comprehensive data, including molecular information, from patients with low-grade glioma to enhance understanding of tumor biology and facilitate the development of new treatment strategies" (35). Given the excellent long-term survival prognosis associated with low-grade gliomas, all therapeutic considerations should prioritize preserving CNS function and the patient's quality of life.

New targets in therapy

The advancing *understanding of the biology* of LGG opens up possibilities for targeted therapy with small inhibitory molecules. For patients with NF1 and plexiform neurofibromas, the known molecular genetic abnormalities have already become the target of therapy. Since activation in the MAPK/ERK signaling pathway can be detected in 100% of pilocytic astrocytomas, targeted therapies have been used in initial studies after uncovering relevant feedback and escape mechanisms of pathway inhibition (27,29). MEK inhibitors BRAFV600E inhibitors and type II RAF inhibitors like Tovorafenib as well as a combination therapy of Dabrafenib and Trametinib represent promising classes of substances (37,40,41,44,47). Their value compared to conventional chemotherapy needs to be evaluated in future studies, as well as the acute, subacute, and long-term toxicities of these new substances. Recent research focus on a new target, vemurafenib, a protein kinase inhibitor (24).

Biomarkers

Biomarkers of LGG can be separated in *two groups*; group 1 with focused extension of LGG are Aquaporin-4, Nideogen-1-expression, BRAF-1-mutation and C11orf95-RELA-fusion; group 2 includes biomarkers in diffuse glioma like IDH ½, 1 p/19q Co-deletion, ATRX, TERT, FUBPI, FGFR3/TACC3 fusion, T2-FLAIR-mismatch, MYB/MYBL1-alteration and MIB-1 labeling index (18,24,30,31,33,34,37,38,40,44,46).

Follow-up diagnostics

Follow-up diagnostics and aftercare serve the oncological assessment of the course and the determination of the extent of functional losses and rehabilitation needs caused by the tumor and therapy. The type and frequency of examinations, such as visual and auditory testing, EEG and evoked potentials, endocrinological testing, blood count, and kidney function testing, must be tailored to the individual case and local conditions. To ensure psychosocial reintegration into everyday life, school, and work, extensive examinations and regular follow-up assessments of neuropsychological functions, quality of life, and adaptive behavior are of particular importance (32). This helps to identify cognitive late effects, as well as individual strengths and weaknesses, to implement targeted interventions derived from them, and thus improve children's participation in everyday life. In interdisciplinary care, especially neuropediatricians, neuropsychologists, psychologists, social workers, and teachers, in cooperation with physiotherapists, occupational therapists, and speech therapists, must be involved. School rehabilitation for often visually impaired children must be carried out with the involvement of country-specific institutions. The individual coping with the disease can be supported by psychotherapeutic care. The current need for such support should be continuously assessed in outpatient care by the responsible psychologist. Rehabilitation is often a long-term or continuous process that is primarily carried out on an outpatient basis and occasionally focused in rehabilitation clinics with specific expertise in the treatment of pediatric brain tumor patients through optimized diagnostic and therapeutic measures. Family-oriented rehabilitation also offers the opportunity to train parents in dealing with limitations, stabilize the entire family system regarding the frequent and long-term consequences of the disease, and develop life perspectives. Due to the long progression times of tumors, lifelong follow-up appears advisable for individual subgroups such as neurofibromatosis patients and patients with optic pathway gliomas with pituitary deficits, necessitating appropriate transition care.

Conclusion

Low-grade gliomas are slow-growing primary brain tumors that typically progress to a malignant state. Treatment involves surgical removal, possible chemoradiation for high-risk cases, and ongoing monitoring to delay progression and enhance quality of life (26,28,39). The approach for low-risk patients is less clear. Advances in molecular profiling will help refine risk assessment and prognosis for low-grade gliomas, leading to more personalized treatments that enhance survival and reduce side effects.

Disclaimer (Artificial intelligence)

The author hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

References

(1) Kilburn LB, Khuong-Quang DA, Hansford JR, Landi D, van der Lugt J, Leary SES, Driever PH, Bailey S, Perreault S, McCowage G, Waanders AJ, Ziegler DS, Witt O, Baxter PA, Kang HJ, Hassall TE, Han JW, Hargrave D, Franson AT, Yalon Oren M, Toledano H, Larouche V, Kline C, Abdelbaki MS, Jabado N, Gottardo NG, Gerber NU, Whipple NS, Segal D, Chi SN, Oren L, Tan EEK, Mueller S, Cornelio I, McLeod L, Zhao X, Walter A, Da Costa D, Manley P, Blackman SC, Packer RJ, Nysom K. Author Correction: The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial. Nat Med. 2024 May;30(5):1500. doi: 10.1038/s41591-024-02910-1. Erratum for: Nat Med. 2024 Jan;30(1):207-217. doi: 10.1038/s41591-023-02668-y. PMID: 38467878; PMCID: PMC11108768.
(2) Fangusaro J, Avery RA, Fisher MJ, Packer RJ, Walsh KS, Schouten-van Meeteren A, Karres D, Bradford D, Bhatnagar V, Singh H, Kluetz PG, Donoghue M, Duke ES. Considering Functional Outcomes as Efficacy Endpoints in Pediatric Low-Grade Glioma Clinical Trials: An FDA Educational Symposium. Clin Cancer Res. 2024 Jun 3;30(11):2303-2308. doi: 10.1158/1078-0432.CCR-23-3386. PMID: 38358393; PMCID: PMC11147731.
(3) Dar MS, Shahid N, Waqas A, Baig YA, Khan AW. Dabrafenib plus Trametinib: A breakthrough in pediatric low-grade glioma therapy. Health Sci Rep. 2024 Jan 25;7(1):e1841. doi: 10.1002/hsr2.1841. PMID: 38274133; PMCID: PMC10809164.
(4) Ziegler DS, Lehmann R, Eisenstat DD. A paradigm shift in how we treat pediatric low-grade glioma-Targeting the molecular drivers. Neuro Oncol. 2024 Apr 5;26(4):593-595. doi: 10.1093/neuonc/noae008. PMID: 38243845; PMCID: PMC10995501.
(5) Milde T, Fangusaro J, Fisher MJ, Hawkins C, Rodriguez FJ, Tabori U, Witt O, Zhu Y, Gutmann DH. Optimizing preclinical pediatric low-grade glioma models for meaningful clinical translation. Neuro Oncol. 2023 Nov 2;25(11):1920-1931. doi: 10.1093/neuonc/noad125. PMID: 37738646; PMCID: PMC10628935.
(6) Siegel BI, Duke ES, Kilburn LB, Packer RJ. Molecular-targeted therapy for childhood low-grade glial and glioneuronal tumors. Childs Nerv Syst. 2024 Jun 15. doi: 10.1007/s00381-024-06486-6. Epub ahead of print. PMID: 38877124.
(7) Kotch C, de Blank P, Gutmann DH, Fisher MJ. Low-grade glioma in children with neurofibromatosis type 1: surveillance, treatment indications, management, and future directions. Childs Nerv Syst. 2024 May 5. doi: 10.1007/s00381-024-06430-8. Epub ahead of print. PMID: 38704493.
(8) Baticulon RE, Wittayanakorn N, Maixner W. Low-grade glioma of the temporal lobe and tumor-related epilepsy in children. Childs Nerv Syst. 2024 May 24. doi: 10.1007/s00381-024-06468-8. Epub ahead of print. PMID: 38789690.
(9) Papangelopoulou D, Bison B, Behrens L, Bailey S, Ansari M, Ehlert K, Martinez OC, Kramm CM, Morales La Madrid A, von Bueren AO. Brain stem tumors in children less than 3 months: Clinical and radiologic findings of a rare disease. Childs Nerv Syst. 2024 Apr;40(4):1053-1064. doi: 10.1007/s00381-023-06272-w. Epub 2024 Feb 20. PMID: 38376530; PMCID: PMC10972984.
(10) Bianchi F, Cocilovo FM, Ruggiero A, Tamburrini G. Optic Pathway Gliomas: The Trends of Basic Research to Reduce the Impact of the Disease on Visual Function. Adv Tech Stand Neurosurg. 2023;48:123-137. doi: 10.1007/978-3-031-36785-4_6. PMID: 37770684.
(11) Targeted Therapy Win in BRAF-Mutant Gliomas. Cancer Discov. 2023 Nov 1;13(11):2299-2300. doi: 10.1158/2159-8290.CD-NB2023-0071. PMID: 37732735.
(12) Liu Z, Hong X, Wang L, Ma Z, Guan F, Wang W, Qiu Y, Zhang X, Duan W, Wang M, Sun C, Zhao Y, Duan J, Sun Q, Liu L, Ding L, Ji Y, Yan D, Liu X, Cheng J, Zhang Z, Li ZC, Yan J. Radiomic features from multiparametric magnetic resonance imaging predict molecular subgroups of pediatric low-grade gliomas. BMC Cancer. 2023 Sep 11;23(1):848. doi: 10.1186/s12885-023-11338-8. PMID: 37697238; PMCID: PMC10496393.
(13) Al Assaad M, Gundem G, Liechty B, Sboner A, Medina J, Papaemmanuil E, Sternberg CN, Marks A, Souweidane MM, Greenfield JP, Tran I, Snuderl M, Elemento O, Imielinski M, Pisapia DJ, Mosquera JM. The importance of escalating molecular diagnostics in patients with low-grade pediatric brain cancer. Cold Spring Harb Mol Case Stud. 2024 Jan 10;9(4):a006275. doi: 10.1101/mcs.a006275. PMID: 37652664; PMCID: PMC10815291.
(14) Gojo J, Preusser M. Improving long-term outcomes in pediatric low-grade glioma. Nat Cancer. 2024 Apr;5(4):533-535. doi: 10.1038/s43018-024-00741-0. PMID: 38429416.
(15) Ramírez-Melo JL, Moreira DC, Orozco-Alvarado AL, Sánchez-Zubieta F, Navarro-Martín Del Campo RM. Challenges in treating children with optic pathway gliomas: an 18-year experience from a middle-income country. Front Oncol. 2024 Feb 13;14:1329729. doi: 10.3389/fonc.2024.1329729. PMID: 38414749; PMCID: PMC10898851.
(16) Kocher D, Cao L, Guiho R, Langhammer M, Lai YL, Becker P, Hamdi H, Friedel D, Selt F, Vonhören D, Zaman J, Valinciute G, Herter S, Picard D, Rettenmeier J, Maass KK, Pajtler KW, Remke M, von Deimling A, Pusch S, Pfister SM, Oehme I, Jones DTW, Halbach S, Brummer T, Martinez-Barbera JP, Witt O, Milde T, Sigaud R. Rebound growth of BRAF mutant pediatric glioma cells after MAPKi withdrawal is associated with MAPK reactivation and secretion of microglia-recruiting cytokines. J Neurooncol. 2024 Jun;168(2):317-332. doi: 10.1007/s11060-024-04672-9. Epub 2024 Apr 17. PMID: 38630384; PMCID: PMC11147834.
(17) 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 (Basel). 2021 Oct 26;13(21):5362. doi: 10.3390/cancers13215362. PMID: 34771529; PMCID: PMC8582451.
(18) Miller JJ, Gonzalez Castro LN, McBrayer S, Weller M, Cloughesy T, Portnow J, Andronesi O, Barnholtz-Sloan JS, Baumert BG, Berger MS, Bi WL, Bindra R, Cahill DP, Chang SM, Costello JF, Horbinski C, Huang RY, Jenkins RB, Ligon KL, Mellinghoff IK, Nabors LB, Platten M, Reardon DA, Shi DD, Schiff D, Wick W, Yan H, von Deimling A, van den Bent M, Kaelin WG, Wen PY. Isocitrate dehydrogenase (IDH) mutant gliomas: A Society for Neuro-Oncology (SNO) consensus review on diagnosis, management, and future directions. Neuro Oncol. 2023 Jan 5;25(1):4-25. doi: 10.1093/neuonc/noac207. PMID: 36239925; PMCID: PMC9825337.
(19) Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, Gilbert MR, Yang C. IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. Br J Cancer. 2020 May;122(11):1580-1589. doi: 10.1038/s41416-020-0814-x. Epub 2020 Apr 15. PMID: 32291392; PMCID: PMC7250901.
(20) Miller JJ, Gonzalez Castro LN, McBrayer S, Weller M, Cloughesy T, Portnow J, Andronesi O, Barnholtz-Sloan JS, Baumert BG, Berger MS, Bi WL, Bindra R, Cahill DP, Chang SM, Costello JF,

Horbinski C, Huang RY, Jenkins RB, Ligon KL, Mellinghoff IK, Nabors LB, Platten M, Reardon DA, Shi DD, Schiff D, Wick W, Yan H, von Deimling A, van den Bent M, Kaelin WG, Wen PY. Isocitrate dehydrogenase (IDH) mutant gliomas: A Society for Neuro-Oncology (SNO) consensus review on diagnosis, management, and future directions. Neuro Oncol. 2023 Jan 5;25(1):4-25. doi: 10.1093/neuonc/noac207. PMID: 36239925; PMCID: PMC9825337.

(21) Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, Gilbert MR, Yang C. IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. Br J Cancer. 2020 May;122(11):1580-1589. doi: 10.1038/s41416-020-0814-x. Epub 2020 Apr 15. PMID: 32291392; PMCID: PMC7250901.

(22) Yan D, Li W, Liu Q, Yang K. Advances in Immune Microenvironment and Immunotherapy of Isocitrate Dehydrogenase Mutated Glioma. Front Immunol. 2022 Jun 13;13:914618. doi: 10.3389/fimmu.2022.914618. PMID: 35769466; PMCID: PMC9234270.

(23) Wu C, Song H, Fu X, Li S, Jiang T. Transcriptomic Analysis of Glioma Based on IDH Status Identifies ACAA2 as a Prognostic Factor in Lower Grade Glioma. Biomed Res Int. 2020 Mar 21;2020:1086792. doi: 10.1155/2020/1086792. PMID: 32280672; PMCID: PMC7115055.

(24) Nelson MV, Kim A, Williams PM, Roy-Chowdhuri S, Patton DR, Coffey BD, Reid JM, Piao J, Saguilig L, Alonzo TA, Berg SL, Ramirez NC, Jaju A, Fox E, Weigel BJ, Hawkins DS, Mooney MM, Takebe N, Tricoli JV, Janeway KA, Seibel NL, Parsons DW. Phase II study of vemurafenib in children and young adults with tumors harboring BRAF V600 mutations: NCI-COG pediatric MATCH trial (APEC1621) Arm G. Oncologist. 2024 Jun 14:oyae119. doi: 10.1093/oncolo/oyae119. Epub ahead of print. PMID: 38873934.

(25) Zhou T, Qiao B, Peng B, Liu Y, Gong Z, Kang M, He Y, Pang C, Dai Y, Sheng M. Predicting histological grade in pediatric glioma using multiparametric radiomics and conventional MRI features. Sci Rep. 2024 Jun 13;14(1):13683. doi: 10.1038/s41598-024-63222-5. PMID: 38871755; PMCID: PMC11176337

(26) Lassaletta A, Zapotocky M, Bouffet E. Chemotherapy in pediatric low-grade gliomas (PLGG). Childs Nerv Syst. 2024 May 31. doi: 10.1007/s00381-024-06458-w. Epub ahead of print. PMID: 38819670.

(27) Sigaud R, Brummer T, Kocher D, Milde T, Selt F. MOST wanted: navigating the MAPK-OIS-SASP-tumor microenvironment axis in primary pediatric low-grade glioma and preclinical models. Childs Nerv Syst. 2024 May 25. doi: 10.1007/s00381-024-06463-z. Epub ahead of print. PMID: 38789691.

(28) Bansal I, Merchant TE. Radiotherapy for pediatric low-grade glioma. Childs Nerv Syst. 2024 May 22. doi: 10.1007/s00381-024-06460-2. Epub ahead of print. PMID: 38775957.

(29) O'Hare P, Cooney T, de Blank P, Gutmann DH, Kieran M, Milde T, Fangusaro J, Fisher M, Avula S, Packer R, Fukuoka K, Mankad K, Mueller S, Waanders AJ, Opocher E, Bouffet E, Raabe E, Werle NE, Azizi AA, Robison NJ, Hernáiz Driever P, Russo M, Schouten N, van Tilburg CM, Sehested A, Grill J, Bandopadhayay P, Kilday JP, Witt O, Ashley DM, Ertl-Wagner BB, Tabori U, Hargrave DR. Resistance, rebound, and recurrence regrowth patterns in pediatric low-grade glioma treated by MAPK inhibition: A modified Delphi approach to build international consensus-based definitions-International Pediatric Low-Grade Glioma Coalition. Neuro Oncol. 2024 May 14:noae074. doi: 10.1093/neuonc/noae074. Epub ahead of print. PMID: 38743009.

(30) Marastoni E, Mulone D, Barresi V. Diffuse Gliomas with *FGFR3*::*TACC3* Fusion: Morphological and Molecular Features and Classification Challenges. Cancers (Basel). 2024 Apr 25;16(9):1644. doi: 10.3390/cancers16091644. PMID: 38730596; PMCID: PMC11083705.

(31) van Maren EA, Dankbaar JW, Wesseling P, Plasschaert S, Muhlebner A, Hoving EW, Robe PA, Snijders TJ, Hoogendijk R, Kranendonk MEG, Lequin MH. T2-FLAIR Mismatch: An Imaging Biomarker for Children's *MYB/MYBL1*-Altered Diffuse Astrocytoma or Angiocentric Glioma. AJNR Am J Neuroradiol. 2024 Jun 7;45(6):747-752. doi: 10.3174/ajnr.A8203. PMID: 38724203.

(32) Kim EY, Vavere AL, Snyder SE, Chiang J, Li Y, Patni T, Qaddoumi I, Merchant TE, Robinson GW, Holtrop JL, Shulkin BL, Bag AK. [11C]-methionine positron emission tomography in the evaluation of pediatric low-grade gliomas. Neurooncol Adv. 2024 Apr 5;6(1):vdae056. doi: 10.1093/noajnl/vdae056. PMID: 38680989; PMCID: PMC11055465.

(33) Gorodezki D, Zipfel J, Bevot A, Nägele T, Ebinger M, Schuhmann MU, Schittenhelm J. Prognostic utility and characteristics of MIB-1 labeling index as a proliferative activity marker in childhood low-grade glioma: a retrospective observational study. J Cancer Res Clin Oncol. 2024 Apr 5;150(4):178. doi: 10.1007/s00432-024-05701-w. PMID: 38580878; PMCID: PMC10997709.

(34) Moreira DC, Qaddoumi I, Spiller S, Bouldin TW, Davidson A, Saba-Silva N, Sullivan DV, Tanaka R, Wagner AS, Wood M, Klimo P, Job G, Devidas M, Li X, Gajjar A, Robinson GW, Chiang J. Comprehensive analysis of MYB/MYBL1-altered pediatric-type diffuse low-grade glioma. Neuro Oncol. 2024 Mar 11:noae048. doi: 10.1093/neuonc/noae048. Epub ahead of print. PMID: 38466086.

(35) Traunwieser T, Loos E, Ottensmeier H, Gastberger K, Nemes K, Mynarek M, Bison B, Kandels D, Neumayer P, Neumann-Holbeck A, Lüttich P, Baust K, Faulstich-Ritter K, John R, Kreisch A, Landmann J, Manteufel E, Nest A, Prüfe J, Schubert L, Stamm W, Timmermann B, Gerss J, Rutkowski S, Schlegel PG, Eyrich M, Gnekow AK, Frühwald MC. Survivors of infant atypical teratoid/rhabdoid tumors present with severely impaired cognitive functions especially for fluid intelligence and visual processing: data from the German brain tumor studies. Pediatr Blood Cancer. 2024 May;71(5):e30910. doi: 10.1002/pbc.30910. Epub 2024 Feb 11. PMID: 38342954.

(36) Yaman I, Bouffet E. How will tovorafenib change our treatment of pediatric low-grade glioma? Expert Opin Emerg Drugs. 2024 Mar;29(1):1-3. doi: 10.1080/14728214.2024.2312817. Epub 2024 Feb 2. PMID: 38293894.

(37) Ali RH, Almanabri M, Ali NY, Alsaber AR, Khalifa NM, Hussein R, Alateeqi M, Mohammed EMA, Jama H, Almarzooq A, Benobaid N, Alqallaf Z, Ahmed AA, Bahzad S, Almurshed M. Clinicopathological analysis of BRAF and non-BRAF MAPK pathway-altered gliomas in paediatric and adult patients: a single-institution study of 40 patients. J Clin Pathol. 2024 Jan 9:jcp-2023-209318. doi: 10.1136/jcp-2023-209318. Epub ahead of print. PMID: 38195220.

(38) Gupta A, Lechpammer M, Brossier NM. Germline BRCA2 pathogenic variants in pediatric ganglioglioma: Case report and review of the literature. Childs Nerv Syst. 2024 May;40(5):1609-1612. doi: 10.1007/s00381-023-06267-7. Epub 2024 Jan 3. PMID: 38168858.

(39) Mueller S, Fangusaro J, Thomas AO, Jacques TS, Bandopadhayay P, de Blank P, Packer RJ, Fouladi M, van Meeteren AS, Jones D, Perry A, Nakano Y, Hargrave D, Riedl D, Robison NJ, Partanen M, Fisher MJ, Witt O. Consensus framework for conducting phase I/II clinical trials for children, adolescents, and young adults with pediatric low-grade glioma: Guidelines established by the International Pediatric Low-Grade Glioma Coalition Clinical Trial Working Group. Neuro Oncol. 2024 Mar 4;26(3):407-416. doi: 10.1093/neuonc/noad227. Erratum in: Neuro Oncol. 2024 May 3;26(5):983. doi: 10.1093/neuonc/noae024. Erratum in: Neuro Oncol. 2024 May 3;26(5):984. doi: 10.1093/neuonc/noae030. PMID: 38146999; PMCID: PMC10912006.
(40) Kudus K, Wagner MW, Namdar K, Nobre L, Bouffet E, Tabori U, Hawkins C, Yeom KW, Ertl-Wagner BB, Khalvati F. Increased confidence of radiomics facilitating pretherapeutic differentiation of BRAF-altered pediatric low-grade glioma. Eur Radiol. 2024 Apr;34(4):2772-2781. doi: 10.1007/s00330-023-10267-1. Epub 2023 Oct 7. PMID: 37803212.
(41) Barbato MI, Nashed J, Bradford D, Ren Y, Khasar S, Miller CP, Zolnik BS, Zhao H, Li Y, Bi Y, Shord SS, Amatya AK, Mishra-Kalyani PS, Scepura B, Al-Matari RA, Pazdur R, Kluetz PG, Donoghue M, Singh H, Drezner N. FDA Approval Summary: Dabrafenib in Combination with Trametinib for BRAFV600E Mutation-Positive Low-Grade Glioma. Clin Cancer Res. 2024 Jan 17;30(2):263-268. doi: 10.1158/1078-0432.CCR-23-1503. PMID: 37610803; PMCID: PMC10841289.
(42) Gil-Benso R, Lopez-Gines C, Benito R, López-Guerrero JA, Callaghan RC, Pellín A, Roldán P, Cerdá-Nicolas M. Concurrent EGFR amplification and TP-53 mutation in glioblastomas. Clin Neuropathol. 2007 Sep-Oct;26(5):224-31. doi: 10.5414/npp26224. PMID: 17907599.
(43) Zhang B, Xu C, Liu J, Yang J, Gao Q, Ye F. Nidogen-1 expression is associated with overall survival and temozolomide sensitivity in low-grade glioma patients. Aging (Albany NY). 2021 Mar 18;13(6):9085-9107. doi: 10.18632/aging.202789. Epub 2021 Mar 18. PMID: 33735110; PMCID: PMC8034893.
(44) Kudus K, Wagner MW, Namdar K, Nobre L, Bouffet E, Tabori U, Hawkins C, Yeom KW, Ertl-Wagner BB, Khalvati F. Increased confidence of radiomics facilitating pretherapeutic differentiation of BRAF-altered pediatric low-grade glioma. Eur Radiol. 2024 Apr;34(4):2772-2781. doi: 10.1007/s00330-023-10267-1. Epub 2023 Oct 7. PMID: 37803212.
(45) Bianchi F, Cocilovo FM, Ruggiero A, Tamburrini G. Optic Pathway Gliomas: The Trends of Basic Research to Reduce the Impact of the Disease on Visual Function. Adv Tech Stand Neurosurg. 2023;48:123-137. doi: 10.1007/978-3-031-36785-4_6. PMID: 37770684.
(46) Targeted Therapy Win in BRAF-Mutant Gliomas. Cancer Discov. 2023 Nov 1;13(11):2299-2300. doi: 10.1158/2159-8290.CD-NB2023-0071. PMID: 37732735.
(47) Barbato MI, Nashed J, Bradford D, Ren Y, Khasar S, Miller CP, Zolnik BS, Zhao H, Li Y, Bi Y, Shord SS, Amatya AK, Mishra-Kalyani PS, Scepura B, Al-Matari RA, Pazdur R, Kluetz PG, Donoghue M, Singh H, Drezner N. FDA Approval Summary: Dabrafenib in Combination with Trametinib for BRAFV600E Mutation-Positive Low-Grade Glioma. Clin Cancer Res. 2024 Jan 17;30(2):263-268. doi: 10.1158/1078-0432.CCR-23-1503. PMID: 37610803; PMCID: PMC10841289.
(48) Stieber VW. Low-grade gliomas. Current treatment options in oncology. 2001 Nov;2:495-506.
(49) Soffietti R, Baumert BG, Bello L, Von Deimling A, Duffau H, Frénay M, Grisold W, Grant R, Graus F, Hoang-Xuan K, Klein M. Guidelines on management of low-grade gliomas: report of an EFNS–EANO* Task Force. European journal of neurology. 2010 Sep;17(9):1124-33.
(50) Yiallouros M. Low-Grade Glioma (LGG)-Brief Information.