Guideline Resource Unit
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IDH-Mutant CNS WHO Grade 2 and 3 Gliomas

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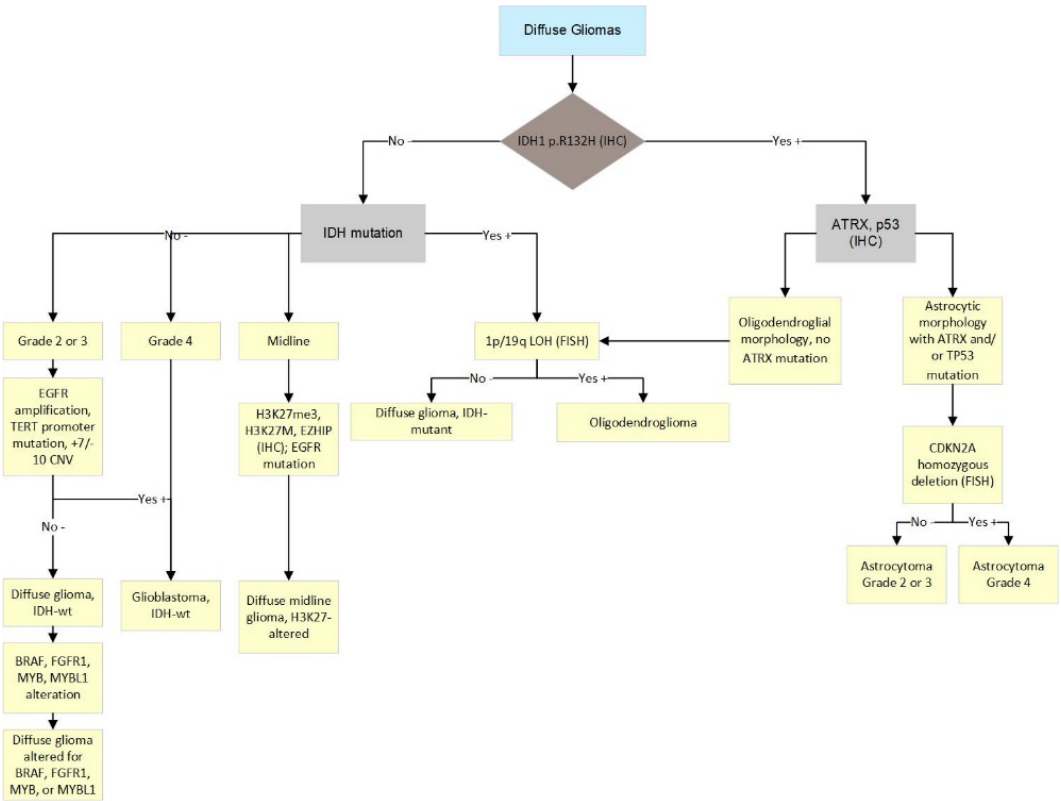
Glioma Overview

Gliomas develop within the central nervous system (CNS) and represent 78% of primary malignant brain tumours.[1] IDH-mutant adult-type gliomas are typically diagnosed in young adults (median age of 36 years for grades 2 and 3 (combined), and 38 years for grade 4).[2] This is substantially younger than glioblastoma IDH-wildtype tumours (median 50-60 years of age). Since isocitrate dehydrogenase (IDH) mutations were discovered, classification of gliomas has changed. The treatment options are now considered separately for IDH-mutant astrocytomas, IDH-wildtype astrocytomas (eg, glioblastoma or lower grade) and oligodendrogliomas.[3]

The 2021 WHO Classification of CNS Tumors incorporates molecular features, morphology and traditional histologic grades to provide a comprehensive diagnosis of CNS cancers, including astrocytoma and oligodendroglioma. The 5th edition update to the WHO Classification of CNS Tumors has substantially changed the classification of IDH-mutant astrocytic tumours, now all coming under the one diagnosis, based on the presence of IDH-mutation and the demonstrated absence of 1p/19q codeletion, which, if present, would_ meet the diagnosis criteria for an oligodendroglioma. Glioblastoma is now considered a separate entity and distinct as IDH-wildtype, and is therefore.[3] Glioblastoma is now considered a separate entity and distinct as IDH-wildtype, and is therefore discussed separately.

The grading of IDH-mutant gliomas is based on histological features and certain molecular markers (e.g. homozygous CDKN2A/B deletion (introduced in the 5th edition (2021) WHO Classification of CNS Tumors).

Figure 1. Molecular Classification of Diffuse Gliomas[3,4]



Guideline Questions

- Is resection better than biopsy in the management of WHO grade 2 and grade 3 gliomas?
- What is the optimal radiation therapy plan for WHO grade 2 and grade 3 gliomas?
- What is the role of radiation and chemotherapy in the adjuvant treatment of WHO grade 2 and grade 3 gliomas?

Search Strategy

The PubMed database was searched for relevant studies, guidelines and consensus documents published up to December 2023. The specific search strategy, search terms and evidence tables are available upon request. Online resources from oncology-based health organizations and guideline developers were also systematically searched and relevant guidelines from the following organizations were considered in the development of our recommendations: American Society of Clinical Oncology (ASCO)[5] American Society for Radiation Oncology (ASTRO),[4] Society for Neuro-Oncology (SNO)[5] and the National Comprehensive Cancer Network (NCCN).[6]

Target Population

The following recommendations apply to adult patients with IDH-mutant gliomas.

Recommendations

Diagnosis *(Level of evidence: II, Strength of recommendation: B)* [5,6]

1. Magnetic resonance imaging (MRI) is the best imaging modality for diagnosing gliomas.

2. If there is any contraindication for MRI, such as MRI incompatible joint implants or pacemakers, computed tomography (CT) may be performed.

3. Biopsy or resection is required to diagnose IDH-mutant gliomas. Please note that biopsy, depending on size and cellularity, may not always be representative of the entire tumour.

Treatment

IDH-mutant, CNS WHO Grade 2 Astrocytoma[4,5]

Surgical Intervention: *(Level of evidence: I, Strength of recommendation: A)*[5,7]

4. Surgery is recommended as the first-line treatment for presumed gliomas, encompassing tumour diagnosis, biopsy or resection for symptom relief, and tissue collection (including tumour banking) for research.

5. Maximal safe resection of the tumour is recommended. Repeat surgery may be necessary following an initial biopsy for a resectable lesion. For patients with WHO grade 2 astrocytoma and a gross total resection, surveillance after maximal safe resection may be appropriate if no high-risk factors are present.

Radiation Therapy (RT):[4,6] *(Level of evidence: II, Strength of recommendation: B)*[8-10]

6. Based on extrapolation from CATNON, RT with sequential chemotherapy is recommended for high-risk WHO grade 2 astrocytomas.[8]
    - High-risk prognostic factors include Subtotal resection, age ≥ 40, tumour size ≥4-6 cm, tumour crosses midline, refractory seizures or presurgical neurologic symptoms from tumour.
    - Treatment planning – A dose of 50.4 to 54 Gy delivered in 28 to 30 fractions is recommended.
    - A referral for proton beam radiation therapy can be considered after consulting the proton beam referral guidelines if the patient is eligible. Proton Beam Radiation Therapy Guideline

Chemotherapy: *(Level of evidence: II, Strength of recommendation: B)*[8,11,12]

7. Approximately 1 month after the completion of radiation therapy, adjuvant chemotherapy with temozolomide (150-200 mg/m2) given orally once daily for 5 days every 4 weeks for twelve cycles is recommended.

8. Alternatively, PCV may be used instead of temozolomide for adjuvant chemotherapy (procarbazine 60 mg/m2 orally once daily on days 8 to 21, lomustine 110 mg/m2 orally once daily on day 1, and vincristine 1.4 mg/m2 IV once daily on days 8 and 29 every six to eight weeks for a total of six cycles).[5]

9. Vorasidenib may be offered to patients with non-enhancing astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 2, where, after one or more surgeries, further treatment with radiation and chemotherapy has been or can be deferred.[5] *This drug is not currently covered on the Alberta Outpatient Cancer Drug Benefit Program.*

IDH-mutant, CNS WHO Grade 3 Astrocytoma

Radiation Therapy (RT): *(Level of evidence: II, Strength of recommendation: B)*[8-10]

10. For patients with astrocytoma, IDH-mutant, WHO grade 3, with any extent of surgery, RT with sequential chemotherapy is recommended. Temozolomide doses and timing are the same as WHO grade 2 astrocytoma.[5]

11. For patients with WHO grade 3 astrocytoma, total prescribed dose of 59.4 to 60 Gy in 1.8 to 2 Gy / fraction is recommended. For some patients (based on age or performance status) a shorter radiotherapy regimen may be appropriate.[8]

Chemotherapy: *(Level of evidence: II, Strength of recommendation: B)*[8-10]

12. Approximately 1 month after the completion of radiation therapy, adjuvant chemotherapy with temozolomide (150-200 mg/m2) given orally once daily for 5 days every 4 weeks for twelve cycles is recommended.

13. WHO grade 4, IDH-mt astrocytoma can be treated as a WHO grade 3 astrocytoma or as a glioblastoma.

IDH-mutant, CNS WHO Grade 2 Oligodendroglioma
(Level of evidence: II, Strength of recommendation: B)[8-10,13]

14. For patients with oligodendroglioma, IDH-mutant, WHO grade 2 with high-risk features, radiation therapy followed by adjuvant PCV is recommended. The CCTG CEC6 clinical trial was designed to address this question of adjuvant PCV vs TMZ, but the trial is closed, and data has not been presented yet. In that study, TMZ was given concurrently with radiation therapy followed by adjuvant TMZ.

15. TMZ is a reasonable alternative to PCV when toxicity is a concern.

16. High-risk prognostic factors include: subtotal resection, age ≥ 40, tumour size ≥4-6 cm, tumor crosses midline, refractory seizures or presurgical neurologic symptoms from tumour. For patients with WHO grade 2 oligodendroglioma who are under the age of 40, have had a gross total resection, and/or have low-risk prognostic factors as defined above, adjuvant therapy may be deferred post-resection until radiographic or symptomatic progression.

17. Vorasidenib may be offered to patients with non-enhancing CNS WHO grade 2, IDH-mutant, 1p/19q codeleted oligodendroglioma, where, after one or more surgeries, further treatment with radiation and chemotherapy has been or can be deferred.[13] *This drug is not currently covered on the Alberta Outpatient Cancer Drug Benefit Program.*

18. A referral for proton beam radiation therapy can be considered after consulting the proton beam referral guidelines if the patient is eligible. Proton Beam Radiation Therapy Guideline

IDH-mutant, CNS WHO Grade 3 Oligodendroglioma

19. Patients with WHO grade 3, IDH-mutant oligodendroglioma, should be offered radiation therapy followed by PCV. TMZ is a reasonable alternative to PCV when toxicity is a concern.[11]

20. In patients of advanced age or with suboptimal performance status, hypofractionated radiation therapy followed by temozolomide may be considered. A multidisciplinary tumour board discussion is recommended to tailor treatment based on individual performance status
    - A referral for proton beam radiation therapy can be considered after consulting the proton beam referral guidelines if the patient is eligible. Proton Beam Radiation Therapy Guideline

Follow-up and Surveillance

21. The following schedule should be considered to manage complications related to treatment, to detect disease recurrence and/or the development of new disease:

    - *WHO grade 2 and WHO grade 3 IDH-mutant glioma* - Brain MRI every 3–6 months for 5 years then at least every 6 months or as clinically indicated.[6]
    - *WHO Grade 4, IDH-mutant glioma* - Brain MRI 4–8 weeks after standard radiation therapy, then every 2–4 months for 3 years, then every 3–6 months indefinitely.[6]

Recurrent Disease *(Level of evidence: III, Strength of recommendation: C)*[5,6]

22. There is no standard treatment for patients with recurrent disease so consideration can be given on a case-by-case basis. Options may include resection, RT or chemotherapy.

23. Patients should be presented and discussed at a multidisciplinary tumour board to decide the best treatment option for each patient.

24. Whenever possible, patients with IDH-mutant WHO grade 2 and 3 gliomas should be encouraged to participate in ongoing clinical trials. Up to date information on trials offered in Alberta is available on the Alberta Cancer Clinical Trials website.

25. For patients with recurrent WHO grade 2 astrocytoma or WHO grade 2 oligodendroglioma who have not previously received radiation and/or chemotherapy in their management, vorasidenib can be considered. *This drug is not covered on the Alberta Cancer Care drug benefit list.*

Discussion

Based on the most recent WHO classification, IDH-mutant astrocytomas do not have a 1p/19q codeletion and are subdivided into WHO grade 2 (formerly diffuse astrocytoma), WHO grade 3 (formerly anaplastic astrocytoma), and CNS WHO grade 4 (previously known as IDH-mutant glioblastoma).[3,14,15] Oligodendrogliomas have a 1p/19q codeletion which is subdivided into WHO grade 2 and WHO grade 3. Younger age and better performance status at diagnosis are major therapy-independent prognostic factors associated with favourable outcomes in adults with glioma.[16]

Surgery

Surgery is the first step in the treatment of gliomas and maximum safe resection is the preferred surgical approach. The majority of observational studies demonstrate an association between a higher extent of resection and prolonged tumor control and survival.[17] The study by Jakola et al. also suggested that early surgical resection resulted in a clinically relevant survival benefit. [7]

Radiotherapy

The goal of radiotherapy (RT) is to improve overall survival without inducing neurotoxicity. The timing, dosing and scheduling of RT depends on disease subtype and prognostic factors, including age, size, patients' functional status and residual tumour volume. RT should start within 3–5 weeks after surgery[9] and is commonly administered at 50.4–60 Gy in 1.8–2 Gy daily fractions for both grade 2 and grade 3 glioma. There is no evidence to support the use of higher doses of radiation in patients with WHO grade 2 gliomas[10] and, for those with higher WHO grade tumours, data from randomized studies do not support the use of doses >60 Gy.[18] The Phase III trial by Galanis et al. suggested that there is no benefit of high-dose over low-dose radiation (high dose, 15.2% vs low dose, 9.5%; P = 0.7142) for low grade astrocytoma.

The RTOG9006 trial[19] and the NCCTG 86-72-51 trial[10] both investigated the alternative doses of RT for low grade astrocytoma and oligodendroglioma patients but found no significant difference in OS or PFS between their arms. The study by Green et al. randomized (1:1) the low-grade gliomas patients with 50.4 Gy in 28 fractions versus 64.8 Gy in 36 fractions after resection. High-dose radiation did not improve 15-year OS vs low-dose (22.4% vs 24.9%) or PFS (high dose, 15.2% vs low dose, 9.5%; P = 0.7142). The trial addressed the role of RT only, and data supported the role of RT as a backbone of therapy for diffuse astrocytoma (grade 2, low-grade gliomas).

Temozolomide

Based on results from the CATNON clinical trial, RT with sequential chemotherapy is recommended for WHO grade 3 astrocytomas.[8] The phase III trial investigated the addition of concurrent, adjuvant, and both current and adjuvant temozolomide to RT in adults with newly diagnosed 1p/19q non-codeleted grade 3 gliomas.[8] Patients were randomly assigned to treatment either with RT alone (59.4 Gy in 33 fractions; three-dimensional conformal RT or intensity-modulated RT), RT with concurrent oral temozolomide (75 mg/m2 per day), RT with adjuvant oral temozolomide (12 4-week cycles of 150–200 mg/m2 temozolomide given on days 1–5), or RT with both concurrent and adjuvant temozolomide. The study showed that adjuvant temozolomide improves overall survival compared with no adjuvant temozolomide (median OS 82·3 months vs 46·9 months [37·9–56·9]; HR 0·64 [95% CI 0·52–0·79], p<0·0001). The study concluded that adjuvant temozolomide chemotherapy, but not concurrent temozolomide chemotherapy, was associated with a survival benefit in patients with 1p/19q non-codeleted grade 3 gliomas.

Procarbazine, Lomustine, and Vincristine

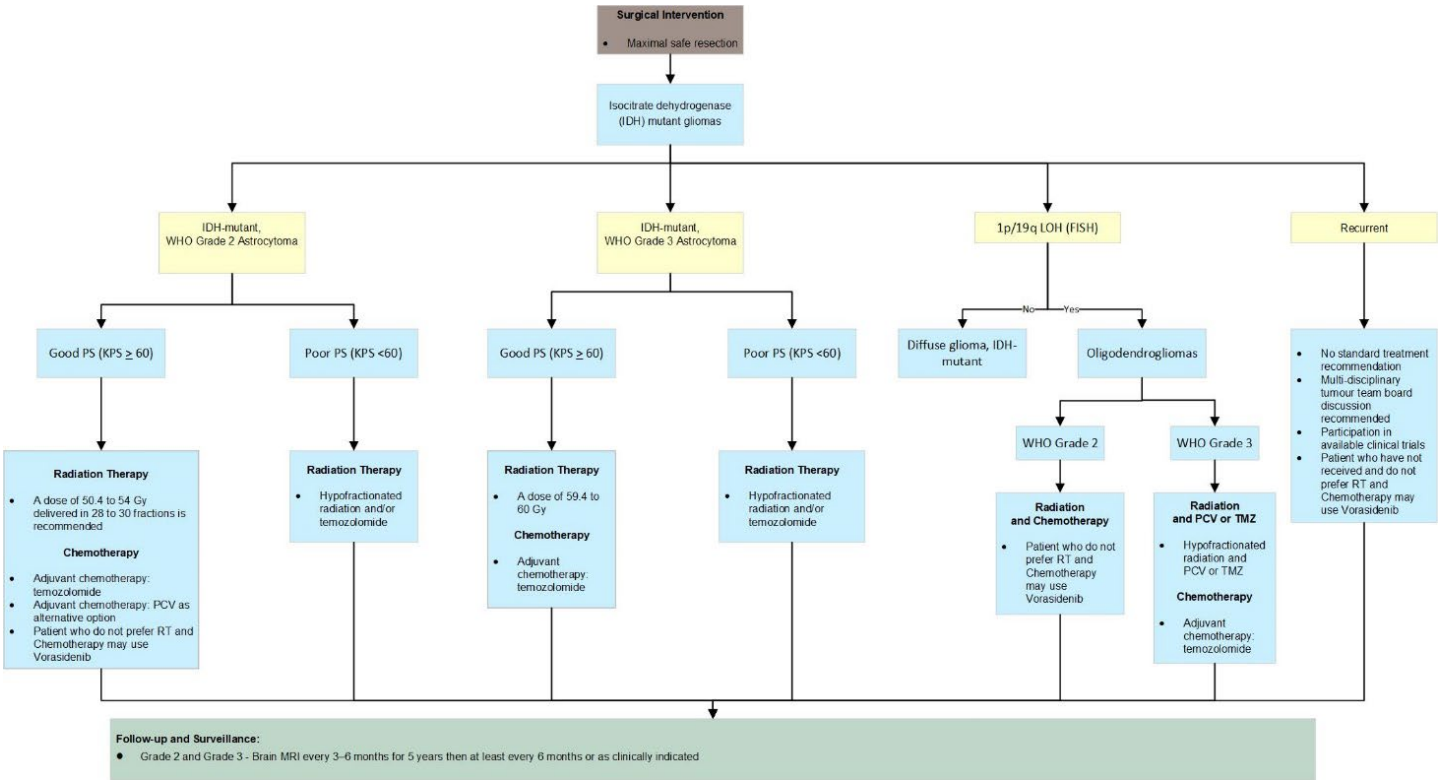
Many trials investigated the role of PCV versus no PCV in patients with low-grade gliomas. The RTOG 9802 trial evaluated the role of chemotherapy in high-risk low-grade gliomas and included patients with oligodendroglioma and astrocytoma. The trial showed significant improvement in OS (median 13.3 years v 7.8 years) in patients who received RT and PCV when compared to patients who received RT alone.[11] EORTC26951 trial also investigated the role of PCV in patients who were classified as anaplastic oligodendroglioma based on histological criteria. The trial showed significant increase in OS (42.3 vs 30.6 months) for RT/PCV treatment as compared to RT only.[20] Based on these studies, it is recommended to use PCV for patients with astrocytoma and oligodendroglioma. Buckner et al. also investigated the role of PCV in low grade gliomas who were 40 years of age or older and had undergone biopsy or resection of any of the tumour. Patients who received radiation therapy plus chemotherapy had longer median OS than did those who received radiation therapy alone (13.3 vs. 7.8 years; hazard ratio for death, 0.59; P=0.003).[12]

Chemotherapy Alone

Clinical trials have also investigated the role of chemotherapy as monotherapy for low-grade (WHO grade 2) and anaplastic (WHO grade 3) astrocytoma. The EORTC 22033-26033 trial patients were randomly assigned (1:1) to receive either conformal RT (up to 50.4 Gy; 28 doses of 1.8 Gy once daily, 5 days per week for up to 6-7 weeks) or dose-dense oral temozolomide (75 mg/m2 once daily for 21 days, repeated every 28 days [one cycle], for a maximum of 12 cycles) to determine the overall

survival.[21] The OS data were not considered mature and no significant difference in PFS was found (HR, 1.16; 95% CI, 0.9 to 1.5) between the patients treated with radiation vs chemotherapy.[21]

Treatment Algorithm



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Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial CNS Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial CNS Tumour Team who were not involved in the guideline's development, including neurosurgeons, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2026.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2027. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

CCA, Cancer Care Alberta; ASCO, American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; CT, computed tomography; IDH, Isocitrate dehydrogenase; NCCN, National Comprehensive Cancer Network; PCV, Procarbazine, lomustine and vincristine; RT, radiation therapy; SNO, Society for Neuro-Oncology; TMZ, temozolomide

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial CNS Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Ana Nikolic has nothing to disclose
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