Practical Radiation Oncology® (2022) 000, 1−17

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Clinical Practice Guideline

Radiation Therapy for IDH-Mutant Grade 2 and Grade 3 Diffuse Glioma: An ASTRO Clinical Practice Guideline

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Sources of support: This work was funded by the American Society for Radiation Oncology.

Disclosures: All task force members' disclosure statements were reviewed before being invited and were shared with other task force members throughout the guideline's development. Those disclosures are published within this guideline. Where potential conflicts were detected, remedial measures to address them were taken. **Albert Attia:** Novocure (consultant); **Lia Halasz (vice chair):** Abbvie (research-ended 2/2020), Kuni Foundation (research); **John Kirkpatrick:** BioMimitex (research), ClearSight RT Products (owner/partnership), Monteris (honoraria), Varian (research); **Nadia Laack:** BMS (research), National Institutes of Health (NIH) (research), Children's Oncology Group (vice chair, bone committee); **Joshua Palmer (Guideline Subcommittee representative):** Genentech (research), The Kroger Co (research), Novocure (advisory board-ended 12/2020), Varian (research and honoraria); **Katherine Peters (ASCO representative):** Abbvie, BioMimitex, Novocure and Varian (research), Boehringer-Ingelheim (research & advisory board-ended 8/2019), Bayer (advisory board-ended 8/2019), Eisai (other), Sapience Therapeutics and Servier (acquired Agios) (research and advisory board), Vivicitas Oncology (advisory board); **Jason Sheehan (American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) representative):** Neuropoint Alliance (board member); **Reena Thomas (Society for Neuro-Oncology (SNO) representative):** BMS and Eisai (research); **Daniel Wahl:** Agios (research), Lycera (stock); **Stephanie Weiss:** AstraZeneca, Regeneron, Pfizer (all stock); **D. Nana Yeboa:** Brockman Foundation and MD-Anderson Shirley Stein Award (research); and **Helen Shih (chair):** UpToDate (honoraria), Abbvie (research). **Lisa Bradfield, Daniel Brat (AANP representative), Nafisha Lalani, Emily Lebow, Arthur Liu, Heather Niemeier (patient representative), Sujay Vora, and Jim Zhong,** reported no disclosures.

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https://doi.org/10.1016/j.prro.2022.05.004

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Received 26 April 2022; accepted 4 May 2022

Abstract

Purpose: This guideline provides evidence-based recommendations for adults with isocitrate dehydrogenase (IDH)−mutant grade 2 and grade 3 diffuse glioma, as classified in the 2021 World Health Organization (WHO) Classification of Tumours. It includes indications for radiation therapy (RT), advanced RT techniques, and clinical management of adverse effects.

Methods: The American Society for Radiation Oncology convened a multidisciplinary task force to address 4 key questions focused on the RT management of patients with IDH-mutant grade 2 and grade 3 diffuse glioma. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.

Results: A strong recommendation for close surveillance alone was made for patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2 after gross total resection without high-risk features. For oligodendroglioma, WHO grade 2 with any high-risk features, adjuvant RT was conditionally recommended. However, adjuvant RT was strongly recommended for oligodendroglioma, WHO grade 3. A conditional recommendation for close surveillance alone was made for astrocytoma, IDH-mutant, WHO grade 2 after gross total resection without high-risk features. Adjuvant RT was conditionally recommended for astrocytoma, WHO grade 2, with any high-risk features and strongly recommended for astrocytoma, WHO grade 3. Dose recommendations varied based on histology and grade. Given known adverse long-term effects of RT, consideration for advanced techniques such as intensity modulated radiation therapy/volumetric modulated arc therapy or proton therapy were given as strong and conditional recommendations, respectively. Finally, based on expert opinion, the guideline recommends assessment, surveillance, and management for toxicity management.

Conclusions: Based on published data, the American Society for Radiation Oncology task force has proposed recommendations to inform the management of adults with IDH-mutant grade 2 and grade 3 diffuse glioma as defined by WHO 2021 classification, based on the highest quality published data, and best translated by our task force of subject matter experts.

Preamble

As the leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy — ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplemental materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members — ASTRO strives to avoid bias by selecting a multidisciplinary group of experts with variation in geographic region, gender, ethnicity, race, practice setting, and areas of expertise. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology — ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the Population, Intervention, Comparator, Outcome, Timing, Setting (PICOTS)

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ should"
Conditional	• Benefits are finely balanced with risks and burden, or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 1 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 2 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

* A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Supplemental materials, Appendix E2 for a list of abbreviations used in the guideline.

Consensus Development — Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree." A prespecified threshold of ≥75% (≥90% for expert opinion

recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates — Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, the Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Introduction

The optimal treatment strategies for adults with isocitrate dehydrogenase (IDH)−mutant grade 2 and grade 3 diffuse glioma have been controversial given clinical trials demonstrating improved progression-free survival (PFS) and/or overall survival (OS) with a variety of interventions. Interpretation of the evidence has been further complicated by heterogeneous study cohorts defined by histologic classifications, until recent years, when molecular markers have become both more available and more meaningful in prognostication.

The World Health Organization (WHO) Classification of Tumours of the Central Nervous System first incorporated biomarkers, most notably IDH-mutational and 1p/19q codeletion status, into an integrated diagnosis of diffuse glioma in 2016[3] (Fig. 1). This change was based on evidence that compared with histologic classification, IDH and 1p/19q codeletion status provided a more reproducible and clinically meaningful classification of diffuse glioma.[3] In the WHO 2021 classification,[4,5] IDH-wildtype diffuse glioma is clearly distinguished from IDH-mutant

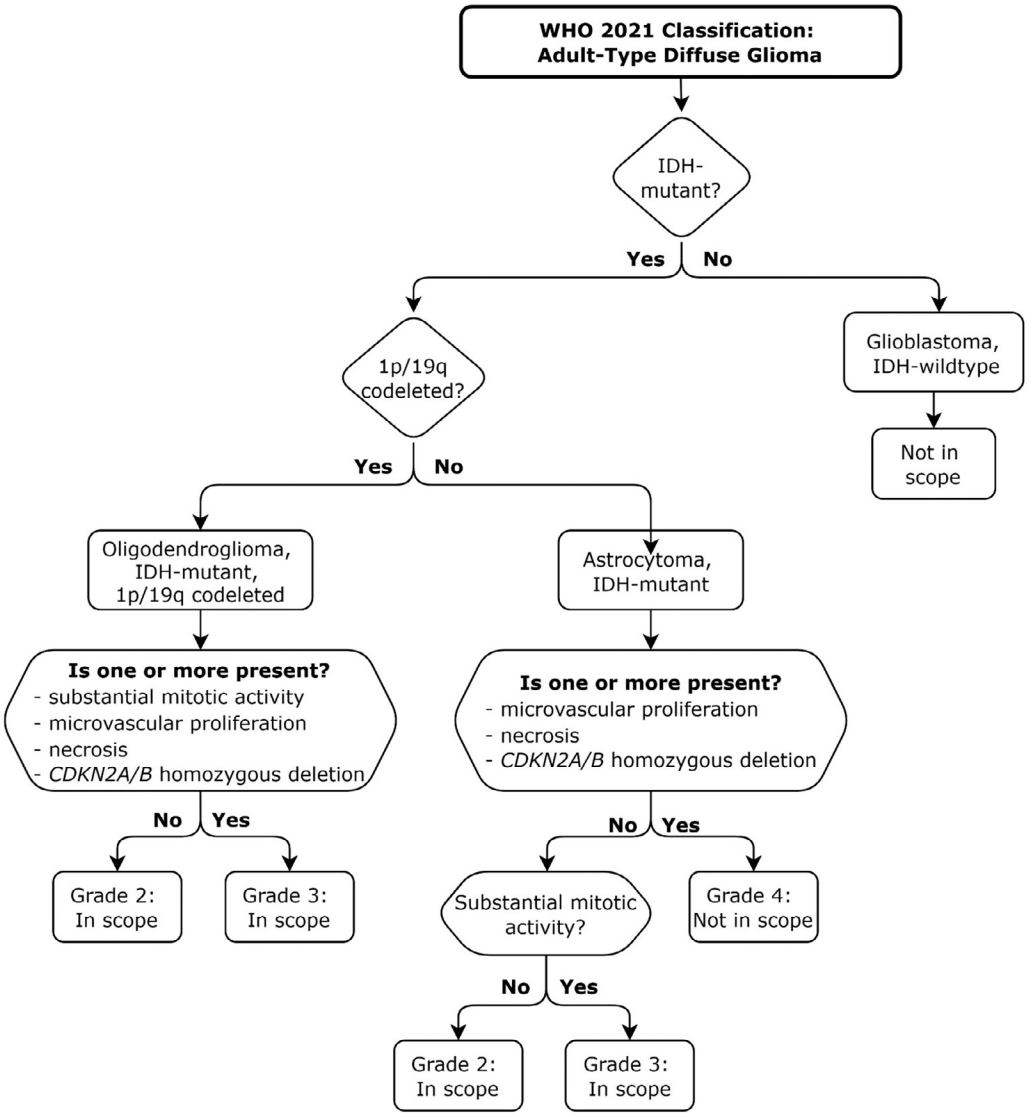


Fig. 1 WHO 2021 classification: Adult-type diffuse glioma.
Abbreviations: IDH = isocitrate dehydrogenase; WHO = World Health Organization.

diffuse glioma as a different clinical and genetic entity with a worse prognosis.[6,7] Although the WHO has continued to report grade based on morphologic features (mitotic activity, anaplastic nuclear features, microvascular proliferation, and necrosis), new molecular criteria are also used in forming an integrated diagnosis. IDH-wildtype diffuse glioma that display histologic features of grade 2 or 3, yet harbor specific molecular alterations (EGFR amplification, +7/−10 cytogenetic signature, or TERT promoter mutation) are now classified as glioblastoma, IDH-wildtype, WHO grade 4. For IDH-mutant diffuse astrocytoma, grade 4 is established based on morphologic criteria (microvascular proliferation and/or necrosis) or CDKN2A/B homozygous deletion, and these tumors are now called "astrocytoma, IDH-mutant, WHO grade 4."[4,5] The criterion for distinguishing grade 3 from grade 2 IDH-mutant astrocytoma is currently based on mitotic activity, yet its clinical utility for stratifying risk has been questioned.[8-11] Oligodendroglioma, IDH-mutant, 1p/19q codeleted, grade 3 is distinguished from grade 2 by substantial mitotic activity, microvascular proliferation, or necrosis. Furthermore, homozygous deletion of CDKN2A/B is a feature of grade 3, but not grade 2 oligodendroglioma.[12]

Studies regarding patterns of care in the United States for the treatment of IDH-mutant grade 2 and grade 3 diffuse glioma highlight the variation in use of RT in this patient population.[13,14] In Surveillance, Epidemiology, and End Results (SEER) data from 2000 to 2014, the incidences of nonglioblastoma astrocytic and oligodendroglial tumors were higher among non-Hispanic white individuals than those of other races. On multivariable analysis including extent of resection and age, there was no significant association between survival and any race or ethnicity group.[15] However, a SEER analysis of patients with supratentorial low-grade glioma from 1973 to 2001 found white race to be significantly associated with receiving surgery and improved survival.[16] The use of RT did not differ by race. A smaller series reported that individuals with lower socioeconomic status have lower survival rates compared with those with higher socioeconomic status.[17] Overall, relatively few analyses have examined racial, ethnic, and socioeconomic status disparities in the treatment of brain tumors.

This guideline aims to guide practitioners on the best management of patients with IDH-mutant grade 2 and grade 3 diffuse glioma, including astrocytoma and oligodendroglioma. Current clinical guideline development is challenged by the predication of the available evidence on histologic tumor classification and grading that was standard at the time the studies were conducted. The lack of IDH mutation and 1p/19q codeletion status in most studies complicates the application of these results to current clinical practice, which is now using the integrated molecular and histologic diagnoses of the 2021 WHO classification system. Also, it is recognized that the study cohorts considered in this guideline included patients with IDH-mutant diffuse glioma combined with IDH-wildtype and other high-grade glioma subtypes, which are not intended for this guideline. Ultimately, this guideline addresses the management of adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma as defined by WHO 2021 classification, based upon the highest quality data and best translated by our task force of subject matter experts.

Methods

Task force composition

The task force consisted of a multidisciplinary team of radiation oncologists, neuro-oncologists, a neurosurgeon, a neuropathologist, a radiation oncology resident, and a patient representative. This guideline was developed in collaboration with the American Association of Neurological Surgeons/Congress of Neurological Surgeons, the American Association of Neuropathologists, the American Society of Clinical Oncology, and the Society for Neuro-Oncology, who provided representatives and peer reviewers.

Document review and approval

The guideline was reviewed by 14 official peer reviewers (Supplementary Materials, Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from December 2021 through January 2022. The final guideline was approved by the ASTRO Board of Directors and endorsed by the Canadian Association of Radiation Oncology, European Society for Radiotherapy and Oncology, Royal Australian and New Zealand College of Radiologists, and Society for Neuro-Oncology.

Evidence review

A systematic search of human participant studies retrieved from the Ovid MEDLINE database was conducted for English publications from January 1996 (for randomized controlled trials [RCTs], meta-analyses, prospective studies) and January 2005 (for retrospective studies and dosimetric studies) through July 2020. The inclusion criteria for the literature review required studies to involve adults (age ≥18 years) with a diagnosis of WHO grade 2 or 3 glioma. Retrospective and dosimetric studies included were limited to more recent publications to reflect modern treatment techniques, whereas the date range for prospective studies allowed inclusion of primary trials in the evidence base. For KQ1, the literature review included studies with ≥50 participants. For KQ2, KQ3, and KQ4, there were no patient number limits set. For specific subquestions where there were limited data

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1.	**What are the indications and optimal timing for RT in adult patients with newly diagnosed or previously unirradiated IDH-mutant grade 2 and grade 3 diffuse glioma based on risk stratification?**			
	Adults with IDH-mutant grade 2 and grade 3 diffuse glioma	• RT	• Surgery alone • Surgery + Chemotherapy	• Local control • PFS • Overall survival • Local failure • Local progression • Toxicity
2.	**What is the optimal dose of RT and target volume for adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma based on risk stratification?**			
	Adults with IDH-mutant grade 2 and grade 3 diffuse glioma	• RT • Imaging modalities	N/A	• Local control • PFS • Overall survival • Local failure • Local progression • Toxicity
3.	**What are the optimal RT techniques and field design for adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma?**			
	Adults with IDH-mutant grade 2 and grade 3 diffuse glioma	• IMRT/VMAT • Protons • SRS • Brachytherapy	• 3-D CRT	• Local control • PFS • Overall survival • Local failure • Local progression • Toxicity
4.	**What are the adverse effects of RT and subsequent clinical management for adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma?**			
	Adults with IDH-mutant grade 2 and grade 3 diffuse glioma	• RT	N/A	• Neurocognitive function • Neuroendocrine function • Hearing • Vision • Permanent alopecia • Quality of life • Other toxicities

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; IDH = isocitrate dehydrogenase; IMRT = intensity modulated radiation therapy; KQ = key question; N/A = not applicable; PFS = progression-free survival; PICO = Population, Intervention, Comparator, Outcome; RT = radiation therapy; SRS = stereotactic radiosurgery; VMAT = volumetric modulated arc therapy.

available, expert opinion was relied upon to support recommendations as reflected in the low-to-moderate quality of evidence cited in these cases.

The following concepts were searched using Medical Subject Heading (MeSH) terms and key search terms: *glioma, astrocytoma, oligodendroglioma, oligoastrocytoma, IDH-mutant glioma, low-grade, grade 2/II, grade 3/III, WHO classification, radiotherapy, radiation therapy, brachytherapy, external beam radiation therapy, intensity modulated radiation therapy, protons, photons, irradiation, chemotherapy, chemoradiation, radiosurgery, and neoplasm recurrence.* Additional terms specific to the KQs and hand searches supplemented the electronic searches. Preclinical/nonhuman studies, health economics and cost analyses, large registry/database studies, abstracts, review articles, comments, and editorials were excluded.

The data used by the task force to formulate recommendations are summarized in evidence tables available in Supplemental materials, Appendix E4. References selected and published in this document are representative and not all-inclusive. The outcomes of interest are listed in Table 2. Most salient of these are local control, PFS, OS, recurrence rates, acute and late toxicity, and quality of life (QoL).

See the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing

the number of articles screened, excluded, and included in the evidence review, and Supplemental Materials, Appendix E3 for the complete literature search strategy, which includes the evidence search parameters and inclusion/exclusion criteria.

Scope of the guideline

The scope of this guideline is focused on patients with astrocytoma, IDH-mutant, WHO grade 2; astrocytoma, IDH-mutant, WHO grade 3; oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2; and oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 3 (Fig. 1). This guideline does not cover patients <18 years of age; reirradiation; glioblastoma, IDH-wildtype, WHO grade 4; astrocytoma, IDH-mutant, WHO grade 4, astrocytoma with CDKN2A/B homozygous deletion; pediatric-type diffuse low-grade glioma; pediatric-type diffuse high-grade glioma; circumscribed astrocytic glioma; glioneuronal and neuronal tumors; ependymal tumors; or disseminated disease.

This guideline addresses only the subjects specified in the KQs (Table 2). Outside the scope of this guideline are many other important questions that may be subjects of other guidelines, including the optimal treatment of WHO grade 4 or IDH-wildtype glioma, brainstem glioma, gliomatosis cerebri, disseminated disease, or salvage treatment after initial radiation therapy (RT).

Key Questions and Recommendations

KQ1: Indications and timing for RT (Table 3)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ1 and Figure 2 for a visual representation of the recommendations.

What are the indications and optimal timing for RT in adult patients with newly diagnosed or previously unirradiated IDH-mutant grade 2 and grade 3 diffuse glioma based on risk stratification?

Table 3 Indication and timing for RT

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
Oligodendroglioma, IDH-mutant, and 1p/19q codeleted		
1. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2, <4-6 cm tumor, with gross total resection (defined as <1 cm residual tumor on MRI) and age <40 y, close surveillance alone is recommended.	Strong	Low [18,19]
2. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2, with high-risk features, either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy is conditionally recommended. Implementation remark: High-risk features include any of the following: subtotal resection, age ≥40 y, tumor size ≥4-6 cm, tumor crosses midline, refractory seizures, or presurgical neurologic symptoms from tumor.	Conditional	Low [19-24]
3. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 3, with any extent of surgery, either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy is recommended.	Strong	Moderate [25-29]
Astrocytoma, IDH-mutant		
1. For patients with astrocytoma, IDH-mutant, WHO grade 2, <4-6 cm tumor, with gross total resection (defined as <1 cm residual tumor on MRI), and age <40 y, close surveillance alone is conditionally recommended.	Conditional	Low [18,19]
2. For patients with astrocytoma, IDH-mutant, WHO grade 2, with high-risk features, either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy is conditionally recommended. Implementation remark: High-risk features include any of the following: subtotal resection, age ≥40 y, tumor size ≥4-6 cm, tumor crosses midline, refractory seizures, or presurgical neurologic symptoms from tumor.	Conditional	Low [19-24,30]
3. For patients with astrocytoma, IDH-mutant, WHO grade 3, with any extent of surgery, either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy is recommended.	Strong	Low [27,28,31]

Abbreviations: IDH = isocitrate dehydrogenase; KQ = key question; MRI = magnetic resonance imaging; RT = radiation therapy; WHO = World Health Organization.

The optimal indications and timing for RT in patients with IDH-mutant diffuse glioma are largely based on data from RCTs[19,21] designed for patients with low-grade glioma, including grade 2 oligodendroglioma and astrocytoma. IDH mutation and 1p/19q codeletion were not initially tested in many of these trials; however, these trials included currently defined IDH-mutant grade 2 and grade 3 diffuse glioma. European Organization for Research and Treatment of Cancer (EORTC) 22845[19] randomized patients 16 to 65 years of age with a good WHO performance status and grade 2 glioma to early adjuvant RT versus RT at progression. Overall, PFS was significantly extended in the early RT group; however, median OS was comparable at 7.2 years and 7.4 years, respectively.[21] Based on EORTC 22845, which showed that adjuvant RT after surgery improved PFS but not OS for patients with low-grade glioma, historically, those with better prognosis (ie, low risk) have been recommended observation and those with poor prognostic factors (ie, high risk) have been recommended to undergo adjuvant RT.[19,21] Importantly, the majority of those observed will eventually have recurrence and undergo RT. This trial did not include IDH status or sequential chemotherapy, which is now standard of care based on Radiation Therapy Oncology Group (RTOG) 9802.[20] Given the limitations of past RCTs that either addressed a heterogeneous study group, did not include chemotherapy, or did not have RT timing as the primary study question, the quality of evidence for recommendations was rated low for this KQ, with the exception of the recommendation for grade 3 oligodendroglioma. Further studies outlined in the following sections have refined our recommendations based on 1p/19q codeletion status.

Oligodendroglioma, IDH-mutant, and 1p/19q codeleted

Optimal treatment for grade 2 oligodendroglioma is evolving.[20,24] In RTOG 9802, patients with low-risk (ie, gross total resection and age <40 years) grade 2 glioma underwent close surveillance without immediate adjuvant therapy.[18] Treatment was given only if radiographic or clinical progression occurred. Gross total resection was defined as <1 cm residual disease on magnetic resonance imaging (MRI). Although the trial included both oligodendroglioma and astrocytoma, it is notable that the 5-year PFS after close surveillance for the entire cohort was 48% whereas it was 70% for the favorable subgroup of oligodendroglioma, tumor <4 cm, and <1 cm of residual disease.[18] This led to a recommendation for close surveillance with MRI and examination every 6 months for patients with a more favorable prognosis, including age <40 years, tumor <4 to 6 cm, and gross total resection. The range 4 to 6 cm for designating high-risk tumor size was adopted in the recommendation given the available data. Although RTOG 9802 identified tumors >4 cm as high risk, analysis of EORTC 22845 identified >5 cm as a high-risk factor and Pignatti criteria used >6 cm.[18,21,22] Close regular surveillance may enable appropriately selected patients to delay the treatment and associated side effects of chemotherapy and RT.

Although it did not address the timing of RT, RTOG 9802 did provide prospective data for patients with high-risk (ie, subtotal resection and/or age ≥40 years) grade 2 oligodendroglioma treated with RT and adjuvant procarbazine, lomustine, and vincristine (PCV), where OS appeared superior to historical data.[18] Importantly, the primary outcome of RTOG 9802 was improved 10-year PFS (51% vs 21%) and OS (60% vs 40%) for patients with grade 2 glioma (including oligodendroglioma or astrocytoma) treated with RT and adjuvant PCV after surgery compared with RT alone. Median OS was improved from 7.8 to 13.3 years.[20,24] Based on these results and data from EORTC 22845,[19] which showed improved PFS for patients with grade 2 glioma treated with adjuvant RT compared with surveillance alone, it is recommended that after a discussion of the potential benefits, adjuvant therapy after surgery is appropriate for patients with any high-risk features. These risk features are based on multiple studies or trials that have identified a worse PFS with surveillance alone.[18,20-23] Along with subtotal resection, adverse risk factors for histologic grade 2 oligodendroglioma include larger tumor size (defined range of ≥4 to ≥6 cm in different studies), tumor crossing midline, and refractory seizures or presurgical neurologic deficits due to tumor.[18,21,22] In EORTC 22844 and 22845,[19,21] neurologic deficit was defined as causing moderate (eg, able to move limbs only with difficulty, moderate dysphasia, moderate paresis, some visual disturbances) or major (eg, inability to use limbs, gross speech or visual disturbances) functional impairment.[22] Although several of these trials have identified age ≥40 years as a high-risk feature, the challenge with identifying a concrete cut off for age to determine immediate adjuvant treatment includes the fact that none of these trials focused specifically on oligodendroglioma, and a meta-analysis suggested that age was less prognostic when adjusting for other factors.[23] Overall, current data support patients with high-risk features as benefiting from early adjuvant therapy, while those deemed truly low risk may be managed under close surveillance. However, the recommendation is conditionally made given the lack of OS benefit with adjuvant RT versus surveillance in EORTC 22845 and the absence of RCTs regarding the timing of either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy.

Though in past studies, grade 3, or "anaplastic" oligodendroglioma, has been separated from grade 2 oligodendroglioma in clinical trials, it is important to note that both grade 2 and grade 3 oligodendroglioma have relatively favorable long-term outcomes. The RTOG 9402 trial including anaplastic oligodendroglioma and oligoastrocytoma initially reported a PFS benefit for sequential PCV followed by RT compared with adjuvant RT alone.[27]

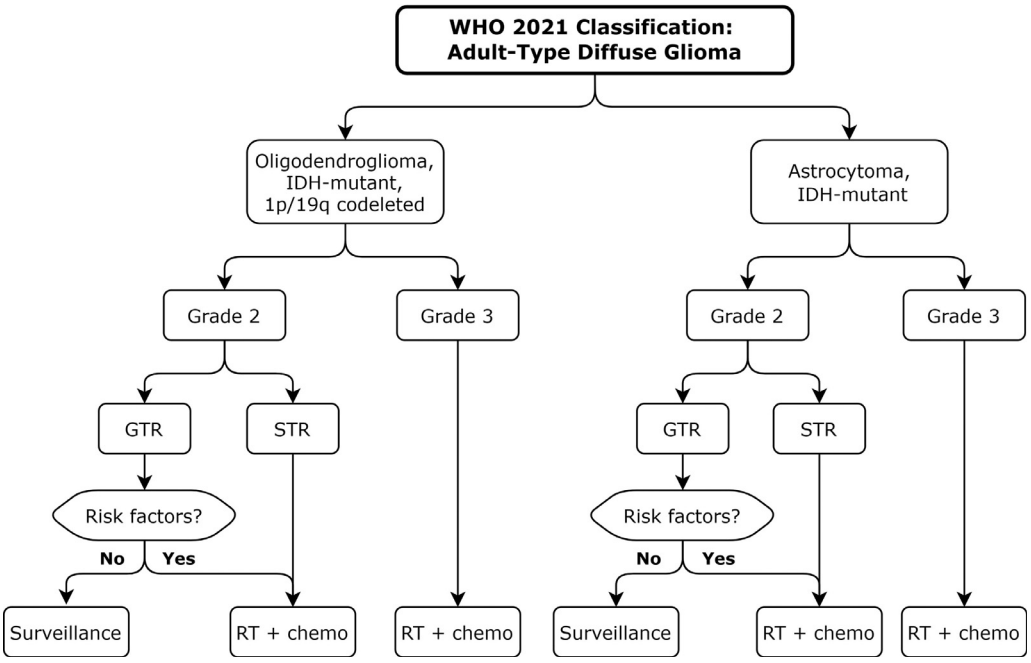


Fig. 2 IDH-mutant diffuse glioma: indications and timing for RT.
Abbreviations: chemo = chemotherapy; GTR = gross total resection; IDH = isocitrate dehydrogenase; RT = radiation therapy; RT + chemo = RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy; STR = subtotal resection (including biopsy); WHO = World Health Organization.

The EORTC 26951 RCT evaluated a reversed sequence of RT followed by PCV compared with RT alone for anaplastic oligodendroglioma and oligoastrocytoma and found a similar improvement in PFS.[25] Importantly, both trials included only a subset of oligodendroglioma that harbored 1p/19q codeletion. In both trials, the patients with confirmed 1p/19q codeletion (22% in EORTC 26951 and 43% in RTOG 9402) had longer survival and greater benefit with PCV.[25,27] Long-term results of RTOG 9402 confirmed that patients with 1p/19q codeleted tumors treated with PCV and RT lived twice as long as those treated with RT alone (14.7 vs 7.3 years).[29] In EORTC 26951, the overall study population experienced improved survival with PCV with more benefit for tumors with 1p/19q codeletion (with median follow-up of 140 months, OS was not reached in the RT plus PCV group vs 112 months in the RT alone group).[26] Although both sequential approaches are acceptable, conventional clinical practice favors the use of RT first based on the higher percentage of patients who experienced RT delay/interruption in RTOG 9402 (39/147) compared with those who did not start RT in the EORTC trial (n = 5/185).[25,27]

Of note, temozolomide (TMZ) is often used instead of PCV for treatment of glioma.[32] Recommendations for chemotherapy regimens are beyond the scope of this guideline, though it is important to note that we are currently awaiting further data from the clinical trial Codeleted Anaplastic Glioma or Low-Grade Glioma (CODEL), which compares adjuvant RT followed by PCV versus adjuvant RT with concurrent and sequential TMZ (*NCT00887146*). Overall, published trials support the practice of planned RT with sequential chemotherapy based on the EORTC and RTOG studies.[25-27,29]

Astrocytoma, IDH-mutant

Although the timing of RT has also not been studied in an RCT specifically for IDH-mutant astrocytoma as a distinct group, RTOG 9802 reported a 5-year PFS of 48% and 5-year OS of 93% after gross total resection alone for young patients with grade 2 glioma (61 astrocytoma or oligoastrocytoma and 50 oligodendroglioma) without knowledge of IDH status.[20] Though overall these results led to a recommendation for younger patients age <40 years with gross total resection and <4 to 6 cm tumor to proceed initially with close surveillance alone,[21] given the finding that astrocytoma was a poor prognostic factor compared with oligodendroglioma, the recommendation is conditionally made. Further data are expected from the ongoing EORTC trial "wait or treat (IWOT)," which randomizes patients with grade 2 or 3 astrocytoma, IDH-mutant without 1p/19q codeletion to early treatment with RT to 5040 cGy and TMZ or close surveillance. Exclusion criteria include functional deficits due to tumor, uncontrolled seizures, and residual enhancing disease (*NCT03763422*).

A conditional recommendation is included for patients with astrocytoma, IDH-mutant, WHO grade 2, with high-risk features to receive adjuvant RT based on

EORTC 22845 showing improvement in PFS.[19,21] The recommendation further includes sequential chemotherapy or concurrent/sequential chemotherapy based on the results of the randomized arms in RTOG 9802, which included patients with high-risk grade 2 astrocytoma, oligodendroglioma, and oligoastrocytoma. High risk was defined as patients ≥40 years, regardless of extent of surgery, or patients 18 to 39 years of age with less than a gross total resection.[20] In RTOG 9802, RT with sequential chemotherapy (PCV) was superior to RT alone, with median OS of 13.3 years for the combination arm and 7.8 years for RT alone.[24] In addition, RTOG 0424, a prospective nonrandomized study, demonstrated that if the patient had a low-grade glioma with 3 or more risk factors for recurrence (age ≥40 years, astrocytoma histology, tumor size ≥6 cm, tumor crossing midline, or moderate-to-severe preoperative neurologic deficits), concurrent TMZ and RT followed by adjuvant TMZ improved outcomes in comparison to historical controls.[30] Finally, significant improvement in 1-year control of refractory seizures has been demonstrated in an RCT comparing early adjuvant RT with RT at disease progression; thus, the spectrum of potential benefits should be considered when deciding when to initiate RT for these patients.[21]

Patients with grade 3 IDH-mutant astrocytoma have been included in multiple trials supporting adjuvant chemotherapy and RT, though often as a subset of the study population.[27,31] There is still some controversy over the timing of RT, with the current EORTC "IWOT" trial including these patients in an observational arm; however, most trials have included adjuvant therapy for grade 3 astrocytoma.[27,28,31] Although the RTOG 9402 trial for anaplastic oligodendroglioma did not focus on histopathologic anaplastic astrocytoma, it is now presumed that the 137 patients with tumors that lacked codeletion of 1p/19q (out of 268 patients with known 1p/19q status) likely had anaplastic astrocytoma.[29] Importantly, IDH status was not available when the study was originally designed. Thus, the cohort likely also included patients with IDH-wildtype tumors that are now classified as WHO grade 4 tumors, more closely related to glioblastoma and outside the scope of this paper. Despite the heterogeneity of the study population in RTOG 9402, the combination of sequential RT and intensive PCV therapy improved OS compared with RT alone when all patients were considered, without regard to their 1p/19q codeletion status.[27] Similarly, the Phase III Trial of Anaplastic Glioma Without 1p/19q LOH (CATNON) (EORTC 26053-22054) included grade 3 IDH-mutant astrocytoma, but also IDH-wildtype astrocytoma, which would be considered glioblastoma in the 2021 WHO classification.[4,31] This trial randomized patients with anaplastic astrocytoma to RT alone, RT with concomitant TMZ, RT with adjuvant TMZ, and RT with concomitant followed by adjuvant TMZ. At interim analysis, OS was improved with adjuvant TMZ. Finally, monotherapy after surgery with either chemotherapy or RT alone failed to demonstrate superiority of any of the 3 arms for grade 3 IDH-mutant astrocytoma in an RCT comparing RT versus PCV versus TMZ.[28] Taken together, either RT with sequential chemotherapy or RT with concurrent/sequential chemotherapy is recommended for patients with IDH-mutant, WHO grade 3 astrocytoma.

KQ2: RT dose and target volume (Table 4)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ2.

What is the optimal dose of RT and target volume for adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma based on risk stratification?

The dose recommendation for IDH-mutant grade 2 diffuse glioma is based upon high quality of evidence in the published literature for grade 2 diffuse glioma, understanding that IDH-mutant glioma represents a subset of the study population in these trials.[19,21,33-37] EORTC 22844[36] and the Intergroup (NCCTG/RTOG/ECOG) trial[37] were both low-grade glioma RCTs that studied optimal dose of RT. EORTC 22844 randomized between 4500 and 5940 cGy whereas the Intergroup trial compared 5040 to 6480 cGy. There was no benefit to dose escalation in either trial; in fact, there were greater toxicities with the higher doses in both studies such that the community has moved forward with the current most common dose of 5400 cGy. To balance the goals of maximizing PFS and minimizing acute- and late-term toxicity, the prescription dose required for these tumor types is lower than for grade 3 glioma encompassed in this guideline. A systematic review and meta-analysis concluded that moderate doses of 4500 to 5500 cGy appear to be as effective as higher doses (5900-6500 cGy) for patients harboring grade 2 glioma.[23] In EORTC 22845, a dose of 4500 cGy to the primary gross tumor volume (GTV) was used with a 900 cGy boost to treat patients with low-grade astrocytoma or oligodendroglioma.[19,21] Significant acute toxicity in EORTC 22845 were rare and included skin erythema, otitis, vomiting, headache, and alopecia. In another study, a dose of 5400 cGy in 180 cGy daily fractions was used for the management of oligodendroglioma and mixed oligoastrocytoma patients with no toxicity of grade >2 reported.[34] Although these studies did not use the current mutational scheme for inclusion criteria, they represent acceptable doses for grade 2 diffuse glioma and were extrapolated to recommend a prescribed dose of 4500 to 5400 cGy in daily 180 cGy fractions.

Among patients with grade 3 diffuse glioma, there are subtle differences in RT recommendations based upon subtype. For patients with oligodendroglioma, IDH-

Table 4 Optimal dose of RT and target volume based on risk stratification

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2 and astrocytoma, IDH-mutant, WHO grade 2, a total prescribed dose of 4500-5400 cGy in 180 cGy daily fractions is recommended.	Strong	High [19,21,33-37]
2. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 3, a total prescribed dose of 5940 cGy in 180 cGy daily fractions is recommended.	Strong	Moderate [26,27,29,38]
3. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 3, a total prescribed dose of 5400-5760 cGy in 180 cGy daily fractions is conditionally recommended as a treatment option.	Conditional	Expert opinion [19,34,36]
4. For patients with astrocytoma, IDH-mutant, WHO grade 3, a total prescribed dose of 5940-6000 cGy in 180-200 cGy daily fractions is recommended.	Strong	Moderate [31,38]
5. For patients with astrocytoma, IDH-mutant, WHO grade 3, a total prescribed dose of 5400-5800 cGy in 180-200 cGy daily fractions is conditionally recommended as a treatment option.	Conditional	Expert opinion [19,36]
6. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2 and astrocytoma, IDH-mutant, WHO grade 2, the following target volumes defined by MRI are recommended: • GTV = residual FLAIR changes, resection cavity, and any residual tumor enhancement on T1 postcontrast • CTV = GTV + 10-15 mm expansion • PTV = CTV + 3-5 mm expansion	Strong	Low [18,21,39]
7. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 3 and astrocytoma, IDH-mutant, WHO grade 3, the following target volumes defined by MRI are recommended: • GTV = residual FLAIR changes, resection cavity and any residual enhancement on T1 postcontrast • CTV = GTV + 10-15 mm expansion • PTV = CTV + 3-5 mm expansion **OR, if cone-down/booth is desired:** • GTV1 = residual FLAIR changes, resection cavity, and any residual enhancement on T1 postcontrast • GTV2 = residual enhancement on T1 postcontrast and resection cavity • CTV1/2 = GTV1/2 + 10-15 mm expansion • PTV1/2 = CTV1/2 + 3-5 mm expansion	Strong	Low [25,27,39]

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; IDH = isocitrate dehydrogenase; KQ = key question; MRI = magnetic resonance imaging; PTV = planning target volume; RT = radiation therapy; WHO = World Health Organization.

mutant, 1p/19q codeleted, WHO grade 3, the dose 5940 cGy delivered in 180 cGy daily fractions is recommended based on multiple RCTs that used this dose regimen.[26,27,29,38] Similarly, for patients with astrocytoma, IDH-mutant, WHO grade 3, the recommended dose range is 5940 to 6000 cGy delivered in 180 to 200 cGy daily fractions.[31,38] Given the inclusion of astrocytoma, IDH-mutant, WHO grade 3 in trials with 6000 cGy in 200 cGy fractions, the slightly different fractionation scheme was included.[41] A conditional recommendation based on expert opinion with somewhat lower doses is also included because data have emphasized that categorization based on IDH and 1p/19q status is associated with less aggressive tumor despite designation as grade 3.[4,19,36] As such, a dose range with lower limit of 5400 cGy may be considered, as this is the historical upper range of dose used for low-grade glioma. Given that there are no RCT data comparing different dose regimens for this patient cohort, the quality of evidence for this recommendation is moderate (where large prospective studies exist) or expert opinion (where the task force determined practice variation is acceptable).

Target volumes for grade 2 diffuse glioma are based on patterns of failure studies demonstrating 80% to 90% of recurrences occurring within 20 mm of the cavity for low-grade glioma.[18,21,39] Many of the historical studies used computed tomography (CT) based studies with margins of 20 mm to block edge for radiation treatment planning.[20,36] Overall, trials have used various methods of

target delineation. However, contemporary trials have used GTV to clinical target volume (CTV) margins of 10 to 15 mm with predominantly MRI-based planning.[30] As such, it is recommended that target volumes be defined by MRI for patients with grade 2 IDH-mutant diffuse glioma. For tumors that have undergone gross total or subtotal resection, the GTV is generated by contouring the residual T2/FLAIR (refers to T2 or Fluid attenuated inversion recovery (FLAIR))-weighted hyperintense volume, resection cavity, and T1-weighted residual contrast-enhancing tissue (if present) on a postoperative MRI and fused to the planning CT scan. For tumors that have undergone biopsy only, the GTV is generated by contouring the T2/FLAIR-weighted hyperintense volume and T1-weighted contrast-enhancing tissue on an MRI. In either case, to account for subclinical extension of tumor,[39] a CTV is created by uniformly expanding the GTV by 10 to 15 mm while respecting anatomic boundaries (eg, the osseous skull, ventricles, falx, and tentorium). When the CTV involves routes of spread along white matter tracts (eg, the corpus callosum or brainstem), the CTV should not be cropped in these structures, even when it crosses midline.

Target delineation in trials of grade 3 diffuse glioma have also varied, but generally were treated with slightly larger CTV margins compared with grade 2.[25,27] However, more recent studies outline the same volume delineation principles for grade 2 diffuse glioma that have been applied to grade 3 IDH-mutant diffuse glioma.[39] The GTV should include the surgical resection cavity with any rare residual enhancement on T1 postcontrast and T2/FLAIR signal. Standard approaches include a CTV margin of 10 to 15 mm with the use of MRI imaging.[20,25,39] Alternatively, a 2-phase approach may be considered including a boost to any residual enhancement on T1 postcontrast imaging.[29,42]

Finally, the planning target volume (PTV) margins are then added to account for set-up uncertainty, including MRI fusion accuracy, mask immobilization, patient movement, patient set-up uncertainties within and between fractions, and beam characteristics. This guideline recommend expansion of CTV by 3 to 5 mm, assuming that image guidance is used as addressed in KQ3. The task force acknowledges that PTV expansion depends on the reproducibility of daily set-up for the particular immobilization and treatment system, and thus is treatment-center specific, though this range has been reported in the literature reviewed. The quality of evidence for these expansion recommendations is low and reflects the consensus opinion of the task force members.

KQ3: RT techniques and field design (Table 5)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ3.

What are the optimal RT techniques and field design for adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma?

Historically, IDH-mutant grade 2 and grade 3 diffuse glioma was treated using 2-dimensional (2-D) conventional RT, which consisted of a finite number of beams with field boundaries drawn on plain radiographs obtained during simulation. Beam shaping or field design was limited, producing low conformality of CTV and

Table 5 Optimal RT techniques and field design

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma, IMRT/VMAT is recommended to reduce acute and late toxicity, especially for tumors located near critical OARs.	Strong	Low [43-46]
2. For patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma, 3-D CRT is recommended as a treatment option, when IMRT/VMAT is unavailable.	Strong	Moderate [20,25,27,29,38,47]
3. For patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma, proton therapy is conditionally recommended as an option to reduce acute and late toxicity, especially for tumors located near critical OARs.	Conditional	Low [43,45,48-52]
4. For patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma, optimization of radiation field design is recommended to ensure target coverage and OAR avoidance.	Strong	Moderate [20,21,28,40,47]
5. For patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma receiving RT, daily image guidance is recommended.	Strong	Expert opinion

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; IDH = isocitrate dehydrogenase; IMRT = intensity modulated radiation therapy; KQ = key question; OARs = organs at risk; RT = radiation therapy; VMAT = volumetric modulated arc therapy; WHO = World Health Organization.

doses of radiation to adjacent normal structures similar to that intended for tumor. This technique was supplanted with the use of CT-based simulation, which allowed for improved treatment planning and field design using 3-dimensional conformal RT (3-D CRT) where tumor volumes and normal tissues are delineated allowing improved shielding of normal tissues and CTV conformality. In prior EORTC, North Central Cancer Treatment Group (NCCTG), and RTOG studies, 2-D planning and 3-D CRT were allowed, but given the conformality and normal tissue dosimetric superiority with 3-D CRT, the majority of patients treated in these trials received 3-D CRT using multiple noncoplanar beams. These large randomized cooperative group trials demonstrated that excellent clinical outcomes may be achieved with the use of 3-D CRT for patients with IDH-mutant grade 2 and 3 glioma.[20,25,27,29,38,47]

High rates of long-term survival after treatment and improvement in the detection of late radiation toxicity have led to the use of more sophisticated techniques for diffuse glioma, including intensity modulated radiation therapy (IMRT) inclusive of volumetric-modulated arc therapy and proton therapy, which allow for high doses to tumor with lower doses to normal tissue. No RCTs have been performed comparing 3-D CRT to IMRT/volumetric modulated arc therapy or proton therapy (VMAT). Retrospective studies report on outcomes after IMRT,[43-46] which is currently being used as the control arm of NRG BN005 (*NCT03180502*), an RCT evaluating neurocognitive outcomes for patients with IDH-mutant grade 2 glioma after proton therapy versus IMRT. Proton therapy has been examined in dosimetric and retrospective studies, as well as in a small prospective nonrandomized trial.[43,45,48-52] Two retrospective studies have looked at the incidence of pseudoprogression or radionecrosis after IMRT or proton therapy for grade 2 and 3 gliomas.[43,45] One of these series suggests that patients with oligodendroglioma, but not astrocytoma, develop pseudoprogression earlier after protons compared with photons.[43] The second series could not determine whether there was a difference in radionecrosis between the 2 modalities, but did identify oligodendroglioma histology as a risk factor.[45] Further studies (eg, NRG BN005) are required to fully understand the toxicities and outcomes after IMRT versus proton therapy. Thus, a strong recommendation is made for IMRT and a conditional recommendation for proton therapy as an option, based on low quality of evidence given the limitations of available data.

Because the standard of care for IDH-mutant grade 2 and grade 3 diffuse glioma has been partial brain RT, optimization of radiation fields to spare organs at risk (OARs) and provide full coverage of the CTV is a strong recommendation. OAR dose tolerance recommendations are beyond the scope of this guideline, but the importance of considering dose tolerance has been emphasized. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) papers are systematic reviews of dose tolerances that serve as good references for guidance.[53-57] Of note, because of the longer survival of patients with IDH-mutant grade 2 and grade 3 diffuse glioma, acceptable tissue tolerances may be different than those followed for treatment of higher grade glioma such as glioblastoma.[24,26,29] The prescription dose may also inform OAR goals and constraints.

Recognizing the lack of evidence and need for physics measurement of uncertainty to guide PTV, daily image guidance to reduce PTV margins is recommended based on expert opinion. Acceptable techniques include using orthogonal (kV) or volumetric imaging (ie, cone beam and megavoltage CT). Using these techniques to allow a reduction in PTV allows for improved radiation planning to achieve greater conformality and achieve dose volume constraints.

KQ4: Adverse effects and clinical management (Table 6)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ4.

What are the adverse effects of RT and subsequent clinical management for adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma?

Patients with IDH-mutant grade 2 and grade 3 diffuse glioma may present with disease-related neurologic deficits. In addition to these baseline symptoms, surgery, cranial RT, and chemotherapy for patients with glioma may result in treatment-related toxicity. Higher doses of RT

Table 6 Adverse effects of RT

KQ4 Recommendation	Strength of Recommendation	Quality of Evidence
1. For patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma, assessment, surveillance, and management by an interprofessional and/or multidisciplinary care team is recommended for toxicity management (Table 7).	Strong	Expert opinion

Abbreviations: IDH = isocitrate dehydrogenase; KQ = key question; RT = radiation therapy; WHO = World Health Organization.

Table 7 Multidisciplinary care team management for common toxicities

Toxicities	Management Considerations − Baseline and Ongoing (As Needed)
Neurocognitive function	Neuropsychological testing (where available)
Neuroendocrine function	Pituitary function testing for patients with hypothalamic/pituitary axis within the radiation treatment field or with clinical symptoms
Neurologic deficit	Rehabilitation medicine (including physical therapy and occupational therapy)
Vision	Acuity and visual field testing for patients with optic pathway within the radiation treatment field or with clinical symptoms
Hearing	Auditory and vestibular testing for patients with cochlea within the radiation treatment field or with clinical symptoms
Permanent alopecia	Wig and hair loss consultation (where available)
Cerebrovascular complications	Vascular medicine consultation (with neurologist and/or neurosurgeon)
Financial/psychosocial	Social services (eg, social worker, adolescent and young adult-life specialist, and financial counselor)
Quality of life	Survivorship and supportive care (eg, palliative care provider, onco-psychologist, and mental health counselor)

may be associated with an increased risk of acute and long-term effects in comparison to lower RT doses.[58]

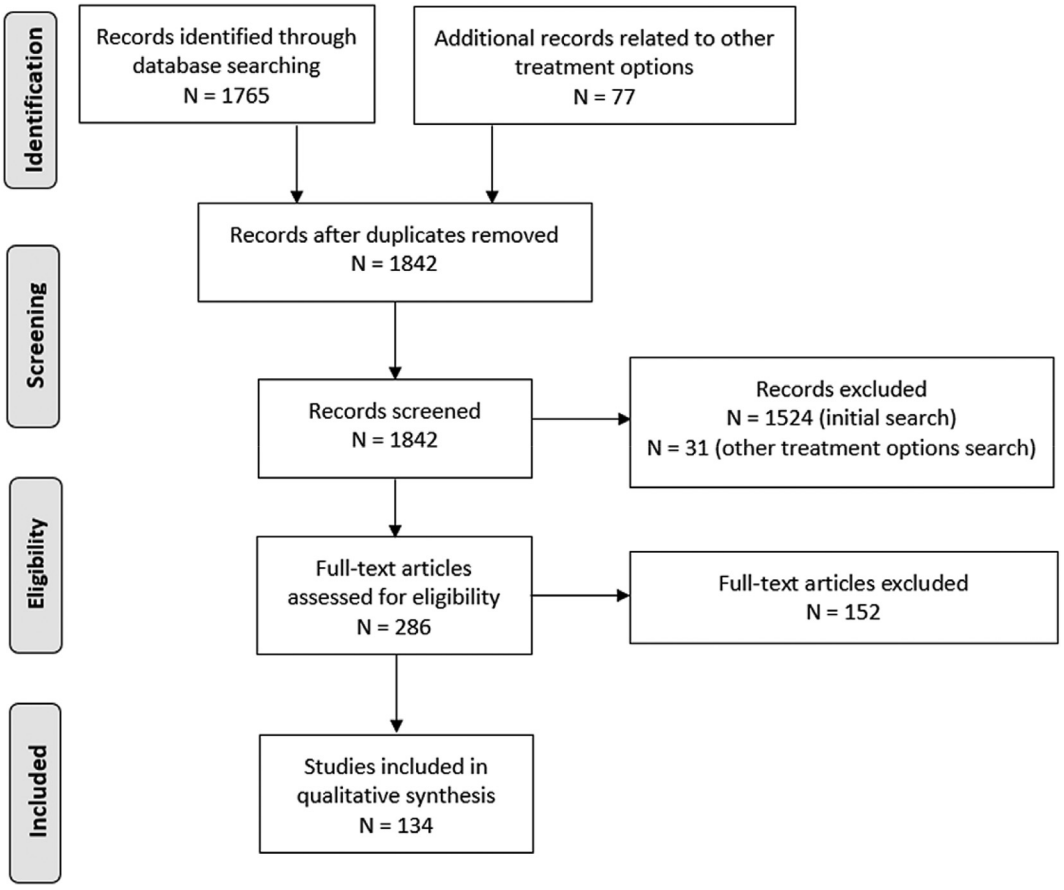
Acute effects of RT and chemotherapy may include neurologic effects (10%), constitutional symptoms (9%), dermatitis (4%), gastrointestinal symptoms (5%), musculoskeletal effects (5%), and sexual/reproductive dysfunction (<5%) in patients.[40,59] Acute side effects directly attributable to RT include fatigue, weight loss, headache, skin erythema, otitis, nausea/vomiting, and alopecia.[19,21,24,27,36-38,60] The development of radionecrosis has been reported in 0 to 13% of patients, with higher doses and oligodendroglioma histology associated with increased risk.[37,61,62] Overall, the development of any grade 3 acute toxicity is expected in 0 to 14% of patients.[37,62] RT may also entail long-term effects on cognitive function[47,63,64] and/or health-related QoL.[35,58,60,63,65] Given the effect of progressive disease or chemotherapy on health-related QoL, some studies did not find that receipt of RT was associated with decreased health-related QoL for patients with grade 2 and grade 3 glioma.[35,48,58,60,63,65,66] Although many acute toxicity will resolve with time, there are late effects that will require follow-up and management. The task force recommends survivorship care including assessment, surveillance, and management by a multidisciplinary care team, as guided by Table 7.

Conclusions and Future Directions

Adjuvant RT after surgery remains a cornerstone of therapy for patients with IDH-mutant grade 2 and grade 3 diffuse glioma to improve PFS. However, the optimal timing of RT remains controversial. Based on the available evidence, this guideline recommends that some low-risk patients, including those with gross total resection and lacking high-risk features, should be initially observed with the understanding that most patients will require RT during their disease course. Currently, IWOT (*NCT03763422*) is enrolling patients with IDH-mutant, 1p/19q noncodeleted glioma, without functional deficits due to tumor, uncontrolled seizures, or residual enhancing disease in an RCT to compare close surveillance versus RT followed by adjuvant TMZ. Importantly, multiple clinical trials have shown that the addition of sequential chemotherapy to adjuvant RT improves OS for adult diffuse glioma. The optimal chemotherapy is being investigated in the current CODEL trial, which randomizes patients with IDH-mutant, 1p/19q codeleted high-risk grade 2 or grade 3 glioma to RT followed by adjuvant PCV or RT concurrent with TMZ followed by adjuvant TMZ NCT00887146.

Late effects of RT and chemotherapy can be particularly devastating in this patient population of largely young adults. Future studies may elucidate those patients who can defer RT and chemotherapy to time of disease progression, for improved long-term QoL without decrement to OS. The many recent technological developments in diagnostic imaging, image guidance, dosimetry, and radiation delivery have afforded significant advancements in target definition and conformal radiation treatments. The guideline recommendations for radiation dose, CTV expansion, and radiation technique reflect an overall effort to reduce the volume of brain irradiation while maximizing disease control. This guideline also underscores the importance of lifelong surveillance for patients with IDH-mutant grade 2 and grade 3 diffuse glioma to assess not only for late failure, but to address side effects that affect QoL, including neurocognitive decline, endocrinopathies, and pseudoprogression or radionecrosis.

Our evidence review emphasizes the importance of the many molecular markers that are now the primary basis of



PRISMA diagram, based on Moher et al.[67]
Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

WHO classification of IDH-mutant grade 2 and grade 3 diffuse glioma. Most of the trials analyzed for this guideline included a molecularly heterogenous mix of patients with many tumors that are beyond the scope of IDH-mutant grade 2 and grade 3 diffuse glioma. Trials such as EORTC 22033 stratified by IDH mutation and highlight how molecular status affects response to different treatment regimens.[60] In this trial of RT alone or TMZ alone for patients with high-risk grade 2 glioma, patients with IDH-mutant, 1p/19q noncodeleted tumors had a longer PFS after RT alone compared with TMZ alone. However, patients with IDH-mutant, 1p/19q codeleted tumors had no difference in PFS after RT alone compared with TMZ alone.[60] Overall, we extrapolated the available data to modern practice to provide maximally useful guidance to patients today.

Future trials designed based upon molecular classifications will refine guidance on the best patients who can be safely observed initially and those who benefit from upfront treatment. They may also identify patients who may benefit from lower RT doses, reduced volumes treated, and/or particular delivery techniques. Finally, it will be important for these trials to address patient-focused needs beyond pathologic and clinical characteristics, including health disparities, QoL, survivorship, and financial toxicity, to achieve the goal of quality, equitable care.

Acknowledgments

We are grateful to Yimin Geng, MSLIS, MS, the UT −MD Anderson Cancer Center research medical librarian, for her assistance with creating the search strategy for this guideline. The task force also thanks Molly H. Blau, MD, Morgan Freret, MD, Emily Lebow, MD, Marina Moskalenko, MD, Divya Natesan, MD, Amber Retzlaff, MD, Anurag Saraf, MD, Shivani Sud, MD, and Jon Van Wickle, MD, for literature review assistance.

The task force thanks the peer reviewers for their comments and time spent reviewing the guideline. See Appendix E1 for their names and disclosures.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2022.05.004.

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