Public Comment Draft

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

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

Disclosure Statements
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.

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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 (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) 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 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.
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.

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Definition</th>
<th>Overall QoE Grade</th>
<th>Recommendation Wording</th>
</tr>
</thead>
</table>
| 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” |

<table>
<thead>
<tr>
<th>Overall QoE Grade</th>
<th>Type/Quality of Study</th>
<th>Evidence Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.</td>
<td>The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.</td>
</tr>
</tbody>
</table>
| Moderate          | 1 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.

Note: 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. While each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.
I. 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 status, into an integrated diagnosis of diffuse glioma in 2016. This change was based on evidence that compared to histologic classification, IDH and 1p/19q codeletion status provided a more reproducible and clinically meaningful classification of diffuse glioma. In the WHO 2021 classification, IDH-wildtype diffuse glioma is clearly distinguished from IDH-mutant diffuse glioma as a different clinical and genetic entity with a worse prognosis. While 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 \textit{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 or necrosis) or \textit{CDKN2A/B} homozygous deletion, and these tumors are now called astrocytoma, IDH-mutant, WHO grade 4. 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. 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 \textit{CDKN2A/B} is a feature of grade 3, but not grade 2 oligodendroglioma.

The challenge with this guideline is that the evidence guiding our current clinical practice is largely based on classifying tumors by histologic grade because of the era when the studies were designed and conducted. This guideline is intended to guide practitioners on the best management of patients with IDH-mutant grade 2 and grade 3 diffuse glioma, including astrocytoma and oligodendroglioma. The pertinent literature includes histologically grade 2 and 3 diffuse glioma and thus study cohorts undoubtably include some proportion of IDH-wildtype and other higher grade glioma that are not intended for this guideline. Most studies lacked inclusion of IDH mutation and 1p/19q codeletion status which posed challenges in applying older data to the 2021 classification system. 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.
2. Methods

2.1. 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, the American Association of Neuropathologists, the American Society of Clinical Oncology, and the Society for Neuro-Oncology, who provided representatives and peer reviewers.

2.2. Document Review and Approval

The guideline was reviewed by 14 official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment (December 2021 through January 2022). The final guideline was approved by the ASTRO Board of Directors and endorsed by the TBD.

2.3. Evidence Review

A systematic search of human subject studies retrieved from the database Ovid MEDLINE was conducted. The inclusion criteria required research to involve adults (age ≥18 years), with a diagnosis of WHO grade 2 or 3 glioma, published in English, from January 1996 (for randomized controlled trials [RCTs], meta-analyses, prospective studies) and January 2005 (for retrospective studies and dosimetric studies) through July 2020. 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. The literature review also excluded preclinical/nonhuman studies, health economics and cost analyses, large registry/database studies, abstracts, review articles, comments, and editorials. For specific sub-questions where there were limited data available, expert opinion was relied upon to support recommendations as reflected in the low-to-moderate quality of evidence cited in these cases.

Both Medical Subject Heading (MeSH) terms and key search terms were used and terms common to all searches included: 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.

The data used by the task force to formulate recommendations are summarized in evidence tables available in the supplementary materials. 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 Appendix E3 for the literature search strategy which includes the evidence search parameters and inclusion/exclusion criteria.

2.4. 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; oligodendrogioma, IDH-mutant, 1p/19q codeleted, WHO grade 2; and oligodendrogioma, IDH-mutant, 1p/19q codeleted, WHO grade 3 (Figure 1). This guideline does not cover patients <18 years old; 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; gliioneuronal 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).

<table>
<thead>
<tr>
<th>KQ</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adults with IDH-mutant grade 2 and grade 3 diffuse glioma</td>
<td>RT</td>
<td>Surgery alone, Surgery + Chemotherapy</td>
<td>Local control, PFS, Overall survival, Local failure, Local progression, Toxicity</td>
</tr>
<tr>
<td>2</td>
<td>What is the optimal dose of RT and clinical target volume for adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma based on risk stratification?</td>
<td>Adults with IDH-mutant grade 2 and grade 3 diffuse glioma</td>
<td>RT, Imaging modalities</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### 3. What are the optimal RT techniques and field design for adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma?

<table>
<thead>
<tr>
<th>Adults with IDH-mutant grade 2 and grade 3 diffuse glioma</th>
<th>IMRT/VMAT</th>
<th>3-D CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Protons</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SRS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brachytherapy</td>
<td></td>
</tr>
</tbody>
</table>

- 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?

<table>
<thead>
<tr>
<th>Adults with IDH-mutant grade 2 and grade 3 diffuse glioma</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

- Neurocognitive function
- Neuroendocrine function
- Hearing
- Vision
- Permanent alopecia
- Quality of life
- Other toxicities

**Abbreviations:**
- 3-D CRT = 3-dimensional conformal radiation therapy
- IMRT = intensity modulated radiation therapy
- VMAT = volumetric modulated arc therapy
- N/A = not applicable
- PFS = progression-free survival
- RT = radiation therapy
- SRS = stereotactic radiosurgery
**Figure 1. WHO 2021 Classification: Adult-Type Diffuse Glioma**

Abbreviation: WHO = World Health Organization.
3. Key Questions and Recommendations

3.1. 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.

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

<table>
<thead>
<tr>
<th>KQ1 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (Refs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oligodendroglioma, IDH-mutant and 1p/19q codeleted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2, &lt;4 to 6 cm tumor, with gross total resection* and age &lt;40 years, close surveillance alone is recommended.</td>
<td>Strong</td>
<td>Low 13,14</td>
</tr>
<tr>
<td>2. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 2, with high-risk features, RT with sequential chemotherapy with or without concurrent chemotherapy are conditionally recommended. Implementation remark: High-risk features include any of the following: subtotal resection, age ≥40 years, tumor size ≥4 to 6 cm, tumor crosses midline, refractory seizures, or presurgical neurological symptoms from tumor.</td>
<td>Conditional</td>
<td>Low 14-19</td>
</tr>
<tr>
<td>3. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 3, with any extent of surgery, RT with sequential chemotherapy with or without concurrent chemotherapy are recommended.</td>
<td>Strong</td>
<td>Moderate 20-24</td>
</tr>
<tr>
<td><strong>Astrocytoma, IDH-mutant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. For patients with astrocytoma, IDH-mutant, WHO grade 2, &lt;4 to 6 cm tumor, with gross total resection* and age &lt;40 years, close surveillance alone is conditionally recommended.</td>
<td>Conditional</td>
<td>Low 13,14</td>
</tr>
<tr>
<td>2. For patients with astrocytoma, IDH-mutant, WHO grade 2, with high-risk features, RT with sequential chemotherapy with or without concurrent chemotherapy are conditionally recommended. Implementation remark: High-risk features include any of the following: subtotal resection, age ≥40 years, tumor size ≥4 to 6 cm, tumor crosses midline, refractory seizures, or presurgical neurological symptoms from tumor.</td>
<td>Conditional</td>
<td>Low 14-19,25</td>
</tr>
</tbody>
</table>
3. For patients with astrocytoma, IDH-mutant, WHO grade 3, with any extent of surgery, RT with sequential chemotherapy with or without concurrent chemotherapy are recommended.  

<table>
<thead>
<tr>
<th>Strong</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>22,23,26</td>
<td></td>
</tr>
</tbody>
</table>

* Gross total resection is defined as <1 cm residual tumor on MRI.

Abbreviations: 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 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. EORTC 22845, randomized patients ages 16 to 65 years 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 age 7.2 years and 7.4 years, respectively. 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. Importantly, the majority of those observed will eventually have recurrence and undergo RT. This trial did not include IDH status nor sequential chemotherapy, which is now standard of care based on RTOG 9802. 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 were rated low for this KQ with the exception of the recommendation for grade 3 oligodendroglioma. Further studies outlined below 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. 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. 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). While the trial included both oligodendroglioma and astrocytoma, it is notable that the 5-year PFS for the entire cohort was 48% with close surveillance whereas it was 70% for the favorable subgroup of oligodendroglioma, tumor <4 cm, and <1 cm of residual disease. This led to a recommendation for close surveillance with MRI and exam 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. While RTOG 9802 identified tumors ≥4 cm as high risk, analysis of EORTC 22844 and
22845 identified ≥6 cm as a high-risk factor.\textsuperscript{13,17} 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.\textsuperscript{13} Importantly, the primary outcome of RTOG 9802 was improved 10-year PFS (51\% versus 21\%) and OS (60\% versus 40\%) for patients with grade 2 glioma (including oligodendroglioma or astrocytoma) treated with RT and adjuvant PCV following surgery, compared to RT alone. Median OS was improved from 7.8 to 13.3 years.\textsuperscript{15,19} Based on these results and data from EORTC 22845,\textsuperscript{14} that showed improved PFS for patients with grade 2 glioma treated with adjuvant RT compared to 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.\textsuperscript{13,15-18}

Along with subtotal resection, adverse risk factors for histologic grade 2 oligodendroglioma include larger tumor size (defined range of ≥4 cm to ≥6 cm in different studies), tumor crossing midline, and refractory seizures or presurgical neurological deficits due to tumor.\textsuperscript{13,16,17} In EORTC 22844 and 22845,\textsuperscript{14,16} 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.\textsuperscript{17} While 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.\textsuperscript{18} 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 RT with sequential chemotherapy with or without concurrent chemotherapy.

Though in past studies, grade 3 or “anaplastic” oligodendroglioma have 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 to adjuvant RT alone.\textsuperscript{22} The EORTC 26951 RCT evaluated a reversed sequence of RT followed by PCV compared to RT alone for anaplastic oligodendroglioma and oligoastrocytoma, and found a similar improvement in PFS.\textsuperscript{20} 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.\textsuperscript{20,22} Long-term results of RTOG 9402 confirmed that patients with 1p/19q
codedeleted tumors treated with PCV and RT lived twice as long as those treated with RT alone (14.7 versus 7.3 years). 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 versus 112 months in the RT alone group). While 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 to those who did not start RT in the EORTC trial (n=5/185). Of note, temozolomide (TMZ) is often used instead of PCV for treatment of glioma. Recommendations for chemotherapy regimen is beyond the scope of this guideline though it is important to note that we are currently awaiting further data from the clinical trial CODEL, which compares adjuvant RT followed by PCV versus adjuvant RT with concurrent and sequential TMZ. Overall, published trials support the practice of planned RT with sequential chemotherapy based on the EORTC and RTOG studies.

**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. 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, given the finding that astrocytoma was a poor prognostic factor compared to oligodendroglioma, the recommendation is conditionally made. Further data is 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. The recommendation further includes sequential chemotherapy with or without concurrent 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. 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. In addition, RTOG 0424, a prospective nonrandomized study, demonstrated that if the patient has astrocytoma, oligodendroglioma, or oligoastrocytoma and ≥2 high-risk
features along with age ≥40 years, tumor size ≥6 cm, tumor crossing midline, or moderate-to-severe
preoperative neurological deficits, concurrent TMZ and RT followed by adjuvant TMZ improved outcomes in
comparison to historical controls.\(^{25}\) 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.\(^{16}\)

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.\(^{22,26}\) There is still some
controversy over the timing of RT, with the current EORTC “IWOT” trial including these patients on an
observational arm, however, most trials have included adjuvant therapy for grade 3 astrocytoma.\(^{22,23,26}\)

Although the RTOG 9402 trial for anaplastic oligodendroglioma did not focus on histopathological 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.\(^{24}\) 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 to RT alone when all patients
were considered, without regard to their 1p/19q codeletion status.\(^{22}\) Similarly, CATNON (EORTC 26053-22054)
included grade 3 IDH-mutant astrocytoma, but also IDH wild-type astrocytoma which would be considered
glioblastoma in the 2021 WHO classification.\(^{4,26}\) 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 in grade 3 IDH-mutant astrocytoma in an RCT
comparing RT versus PCV versus TMZ.\(^{23}\) Taken together, RT with sequential chemotherapy with or without
concurrent chemotherapy is recommended for patients with IDH-mutant, WHO grade 3 astrocytoma.
3.2. 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 clinical target volume for adult patients with IDH-mutant grade 2 and grade 3 diffuse glioma based on risk stratification?

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

<table>
<thead>
<tr>
<th>KQ2 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (Refs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 to 5400 cGy in 180 cGy daily fractions is recommended.</td>
<td>Strong</td>
<td>High 14,16,29-33</td>
</tr>
</tbody>
</table>

Abbreviations: chemo = chemotherapy; GTR = gross total resection; RT = radiation therapy; STR = subtotal resection (including biopsy); WHO = World Health Organization.

RT + chemo = RT with sequential chemotherapy with or without concurrent chemotherapy.
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.  

3. For patients with oligodendroglioma, IDH-mutant, 1p/19q codeleted, WHO grade 3, a total prescribed dose of 5400 to 5760 cGy in 180 cGy daily fractions is conditionally recommended.  

4. For patients with astrocytoma, IDH-mutant, WHO grade 3, a total prescribed dose of 5940 to 6000 cGy in 180 to 200 cGy daily fractions is recommended.  

5. For patients with astrocytoma, IDH-mutant, WHO grade 3, a total prescribed dose of 5400 to 5800 cGy in 180 to 200 cGy daily fractions is conditionally recommended.  

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 post-contrast  
   - CTV = GTV + 10 to 15 mm expansion  
   - PTV = CTV + 3 to 5 mm expansion  

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:  
   - GTV1 = residual FLAIR changes, resection cavity and any residual enhancement on T1 post-contrast  
   - GTV2 = residual enhancement on T1 post-contrast and resection cavity  
   - CTV1/2 = GTV1/2 + 10 to 15 mm expansion  
   - PTV1/2 = CTV1/2 + 3 to 5 mm expansion  
   OR  
   - GTV = residual FLAIR changes, resection cavity and any residual enhancement on T1 post-contrast  
   - CTV = GTV + 10 to 15 mm expansion  
   - PTV = CTV + 3 to 5 mm expansion

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

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. 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 appears to be as effective as higher doses (5900 to 6500 cGy) for patients harboring grade 2 glioma. 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. Significant acute toxicities 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 utilized for the management of oligodendroglioma and mixed oligoastrocytoma patients with no toxicities of grade >2 reported. 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-mutant, 1p/19q codeleted, WHO grade 3, the dose 5940 cGy delivered in 180 cGy daily fractions is recommended based on multiple RCTs which utilized this dose regimen. Similarly, for patients with astrocytoma, IDH-mutant, WHO grade 3, the recommended dose range is 5940 cGy to 6000 cGy delivered in 180 to 200 cGy daily fractions. 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. A conditional recommendation based on expert opinion with somewhat lower doses is also included since data has emphasized that categorization based on IDH and 1p/19q status is associated with less aggressive tumor despite designation as grade 3. As such, a dose range with lower limit of 5400 cGy may be considered as this is the historical upper range of dose utilized 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. Many of the historical studies used computed tomography (CT)-based studies with margins of 20 mm to block edge for radiation treatment planning. Overall, trials have used various methods of target delineation. However, contemporary trials have utilized GTV to clinical target volume (CTV) margins of 10 to 15 mm with predominantly MRI-based planning. 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 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, 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 margins compared to grade 2. However, more recent studies outline the same volume delineation principles for grade 2 diffuse glioma have been applied to grade 3 IDH-mutant diffuse glioma. The GTV should include the surgical resection cavity with any rare residual enhancement on T1 post-contrast and T2/FLAIR signal. Standard approaches include a CTV margin of 10 to 15 mm with the use of MRI imaging. Alternatively, a 2-phase approach may be considered including a boost to any residual enhancement on T1 post-contrast imaging.

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 are low and reflects the consensus opinion of the task force members.

3.3. 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?

**Table 5** Optimal RT techniques and field design

<table>
<thead>
<tr>
<th>KQ3 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (refs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>Strong</td>
<td>Low 38-41</td>
</tr>
<tr>
<td>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.</td>
<td>Strong</td>
<td>Moderate 15,20,22,24,34,42</td>
</tr>
</tbody>
</table>
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 | 38,40,43-47 |

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 | 15,16,23,36,42,48 |

5. For patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma receiving RT, daily image guidance is recommended.  

| Strong | Expert Opinion |

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

Historically, IDH-mutant grade 2 and grade 3 diffuse glioma was treated using 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 conformity of CTV and 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-D conformal radiation therapy (3-D CRT) where tumor volumes and normal tissues are delineated allowing improved shielding of normal tissues and CTV conformity. In prior EORTC, NCCTG and RTOG studies, 2-D planning and 3-D CRT were allowed, but given the conformity and normal tissue dosimetric superiority with 3-D CRT, the majority of patients treated in these trials received 3-D CRT using multiple non-coplanar 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. 15,20,22,24,34,42

High rates of long-term survival following 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 (VMAT), 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/VMAT or proton therapy. Retrospective studies report on outcomes after IMRT, 38-41 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. 38,40,43-47 Two retrospective studies have looked at the incidence of pseudoprogression or radionecrosis after IMRT or proton therapy for grade 2 and 3 gliomas. 38,40 One of these series suggests that patients with oligodendroglioma, but not astrocytoma, develop pseudoprogression earlier after protons compared to photons. 38 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. Further studies (e.g., 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 QUANTEC papers are systematic reviews of dose tolerances that serve as good references for guidance. 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. The prescription dose may also inform OAR goals and constraints.

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

3.4. 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?

Table 6 Adverse effects of RT

<table>
<thead>
<tr>
<th>KQ4 Recommendation</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td>Strong</td>
<td>Expert Opinion</td>
</tr>
</tbody>
</table>

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

Patients with IDH-mutant grade 2 and grade 3 diffuse glioma may present with disease-related neurological deficits. In addition to these baseline symptoms, the provision of cranial RT and chemotherapy for patients with glioma may result in treatment-related toxicity. Higher doses of RT may be associated with an increased risk of acute and long-term effects in comparison to lower RT doses.
Acute impacts of RT and chemotherapy may include neurologic effects (10%), constitutional symptoms (9%), dermatitis (4%), gastrointestinal symptoms (5%), musculoskeletal effects (5%) and sexual dysfunction (5%) of patients. Acute side effects directly attributable to RT include fatigue, weight loss, headache, skin erythema, otitis, nausea/vomiting, and alopecia. The development of radionecrosis has been reported in 0 to 13% of patients, with higher doses and oligodendroglioma histology associated with increased risk. Overall, the development of any grade 3 acute toxicities is expected in 0 to 14% of patients. RT may also entail long-term impacts on cognitive function or health-related QoL. Though, given the impact 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. While many acute toxicities will resolve with time, there are late effects that will require follow up and management. The task force recommends assessment, surveillance, and management by a multidisciplinary care team as guided by Table 7.

### Table 7 Multidisciplinary care team management for common toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Management Considerations – Baseline and Ongoing (As Needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive function</td>
<td>Neuropsychological testing (where available)</td>
</tr>
<tr>
<td>Neuroendocrine Function</td>
<td>Pituitary function testing for patients with hypothalamic/pituitary axis within the radiation treatment field or with clinical symptoms</td>
</tr>
<tr>
<td>Vision</td>
<td>Acuity and visual field testing for patients with optic pathway within the radiation treatment field or with clinical symptoms</td>
</tr>
<tr>
<td>Hearing</td>
<td>Auditory and vestibular testing for patients with cochlea within the radiation treatment field or with clinical symptoms</td>
</tr>
<tr>
<td>Permanent alopecia</td>
<td>Wig and hair loss consultation (where available)</td>
</tr>
<tr>
<td>Cerebrovascular complications</td>
<td>Vascular medicine consultation (with neurologist and/or neurosurgeon)</td>
</tr>
<tr>
<td>Financial/psychosocial</td>
<td>Social services (eg, social worker, adolescent and young adult-life specialist, and financial counsellor)</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Supportive care (eg, palliative care provider, onco-psychologist, and mental health counselor)</td>
</tr>
</tbody>
</table>

### 4. Conclusions/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 non-codeleted 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.  

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 impact QoL including neurocognitive decline, endocrinopathies, and pseudoprogression or radionecrosis.

Finally, our evidence review emphasizes the importance of the many molecular markers which are now the primary basis of 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 have stratified by IDH mutation and highlighted how molecular status affects response to different treatment regimens. In this trial of RT alone or TMZ alone for patients with high-risk grade 2 glioma, patients with IDH-mutant, 1p/19q non-codeleted tumors had a longer PFS after RT alone compared to TMZ alone. However, patients with IDH-mutant, 1p/19q codeleted tumors had no difference in PFS after RT alone compared to TMZ alone. Overall, we extrapolated the available data to modern practice in order 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 will also identify patients who may benefit from lower RT doses, reduced volumes treated, and/or particular delivery techniques.

5. Acknowledgements

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.

**PRISMA Diagram**, based on Moher et al.63

![PRISMA Diagram](image)

**Abbreviation:** PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
References


Appendix E1. Peer Reviewers and Disclosures (Comprehensive)

(added after peer review)

Appendix E2. Abbreviations

3-D = 3-dimensional
3-D CRT = 3-D conformal radiation therapy
cGy = centigray
CT = computed tomography
CTV = clinical target volume
GTV = gross tumor volume
IDH = isocitrate dehydrogenase
IMRT = intensity modulated radiation therapy
KQ = key question
MRI = magnetic resonance imaging
OARs = organs at risk
OS = overall survival
PCV = procarbazine, lomustine, and vincristine
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
PFS = progression-free survival
PTV = planning target volume
QoL = quality of life
RT = radiation therapy
RTOG = Radiation Therapy Oncology Group
TMZ = temozolomide
VMAT = volumetric-modulated arc therapy
WHO = World Health Organization
Appendix E3. Literature Search Strategy

**Search Date(s):** 7.27.2020

**Search Limits:**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Adult (≥18 years old)</th>
</tr>
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<tbody>
<tr>
<td>Language</td>
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<tr>
<td>Species</td>
<td>Humans</td>
</tr>
<tr>
<td>Publication Types</td>
<td>• RCTs ≥50 pts</td>
</tr>
<tr>
<td></td>
<td>• Meta-analyses, systematic reviews ≥50 pts</td>
</tr>
<tr>
<td></td>
<td>• Prospective trials ≥50 pts</td>
</tr>
<tr>
<td></td>
<td>• Retrospective studies - no pt number restrictions</td>
</tr>
<tr>
<td></td>
<td>• Dosimetric studies/contouring - no pt number restrictions</td>
</tr>
<tr>
<td>Timeframe</td>
<td>January 1996 (for RCTs, meta-analyses, prospective studies) and January 2005 (for retrospective and dosimetric studies)</td>
</tr>
</tbody>
</table>

**Universal Exclusion Criteria:**

1. Pre-clinical/non-human studies
2. Health economics/cost analysis studies
3. Studies available in abstract only
4. Comment or editorial
5. Guidelines or review articles
6. Case reports / feasibility / phase 1 studies
7. Pediatric and adolescent patients <18 years old
8. Studies using large databased eg, SEER or NCDB
9. Otherwise not relevant or out of scope (including disseminated disease, glioblastoma, grade 1 tumors, IDH-mutant grade 4, re-irradiation, and brainstem glioma)

<table>
<thead>
<tr>
<th>Item</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key clinical question(s)</strong></td>
<td><strong>Key Question 1:</strong> What are the indications and optimal timing for RT in adult patients with newly diagnosed or previously unirradiated lower grade glioma based on risk stratification?</td>
</tr>
<tr>
<td></td>
<td>• Lower risk – watch and wait vs treatment</td>
</tr>
<tr>
<td></td>
<td>• Higher risk – treat everyone with chemoRT</td>
</tr>
<tr>
<td></td>
<td>• Progressive/recurrent tumors</td>
</tr>
<tr>
<td>Definitions</td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>Radiation therapy and chemotherapy</td>
</tr>
<tr>
<td><strong>Condition or domain being studied</strong></td>
<td>• Low grade glioma</td>
</tr>
<tr>
<td></td>
<td>• Lower grade glioma</td>
</tr>
<tr>
<td></td>
<td>• Astrocytoma</td>
</tr>
<tr>
<td></td>
<td>• Oligodendroglioma</td>
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<tr>
<td></td>
<td>• Oligoastrocytoma</td>
</tr>
<tr>
<td></td>
<td>• IDH mutant grade II-III</td>
</tr>
<tr>
<td></td>
<td>• WHO grade II</td>
</tr>
<tr>
<td></td>
<td>• WHO grade III</td>
</tr>
<tr>
<td>Participants/population</td>
<td>Adults with low grade glioma or lower grade glioma</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------------------------------</td>
</tr>
</tbody>
</table>
| Intervention(s)/exposure(s) | • Surgery: biopsy, subtotal resection, gross total resection  
• Radiation: external beam radiation  
• Chemotherapy: concurrent chemotherapy, adjuvant chemotherapy, temozolomide, PCV |
| Comparator(s)/control | Surgery alone  
Chemo + surgery (without RT) |
| Outcomes: primary/critical | Local control, local failure, local progression, progression free survival, overall survival |
| Outcomes: secondary/important but not critical outcomes | • Acute and late toxicity/morbidity  
• Neurocognitive function, cognitive function, memory, executive function  
• Quality of life  
(reserve most of this for KQ4) |
| Timing | Any |
| Setting/context | Any |
| Study design | • RCTs  
  o Surgery vs surgery + RT  
  o Surgery vs surgery + chemoRT  
  o Postoperative RT vs postoperative chemoRT  
  o Postoperative chemo vs postop ChemoRT  
• Meta-analyses, systematic reviews  
• Prospective trials  
• Retrospective studies  
• Dosimetric studies/contouring |
| Summary of the key selection criteria | **Inclusion criteria:** see above  
**Exclusion criteria:** see above |

**Key Question and PICO(TSS) Framework**

**Key clinical question(s)**

*Key Question 2:*

What is the optimal dose of RT and clinical target volume for adult patients with lower grade glioma based on risk stratification?

• Optimal RT dose  
• Optimal target volume

**Definitions**

• GTV: gross tumor volume  
• CTV: clinical target volume  
• PTV: planning target volume  
• OARs: organs at risk  
• Conventional fractionation (180-200 cGy/fraction)  
• Hypofractionation >200 cGy/fraction

**Condition or domain being studied**

• Low grade glioma  
• Lower grade glioma  
• Astrocytoma  
• Oligodendroglioma  
• Oligoastrocytoma
<table>
<thead>
<tr>
<th>Item</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Key clinical question(s)** | Key Question 3: What are the optimal RT techniques and field design for adult patients with lower grade glioma?  
• Including 3D vs IMRT/VMAT vs protons |
| Definitions | Photons, 3D, 3D-CRT, 3D conformal radiation therapy, IMRT, intensity modulated radiation therapy, proton therapy, protons, margin, expansion, T1, T2, FLAIR, enhancement, enhancing tumor |
| Condition or domain being studied |  
• Low grade glioma  
• Lower grade glioma  
• Astrocytoma  
• Oligodendrogliaoma  
• Oligoastrocytoma  
• IDH mutant glioma |
| Participants/ population | Adults with low grade or lower grade glioma |
| Intervention(s)/ exposure(s) | IMRT, proton therapy, protons, SRS, brachytherapy |
| Comparator(s)/ control | 3D conformal |
| Outcomes: primary/critical | Local control, local failure, local progression, progression free survival, overall survival |
Outcomes: secondary/important but not critical outcomes
- Acute and late toxicity/morbidity
- Neurocognitive function, cognitive function, memory, executive function
- Quality of life
(reserve most of this for KQ4)

Timing
Any

Setting/context
Any

Study design
Any

Summary of the key selection criteria
**Inclusion criteria:** see above

**Exclusion criteria:** see above

<table>
<thead>
<tr>
<th>Item</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td><strong>Key clinical question(s)</strong></td>
<td><strong>Key Question 4:</strong> What are the adverse effects of RT, and subsequent clinical management, for adult patients with lower grade glioma?</td>
</tr>
<tr>
<td></td>
<td>• Neurocognitive function</td>
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<tr>
<td></td>
<td>• Neuroendocrine function (including fertility)</td>
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<tr>
<td></td>
<td>• Hearing</td>
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<td></td>
<td>• Vision</td>
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<td></td>
<td>• Permanent alopecia</td>
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<td></td>
<td>• Cerebrovascular complications</td>
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<td>• Financial toxicity / psychosocial distress</td>
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<tr>
<td></td>
<td>• Quality of life</td>
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<tr>
<td></td>
<td>• Secondary tumor/malignancy</td>
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| **Definitions**                           |                                                                        |
|                                           | • Neurocognitive function                                               |
|                                           | • Neuroendocrine function                                               |
|                                           | • Hearing                                                               |
|                                           | • Vision                                                               |
|                                           | • Permanent alopecia                                                   |
|                                           | • Quality of life                                                      |
|                                           | • Toxicity, side effects, adverse effects                              |

| **Condition or domain being studied**    |                                                                        |
|                                           | • Low grade glioma                                                     |
|                                           | • Lower grade glioma                                                   |
|                                           | • Astrocytoma                                                          |
|                                           | • Oligodendroglioma                                                    |
|                                           | • Oligoastrocytoma                                                    |
|                                           | • IDH mutant glioma                                                   |

| **Participants/population**              | Adults with low grade or lower grade glioma                           |

| **Intervention(s)/exposure(s)**          | RT                                                                    |

| **Comparator(s)/control**                | N/A                                                                  |

<p>| <strong>Outcomes: primary/critical</strong>           |                                                                        |
|                                           | • Neurocognitive function                                             |
|                                           | • Neuroendocrine function                                             |
|                                           | • Hearing                                                             |
|                                           | • Vision                                                             |</p>
<table>
<thead>
<tr>
<th>Outcomes: secondary/important but not critical outcomes</th>
<th>Local control</th>
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<tbody>
<tr>
<td></td>
<td>Progression free survival</td>
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<tr>
<td></td>
<td>Overall survival</td>
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<table>
<thead>
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