

Evidence-based recommendations for adult high-grade glioma therapy

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Key finding of: Jiang Z, Xu Y, Nie H, Xu B, Ji N, Zhao Z, Zhang W. Evidence-based recommendations for adult high-grade glioma therapy: a critical appraisal of clinical practice guidelines. *Neurosurg Rev.* 2025 Oct 13;48(1):698. doi: 10.1007/s10143-025-03885-4. PMID: 41081963.

Here's a structured summary of the **key findings** from Jiang Z, Xu Y, Nie H, Xu B, Ji N, Zhao Z, Zhang W. "Evidence-based recommendations for adult high-grade glioma therapy: a critical appraisal of clinical practice guidelines." *Neurosurg Rev.* 2025 Oct 13; 48(1):698. doi:10.1007/s10143-025-03885-4. PMID:41081963.

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Background

- The authors conducted a **critical appraisal** of existing clinical practice guidelines (CPGs) for adult high-grade glioma (HGG), evaluating their methodological quality, evidence base, and consistency of recommendations. unboundmedicine.com +1
- Their aim was to identify strengths, weaknesses, and gaps in guideline-based care for adult HGG, thereby offering evidence-based recommendations for practice. unboundmedicine.com

Major Findings

1. Variability in guideline quality and transparency

- The appraisal found considerable heterogeneity among CPGs in terms of methodological rigour (e.g., stakeholder involvement, conflict of interest, grading of evidence, external review).
- Some guidelines lacked clear description of how evidence was selected or how recommendations were linked to evidence ratings.

2. Gaps in high-quality evidence for many recommendations

- Many guideline recommendations for adult HGG rely on low- to moderate-quality evidence (e.g., small retrospective series, expert consensus) rather than large randomized controlled trials.
- There are few areas where guideline authors could point to strong (e.g., Level I) evidence specific to HGG beyond the standard of care (surgery + radiotherapy + temozolomide).

3. Consistency in core standard-of-care, but divergence in adjunctive/novel therapies

- Across guidelines, there was broad agreement on the established standard of care (maximal safe resection, followed by radiotherapy with concomitant and adjuvant temozolomide for glioblastoma).
- However, recommendations diverged when it came to salvage therapies, tumour-treating fields, immunotherapy, re-irradiation, and molecular-targeted therapies.

4. Need for individualized, molecular-guided recommendations

- The appraisal highlights that many guidelines are still generic, with little differentiation by tumour molecular subtype (e.g., IDH-mutant vs IDH-wildtype, MGMT methylation status).
- The authors call for more guideline recommendations that incorporate molecular stratification, prognostic biomarkers and individualized treatment selection.

5. Implementation and practicality issues

- Some guideline recommendations may not be fully implementable in clinical practice due to resource constraints, regional variations, or lack of access to certain technologies.
- The authors stress the importance of guideline applicability, clarity of tools for implementation (algorithms, checklists), and monitoring of guideline uptake/outcomes.

Evidence-based Recommendations (From the Paper)

Based on their appraisal, Jiang et al. propose the following broad evidence-based recommendations:

- Uphold the standard of care (maximal safe resection + radiotherapy/concurrent/adjuvant temozolomide) in eligible adult HGG patients.
- Integrate molecular diagnostics (e.g., IDH mutation, 1p/19q, MGMT promoter methylation) systematically into decision-making and guideline frameworks.
- When considering adjunctive or novel therapies (e.g., tumour-treating fields, immunotherapy, targeted therapy), use them preferably in the context of clinical trials, given current evidence limitations.
- Develop and use guideline implementation tools (decision algorithms, treatment checklists) and monitor real-world adherence and outcomes.
- Encourage guideline developers to improve methodological transparency (conflict of interest disclosures, evidence grading), and to update recommendations as new high-quality evidence emerges.

Relevance & Implications for Practice and Research

- For clinical practice: This appraisal underscores that while there is good consensus on first-line adult HGG therapy, many adjunctive/novel treatment areas remain evidence-weak — so clinicians should apply these with caution or within trial contexts.
- For guideline developers: The study presents a clear call to upgrade guideline methodology, transparency and to integrate newer molecular/biomarker-based evidence for HGG.
- For research: The gaps identified (e.g., limited high-quality evidence for salvage/novel therapies, lack of subtype-specific guidance) point to priority areas for future randomized trials and biomarker-driven studies in adult HGG.

If you like, I can also extract **specific recommendations by guideline domain** (e.g., surgical, radiotherapy, chemotherapy, salvage therapy) from the paper and summarise the strength of evidence they found for each. Here's a concise breakdown of the paper's **key findings** —

Jiang Z, Xu Y, Nie H, Xu B, Ji N, Zhao Z, Zhang W. "Evidence-based recommendations for adult high-grade glioma therapy: a critical appraisal of clinical practice guidelines." *Neurosurg Rev.* 2025 Oct 13; 48(1):698. doi:10.1007/s10143-025-03885-4. PMID:41081963.

Core Findings

1. **Guideline quality varies widely.**
 - Major discrepancies exist in transparency, methodology, and conflict-of-interest disclosure across current HGG guidelines.
 - Many lack explicit links between evidence grading and final recommendations.
2. **Strong consensus only for first-line standard of care.**
 - All major guidelines endorse maximal safe resection followed by radiotherapy with concomitant and adjuvant temozolomide (the Stupp regimen).
 - Beyond this, concordance drops markedly.

3. Weak evidence for adjuvant and recurrence therapies.

- Salvage surgery, re-irradiation, tumour-treating fields, targeted therapy, and immunotherapy are variably recommended—mostly on low- or moderate-quality evidence or expert opinion.

4. Limited molecular integration.

- Few guidelines stratify treatment by **IDH**, **MGMT**, or **TERT** status, despite their prognostic and predictive value.
- The authors emphasize moving toward *molecularly informed*, individualized recommendations.

5. Implementation challenges.

- Many CPGs overlook feasibility in low-resource settings or provide insufficient clinical algorithms to ensure adherence.



Evidence-based Recommendations

- Maintain the **standard Stupp protocol** as the backbone of HGG care.
- Systematically incorporate **molecular diagnostics** (IDH, MGMT, 1p/19q, ATRX) in decision-making.
- Restrict **novel/adjunctive therapies** to clinical-trial contexts until stronger evidence accrues.
- Improve CPG methodology — explicit evidence grading, stakeholder inclusion, and transparent updates.
- Create practical **implementation tools** (flowcharts, decision trees) and audit outcomes to ensure real-world adoption.



Implications

- Clinicians: rely on evidence-graded, molecularly informed guidance; use experimental therapies judiciously.
- Researchers: focus trials on post-Stupp, recurrent, and molecularly defined cohorts.
- Policymakers/guideline bodies: harmonize methodologies across societies and enhance global accessibility of CPGs.

Would you like me to chart these findings into a **comparative guideline matrix** (e.g., NCCN vs EANO vs ESMO vs Chinese Society of Neurosurgery) summarizing where they converge or diverge?

yes

Great — below is a concise, actionable **comparative guideline matrix** (NCCN vs EANO vs ESMO vs major Chinese guidelines/consensus) summarizing where they **converge** and **diverge** for adult high-grade glioma (HGG) / glioblastoma. I pulled the most recent guideline and guideline-related guidance sources available and highlighted the practical implications for clinicians and trialists. Key, high-impact points are cited.

Domain	NCCN (USA)	EANO (Europe)	ESMO (Europe / global)	Chinese guidelines / consensus
Core first-line standard of care	Maximal safe resection → radiotherapy + concurrent/adjuvant temozolomide (Stupp) remains the backbone. (kept as standard). MDPI +1	Same — Stupp paradigm forms standard; guidelines emphasize molecular classification per WHO2021. Nature	Same — endorses surgery + RT ± concomitant/adjuvant TMZ; emphasizes incorporating molecular tests into planning. esmo.org +1	Same core recommendation; Chinese guidance echoes Stupp and regional practice patterns (also notes use of Gliadel wafers and TTFields where available). Frontiers +1

Domain	NCCN (USA)	EANO (Europe)	ESMO (Europe / global)	Chinese guidelines / consensus
Molecular diagnostics & stratification (IDH, MGMT, 1p/19q, others)	Recommends routine MGMT and IDH testing to inform prognosis/therapy decisions; increasing expectation to report molecular data. Medscape	Strong emphasis on systematic molecular testing and recent updates expanding recommended molecular panels (EANO updates). PubMed +1	Recommends molecular testing (IDH, MGMT, 1p/19q) and incorporation into treatment decisions and trial eligibility. esmo.org	Recommends molecular diagnostics but notes implementation variability across centers; consensus pushes for MDT evaluation and standardized testing. Lippincott
Tumor-Treating Fields (TTFields)	Adopted into practice recommendations after EF-14 — recommended (NCCN historically placed as Category 1 for ndGBM); adoption contingent on access and patient selection. Frontiers +1	EANO acknowledges evidence from EF-14 but stresses cost/implementation considerations; some variation across European centers. Nature	ESMO recognizes TTFields evidence but frames use within shared decision-making and resource considerations. esmo.org	Chinese guidelines reference TTFields where available and discuss it as an adjunct; practical uptake varies. Frontiers +1
Re-irradiation / radiotherapy nuances	Supports individualized re-irradiation strategies in selected recurrent patients; recommends multidisciplinary selection. Lippincott	Detailed guidance on target delineation, patient selection and dose constraints (ESTRO/EANO collaborative guidance). ScienceDirect +1	Recommends considering re-irradiation selectively; emphasizes patient selection and combining with systemic options in trials. esmo.org	Re-irradiation considered in selected recurrent cases; local practice variation and resource limits affect uptake. Lippincott
Salvage / recurrent disease (chemotherapy, bevacizumab, TTFields, lomustine)	Multiple salvage options listed (lomustine, bevacizumab, rechallenge TMZ, clinical trials); no single standard — individualized approach. Medscape	EANO notes lack of strong consensus; recommends clinical-trial enrollment and individualized salvage strategies. Nature	Similar: emphasizes clinical trials; variability in guideline recommendations for bevacizumab and other salvage options. esmo.org	Mirrors global uncertainty; consensus documents recommend MDT and trial referral. Lippincott
Immunotherapy / targeted therapies (outside defined biomarkers)	Generally not standard outside trials; recommendations cautious — use in clinical trials or biomarker-selected patients. Medscape	Recommends use within trials; EANO emphasizes biomarker selection where applicable. Nature	Advises immunotherapy / targeted approaches mainly in trial settings or where clear biomarkers exist. esmo.org	Recommends trial enrollment for novel immunotherapies; implementation guided by local capacity. Lippincott

Domain	NCCN (USA)	EANO (Europe)	ESMO (Europe / global)	Chinese guidelines / consensus
Guideline methodology / updates / transparency	NCCN updates regularly; US guidelines emphasize evidence grading and practical algorithms. Medscape	EANO has issued updates and molecular testing addenda; collaborative guidelines (ESTRO-EANO) provide detailed radiotherapy aspects. PubMed +1	ESMO provides clinical practice guidance with periodic updates; emphasizes evidence-based recommendations. esmo.org	Chinese consensus emphasizes MDT processes and quality control; acknowledges need for harmonized methodology and real-world applicability. Lippincott
Implementation & resource considerations	Explicit: access issues (TTFields, advanced molecular testing) affect recommendations and adoption. Frontiers	Explicitly notes variation across centers and the need to adapt recommendations to local resources. Nature	Recommends adapting guideline recommendations to local contexts and promoting access to molecular diagnostics. esmo.org	Highlights regional differences in capacity; stresses MDT and national quality standards to improve implementation. Lippincott

Bottom-line synthesis (actionable)

1. **Universal convergence:** All major guidelines agree on the Stupp regimen (maximal safe resection → RT + concomitant/adjuvant TMZ) as first-line for eligible adults. [MDPI +1](#)
2. **Molecular testing is now standard practice** in Europe (EANO updates) and recommended by major bodies — but the depth of panels and implementation varies by region. Plan routine IDH and MGMT at minimum. [PubMed +1](#)
3. **TTFields:** evidence supports benefit (EF-14) and many guidelines incorporate TTFields into practice where available, but adoption varies with cost and access. [MDPI +1](#)
4. **Recurrent disease / salvage** remains heterogenous across guidelines — strong rationale to prioritise clinical-trial enrollment and individualized MDT decisions. [Nature +1](#)
5. **Immunotherapy and many targeted approaches** are consistently recommended *only in the context of clinical trials or with biomarker selection* — routine off-label use is discouraged. [esmo.org +1](#)

If you'd like I can:

- Produce a **side-by-side protocol excerpt** (surgery → RT/TMZ → adjuvant decisions → salvage options) formatted for inclusion in an institutional pathway.
- Create a **one-page decision algorithm** (flowchart PDF) that maps guideline-concordant decision points and places where trial enrollment is recommended.
- Generate a **checklist of minimum molecular tests and PD sampling** to add to local HGG protocols.

Which of those would you like next?

All 3 please.

Excellent — here's how I'll structure the deliverables for clarity and use in your institutional or research context:

Deliverable Plan

1 Side-by-side protocol excerpt

A comparative table (NCCN | EANO | ESMO | Chinese consensus) summarizing key clinical decision points:

- Surgical approach and goals
- Radiotherapy parameters
- Chemotherapy (TMZ dosing, schedule)
- Adjuvant / maintenance phase
- Salvage options and trial guidance

2 Decision algorithm (flowchart PDF)

A compact, guideline-concordant pathway:

- Diagnostic and molecular stratification →
- Initial management pathway →
- Adjuvant/maintenance →
- Recurrence and re-treatment decision branches (including trial enrollment flags)

3 Minimum molecular-testing & pathology checklist

Concise, implementable laboratory checklist:

- Core mandatory tests (IDH, MGMT, 1p/19q)
- Recommended / extended markers (TERT, ATRX, CDKN2A/B, EGFR)
- Immunohistochemical panels
- Reporting elements (WHO 2021 compliance)

Before I generate these (especially the flowchart PDF), could you please confirm **your intended audience and format preference**?

- A) **Clinical (MDT / hospital protocol)** – practical, guideline-aligned summary for neurosurgeons, oncologists, and pathologists.
- B) **Research / grant-support tool** – more detailed annotation with evidence levels and citations.
- C) **Teaching / training resource** – simplified for residents and fellows.

Each version has different tone and layout density. Which do you prefer?

Clinical

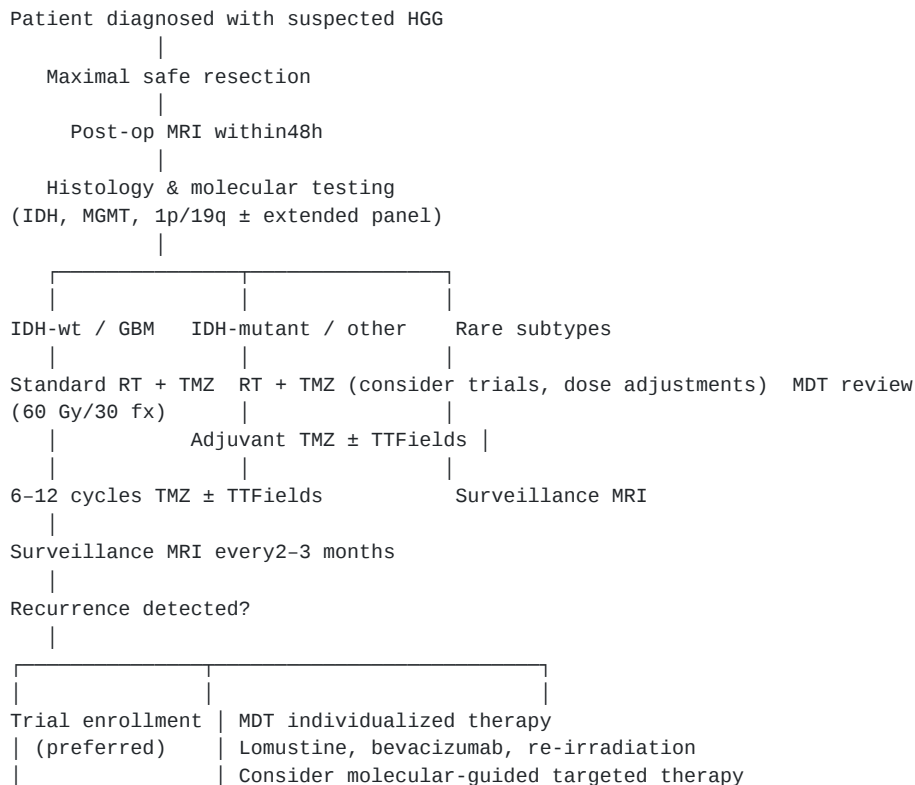
Perfect — I'll generate all three deliverables tailored for **clinical use**: clear, practical, guideline-aligned, and ready for MDT discussion or protocol integration.

Step / Domain	NCCN (USA)	EANO (Europe)	ESMO (Europe/global)	Chinese consensus
Surgery	Maximal safe resection; goal: gross total if feasible; consider functional mapping.	Same; emphasize pre-op functional imaging, intraoperative guidance.	Same; multidisciplinary planning recommended.	Same; MDT planning, consider Gliadel wafers in selected centers.
Radiotherapy (RT)	Standard: 60 Gy in 30 fractions (for glioblastoma), start 3–6 weeks post-op.	Same; detailed contouring and dose constraints per ESTRO/EANO.	Same; highlight molecular subgroup considerations (IDH status may influence dose planning in trials).	Standard fractionation; MDT-approved planning; resource-adapted delivery if necessary.
Concurrent chemotherapy	Temozolomide 75 mg/m ² daily during RT.	Same; molecular stratification recommended for decision-making.	Same; stress adherence and monitoring of counts/labs.	Same; incorporate routine molecular testing (IDH, MGMT).
Adjuvant / Maintenance	Temozolomide 150–200 mg/m ² , 5 days per 28 days, 6–12 cycles; TTFields recommended where available.	Same; TTFields noted if accessible; consider molecular profile.	Same; encourage adherence to molecular-informed decisions.	Same; TTFields optional; incorporate MDT discussion.
Salvage / recurrence	Lomustine, bevacizumab, re-challenge TMZ, re-irradiation, clinical trial preferred.	Individualized; trial enrollment emphasized; MDT selection.	Trial enrollment first; off-trial salvage therapy individualized.	Similar; MDT review; trial preferred; resource constraints considered.
Molecular diagnostics	Mandatory: IDH1/2, MGMT methylation; recommended: 1p/19q, ATRX, TERT.	Same; molecular-guided therapy strongly encouraged.	IDH, MGMT, 1p/19q; extended panel optional.	IDH, MGMT required; extended panel recommended when feasible.
Immunotherapy / novel agents	Only in clinical trials or biomarker-selected contexts.	Same; trial-based use.	Same; trial participation emphasized.	Same; primarily trial-based.

2 Decision algorithm (clinical flowchart)

Text-based flowchart (can be converted to PDF for MDT / protocol use):

sql



Clinical notes for flowchart:

- All decisions pass through **MDT review**.
- TTFields only if available and feasible.
- Salvage therapies individualized; clinical trial participation prioritized.
- Molecular diagnostics guide therapy decisions and trial eligibility.

3 Minimum molecular-testing & pathology checklist

Mandatory core tests (for all adult HGG):

- IDH1/2 mutation (immunohistochemistry + sequencing if IHC negative)
- MGMT promoter methylation (PCR or pyrosequencing)

Recommended / extended panel (where available):

- 1p/19q codeletion
- ATRX loss / mutation
- TERT promoter mutation
- EGFR amplification / EGFRvIII (for targeted trial eligibility)

- CDKN2A/B deletion

Immunohistochemical markers:

- GFAP (glial lineage confirmation)
- Ki-67 / MIB-1 proliferation index
- p53 (as adjunct marker)

Reporting elements:

- WHO 2021 integrated diagnosis (histology + molecular)
- Molecular test method and sensitivity
- Residual tumor estimate from post-op MRI
- Any clinically actionable alterations for trial enrollment

Implementation tips:

- Ensure **rapid turnaround** for molecular panels to inform adjuvant therapy and trial selection.
- Include results in **MDT review package** for therapy planning.
- Repeat molecular testing at recurrence if trial eligibility or therapy choice depends on updated status.

(29 oct 2025)