

ONCOLOGY KNOWLEDGE HUB · FOR HEALTH PROFESSIONALS

Brain Tumours

A mini review for clinicians

For postgraduate residents (medical, radiation and paediatric oncology, neurosurgery, neurology, medicine, paediatrics), practising clinicians and medical students

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Updated 9 October 2026. Educational summary written in our own words from current guidelines and primary trials; no drug doses; not advice for an individual patient. Verify current guidelines and Indian regulatory approvals before treatment decisions. Patients and families: please see the patient guides at drharitha.co.in.

Brain Tumours

Adult glioma · Brain metastases · Paediatric CNS tumours · IDH · 1p/19q · MGMT · BRAF · H3 · Key points for clinicians · Last updated 9 October 2026

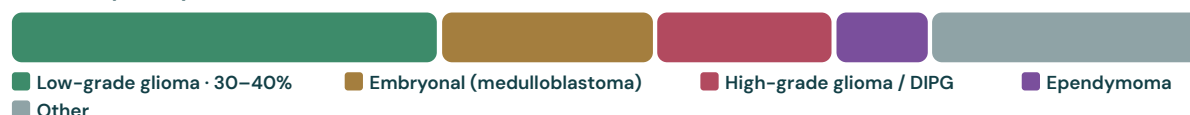
01 At a glance

- India records about **32,000 new brain and CNS cancers and 28,000 deaths a year** (GLOBOCAN 2022; malignant tumours only, so benign meningiomas and most childhood low-grade gliomas are not counted). Brain tumours are among the commonest causes of cancer death in children and young adults.
- In adults over 40, **metastases are commoner than all primary brain tumours combined** (lung, breast, melanoma, kidney, gastrointestinal). Among primary tumours, meningiomas and gliomas make up about two-thirds; **glioblastoma** is the commonest malignant one (median age about 64).
- Diffuse gliomas are now named by **molecular markers** (WHO 2021): IDH-mutant astrocytoma (grade 2–4), IDH-mutant 1p/19q-codeleted oligodendroglioma (grade 2–3) and IDH-wildtype glioblastoma (grade 4). Prognosis ranges from a median of about 15 months to 15–20 years.
- Children have different tumours: low-grade glioma (30–40%), medulloblastoma and other embryonal tumours, ependymoma and diffuse midline glioma, about half in the **posterior fossa**. Many are curable; late effects of treatment shape lifelong care.
- The avoidable harms in Indian practice are **delay and mislabelling**: seizures treated for years without a scan, ring lesions called tuberculoma without proof, steroids given before a biopsy when lymphoma is possible, and morning vomiting in a child blamed on acidity.

Adults (all intracranial tumours): metastases outnumber primary tumours



Children (primary CNS tumours, the commonest solid cancers of childhood)



Adult diffuse glioma

- Defined by IDH, 1p/19q and other markers
- Glioblastoma: commonest malignant primary
- Seizure, focal deficit, raised pressure

Brain metastases

- Lung, breast, melanoma, kidney, GI
- Often found by staging MRI
- SRS and CNS-active drugs changed outcomes

Children

- Half in the posterior fossa
- Vomiting, ataxia, squint, head tilt
- Many cured; late effects matter

Figure 1. Three working groups. In adults most brain masses are metastases; among primary tumours, meningioma and glioma dominate. In children, low-grade glioma and medulloblastoma lead, and about half arise in the posterior fossa. Proportions are approximate (CBTRUS and hospital series).

02 Clinical presentation, common traps & genetic causes

Who is at risk

Factor	Size of risk	Clinical note
Ionising radiation to the head	The only firmly established environmental cause; risk rises with dose and young age at exposure	Childhood cranial RT (leukaemia, tinea capitis era) → meningioma, glioma, nerve sheath tumours decades later.
Hereditary syndromes	About 1–5% of brain tumours	NF1 (optic pathway glioma in 10–15%), NF2-related schwannomatosis (bilateral vestibular schwannoma), tuberous sclerosis (SEGA), Li-Fraumeni (choroid plexus carcinoma, SHH medulloblastoma), von Hippel-Lindau (haemangioblastoma), Gorlin (SHH medulloblastoma), FAP (medulloblastoma).
Constitutional or Lynch mismatch-repair deficiency	Rare; enriched in young adults with glioma	Café-au-lait spots, consanguinity, early bowel or blood cancers in the family: check MMR proteins and refer for genetics.
Age and sex	Glioblastoma peaks at 55–75, commoner in men; meningioma commoner in women	Low-grade gliomas peak in young adults.
Allergy and atopy	Consistently associated with lower glioma risk	Not used clinically.
Not established	Mobile phones, power lines, head injury, diet, stress	Reassure without dismissing the question (see the Myth Buster on phones).

How brain tumours present

Feature	How often	What to know
Headache	Presenting in about 20%; at some point in about half	Usually tension-like; the classic morning headache with vomiting is uncommon (about 5% meet the "triad"). Isolated headache with a normal examination is rarely a tumour.
Seizure	50–80% of primary tumours (most in low-grade and IDH-mutant gliomas); 10–20% of metastases	Often focal (smell, déjà vu, limb jerking) and stereotyped; a first adult seizure needs MRI.
Focal deficit	Common in high-grade glioma and metastases	Weakness that improves on steroids is usually oedema, not tumour destruction.
Cognitive or personality change	Frontal and corpus callosum tumours, multiple metastases	Often mistaken for depression or dementia.
Raised pressure	Posterior fossa, large or haemorrhagic tumours	Headache worse lying down or with coughing, vomiting, papilloedema, transient visual obscurations; a sudden collapse can be a pressure wave, not a seizure.

Image the brain (MRI with contrast) when

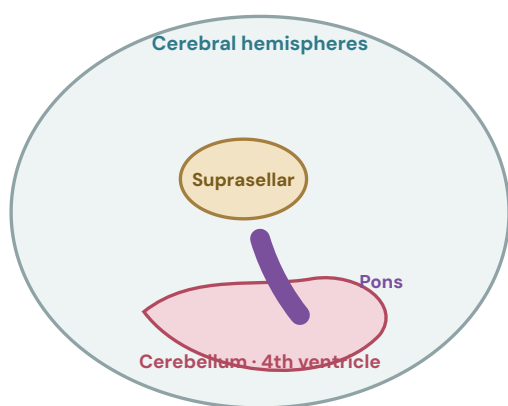
- New headache over 50, or a changed headache pattern
- Headache with vomiting, worse lying down, waking from sleep
- Headache with focal signs, confusion or papilloedema
- First seizure in an adult (not provoked)
- Progressive weakness, speech, vision or personality change
- Any neurological symptom in a person with known cancer
- Child: morning vomiting, ataxia, new squint, head tilt, regression

Common traps in Indian practice

- Ring lesion called tuberculoma or NCC without the full picture
- Steroids started before biopsy when lymphoma is possible
- Seizure treated for years with no scan
- Morning vomiting in a child treated as acidity or worms
- Normal plain CT taken as the end of the work-up
- Confusion in a cancer patient blamed on “weakness”

Isolated headache with a normal neurological examination is rarely a tumour (about 1.5% of headache MRIs); only a small minority of brain tumours present with headache alone.

Figure 2. When to scan, and what delays diagnosis. Headache is common but seldom isolated in brain tumours; the red flags are the pattern, the age and the company it keeps.

**Posterior fossa (~half)**

Pilocytic astrocytoma, medulloblastoma, ependymoma, DIPG (pons).
Morning vomiting, ataxia, head tilt, hydrocephalus.

Suprasellar / optic

Craniopharyngioma, optic pathway glioma (NF1), germ cell tumour.
Vision loss, short stature, polyuria, early puberty.

Hemispheres

Low-grade glioneuronal tumours (seizures), high-grade gliomas.
Seizures, weakness, behaviour change.

Infants

Large head, bulging fontanelle, sunset eyes, loss of milestones.
Embryonal tumours, ATRT.

Figure 3. Children: location predicts the tumour and the symptoms. Image a child with headache that wakes them or is worse lying down, persistent morning vomiting, a new squint, ataxia, regression of skills or age ≤ 6 with headache.

Lesion	Imaging and clinical clue	Next step
Metastasis	Grey-white junction, often multiple, much oedema; known or occult primary	CT chest–abdomen–pelvis; biopsy the easiest site
Glioblastoma	Thick irregular rim, necrosis, crosses corpus callosum	Resection or biopsy; IDH, MGMT
Primary CNS lymphoma	Periventricular, homogeneous, restricted diffusion	NO steroids before biopsy; HIV test; slit-lamp
Pyogenic abscess	Thin smooth rim; centre restricts on diffusion	Source, cultures, drainage
Tuberculoma	Conglomerate rings, basal meningitis, chest TB	Tissue or CSF proof where possible
Neurocysticercosis	Cyst with scolex (dot), often several, seizures	Serology, CT calcifications; usually small
Tumefactive demyelination	Open (incomplete) ring, little mass effect	MRI spine, CSF; biopsy if unsure

Figure 4. A ring-enhancing lesion is not a diagnosis. Diffusion-weighted MRI, the clinical setting and a search for a primary narrow it down; tissue settles it. Give steroids only for threatening oedema until lymphoma has been excluded.

- **Ring lesions in India:** tuberculoma and neurocysticercosis are common and real, but so are metastases, glioblastoma and lymphoma. A single ring lesion that grows on antituberculous treatment, or any lesion in a person over 40 with a smoking history or weight loss, needs a search for a primary and usually tissue.
- **Steroids and lymphoma:** dexamethasone can shrink primary CNS lymphoma within days and make the biopsy non-diagnostic. If a periventricular, homogeneously enhancing, diffusion-restricting lesion is seen and the patient is not deteriorating, withhold steroids until tissue is taken.
- **Known cancer plus a new neurological symptom** is a brain metastasis or leptomeningeal disease until MRI says otherwise; ask for MRI with contrast, not plain CT.
- **Children:** isolated headache at presentation is rare (0–1%); look for the company it keeps: morning vomiting, ataxia, head tilt, new squint, poor school performance, a growing head in an infant, loss of milestones, growth failure or polyuria. Neuroimaging is warranted for headache in a child aged 6 or under.

SHARE WITH PATIENTS: PRESENTATION AND MYTHS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[📄 Telugu–English handout: brain tumour warning signs \(adults and children\) \(తెలుగు · English\)](#)

[Every headache means a brain tumour?](#)

[Brain tumours always cause severe headaches?](#)

[A seizure always means epilepsy, not a brain tumour?](#)

[A normal CT scan completely rules out a brain tumour?](#)

[A tumour found in the brain must have started in the brain?](#)

03 Screening, workup & staging essentials

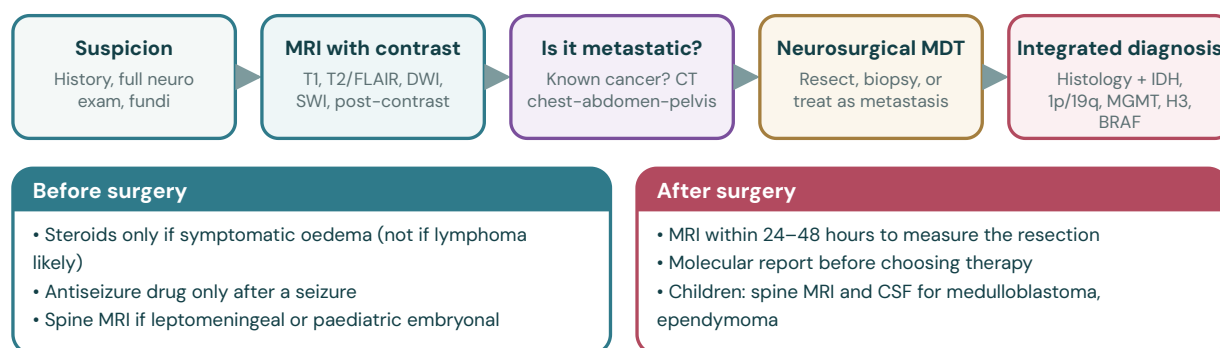


Figure 5. From suspicion to an integrated diagnosis. MRI is usually the only test needed before surgery for a likely glioma; tissue with molecular testing is required for nearly every tumour except typical optic pathway glioma, tectal glioma and DIPG.

Imaging: what each sequence tells you

Finding	Suggests
Non-enhancing T2/FLAIR mass, little oedema	Lower-grade glioma (though up to half of grade 2 oligodendrogliomas enhance faintly, and absence of enhancement does not exclude grade 3)
T2–FLAIR mismatch (bright on T2, dark centre on FLAIR)	IDH-mutant, 1p/19q-intact astrocytoma: highly specific
Calcification on CT, cortical involvement, frontal	Oligodendroglioma
Thick irregular ring, central necrosis, crosses corpus callosum	Glioblastoma (or lymphoma if solid and homogeneous)
Multiple round lesions at the grey–white junction with disproportionate oedema	Metastases
Restricted diffusion in the cavity centre	Abscess; restricted solid tumour: lymphoma, medulloblastoma
Dural-based, dural tail, homogeneous enhancement	Meningioma (or solitary fibrous tumour, dural metastasis)

- MRI with contrast is usually the only test needed before surgery for a likely glioma; CT is for emergencies, bone detail and patients who cannot have MRI. Do not screen the body for a primary when imaging strongly suggests glioma.
- **When a metastasis is likely:** CT chest–abdomen–pelvis (or PET–CT); biopsy the most accessible site. A single lesion without a known primary may be resected for diagnosis.
- **Tissue** is needed for almost every tumour (maximal safe resection or stereotactic biopsy). Exceptions where imaging is enough: typical DIPG, optic pathway glioma (especially with NF1) and tectal glioma.
- **Postoperative MRI within 24–48 hours** measures the extent of resection before surgical changes enhance.
- **Grading in adult glioma** is integrated: histology plus IDH, 1p/19q, CDKN2A/B and, in IDH-wildtype tumours, TERT, EGFR and chromosome 7/10. Ask for an integrated report; sampling error at biopsy can under-grade.

- **Prognosis in metastases:** the disease-specific Graded Prognostic Assessment ([GPA^{\[1\]}](#)) uses performance status, age, extracranial disease, number of lesions and tumour genotype; median survival now ranges from about 8 to 16 months and is longer with CNS-active drugs.
- **Staging in children:** MRI of the whole spine and CSF cytology (lumbar, about 2 weeks after surgery) for medulloblastoma, ependymoma and other embryonal or germ cell tumours; serum and CSF AFP and β -hCG for suprasellar or pineal tumours; endocrine and visual assessment for suprasellar lesions.

Maximal safe resection

- Goal for accessible gliomas
- Gross total → longer survival
- Awake mapping for eloquent areas
- MRI in 24–48 h to confirm

Stereotactic biopsy

- Deep, multifocal or eloquent
- Lymphoma suspected
- Risk: sampling error, undergrading
- Enough tissue for molecular tests

Shunt / ETV / resection

- Obstructive hydrocephalus
- Posterior fossa tumours in children
- Large metastasis with mass effect
- Diagnostic doubt about a "metastasis"

Patchell 1990: in single metastases, 11% turned out not to be metastases at surgery. Tissue is worth having when the story does not fit.

Figure 6. What the neurosurgeon offers. Resection gives tissue, relieves mass effect and, for gliomas, prolongs survival when it is safe; biopsy is for deep, diffuse or lymphoma-like lesions.

04 Biomarkers that change treatment

In this section: [How gliomas develop \(molecular pathogenesis\)](#) · [Molecular markers: what each one means](#)

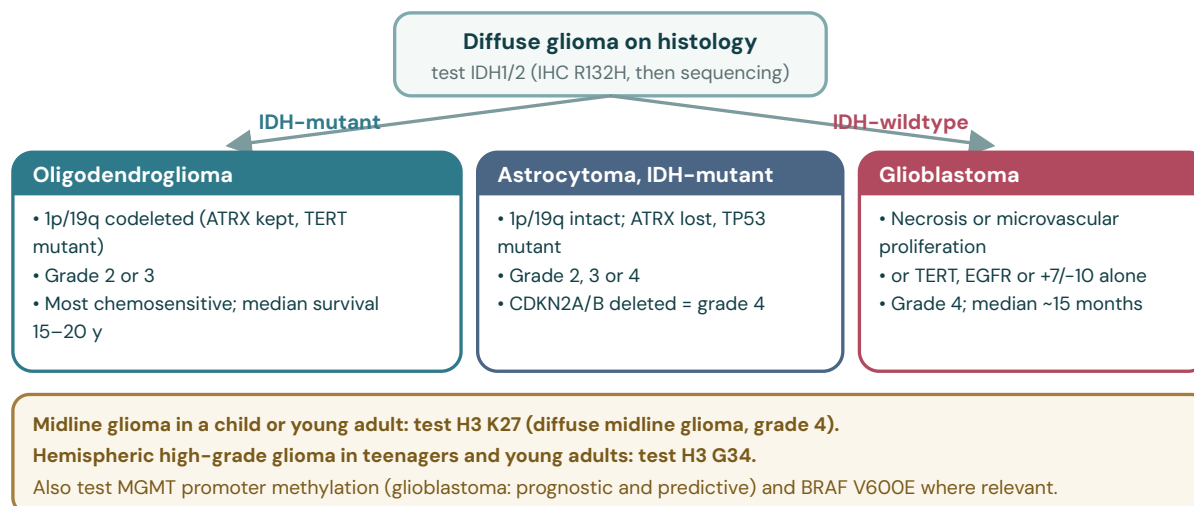


Figure 7. How the 2021 WHO classification names a diffuse glioma. Molecular markers now outrank appearance: an IDH-wildtype astrocytoma with a TERT mutation is a glioblastoma even if it looks low grade, and a CDKN2A/B-deleted IDH-mutant astrocytoma is grade 4.

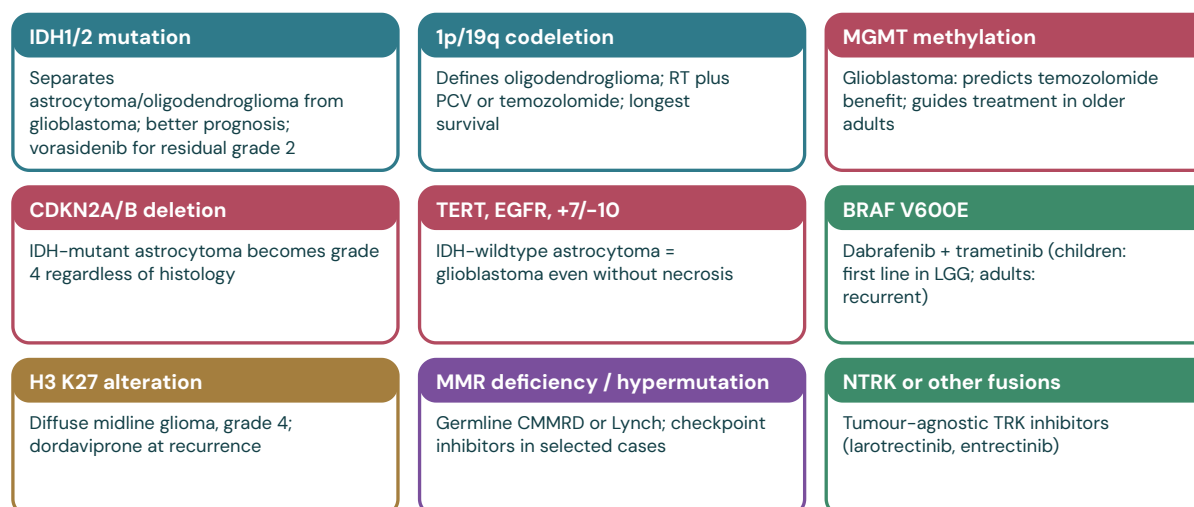


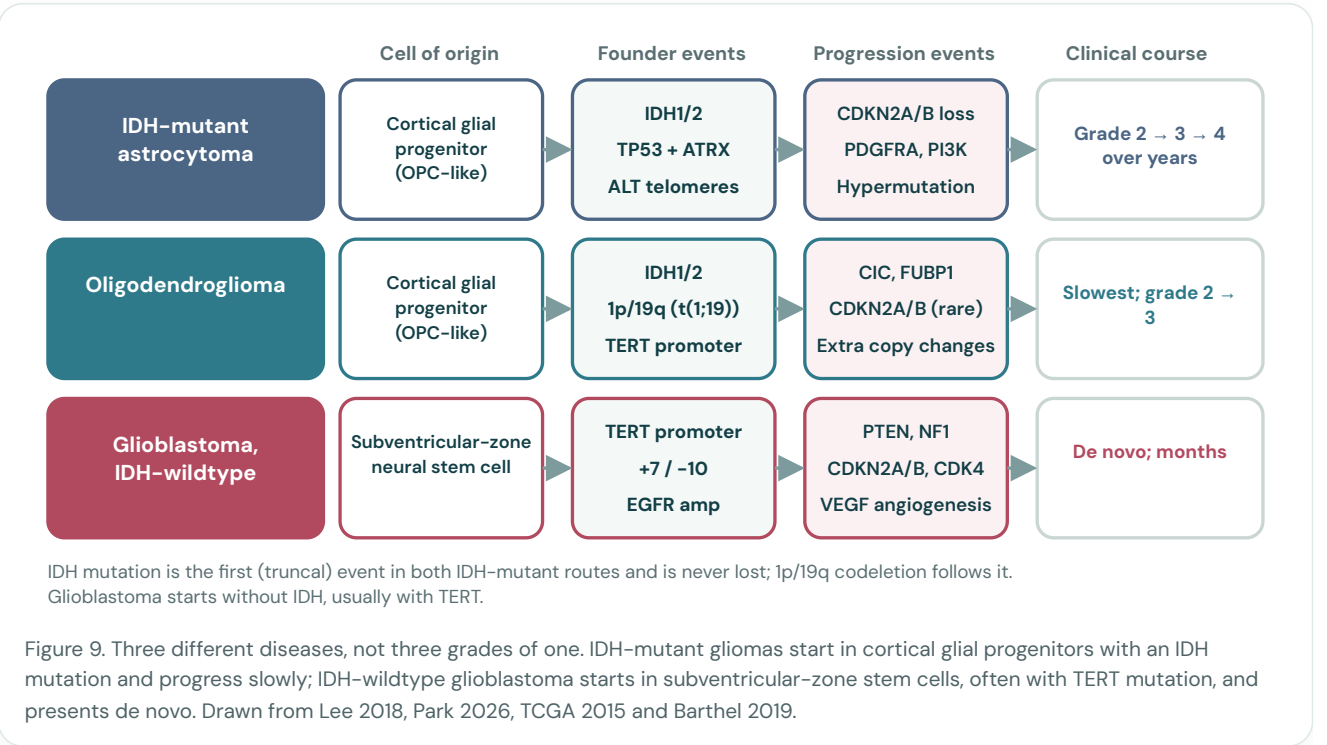
Figure 8. Tests that change treatment. Ask for IDH, 1p/19q and MGMT on every adult diffuse glioma; H3 and BRAF in children and young adults. Many centres in India send blocks for NGS or methylation profiling; plan this at the first MDT.

- **IDH:** immunohistochemistry for IDH1 R132H finds about 90% of mutations; if negative in a grade 2–3 glioma or a patient under 55, sequence IDH1 codon 132 and IDH2 codon 172.
- **1p/19q** must be whole-arm codeletion (NGS, methylation array or LOH); FISH alone can mislead. Retained ATRX with no p53 overexpression in an IDH-mutant tumour points to oligodendroglioma.
- **MGMT:** methylated in about 40–50% of glioblastomas; median survival 21.7 vs 15.3 months with temozolomide when methylated, with little gain when unmethylated ([Hegi 2005^{\[2\]}](#)). Assays vary; if unknown, treat with temozolomide.
- **Methylation profiling** classifies tumours that histology cannot (paediatric-type high-grade gliomas, ependymoma groups, embryonal tumours). Plan referral of tissue blocks early; results take weeks.

- **Paediatric low-grade glioma** almost always has one MAPK-pathway driver: KIAA1549–BRAF fusion (most cerebellar pilocytic astrocytomas), BRAF V600E (about 15–20% overall; worse with chemotherapy alone), FGFR1/2 or NF1 loss. Each now has a matched drug.
- **Medulloblastoma groups:** WNT (excellent prognosis), SHH (test TP53; germline TP53, SUFU or PTCH1 common), group 3 (MYC, worst) and group 4. Group drives risk-adapted therapy and trial entry.
- **Brain metastases:** re-test the metastasis when it changes treatment (EGFR, ALK, HER2, BRAF); genotype also feeds the GPA score.

How gliomas develop: molecular pathogenesis

Diffuse gliomas that look alike under the microscope arise along different molecular routes, from different cells, at different ages. Knowing the route explains the WHO classification, the prognosis, why some tumours respond to chemotherapy and why many targeted drugs have failed. Summarised in our own words from the primary studies ([TCGA 2008](#)^[3], [TCGA 2015](#)^[4], [GLASS 2019](#)^[5]).



Tumour	Starting event	Co-operating events	Progression and recurrence	What it means in clinic
Astrocytoma, IDH-mutant	IDH1/2 mutation in a cortical glial progenitor	TP53 mutation, ATRX loss → alternative lengthening of telomeres (ALT)	CDKN2A/B deletion, PDGFRA amplification, PI3K mutations, genome-wide instability; hypermutation after temozolomide	Slow but relentless; grade rises over years; CDKN2A/B loss = grade 4; IDH inhibitors act on the founding event
Oligodendroglioma	IDH1/2 mutation	Whole-arm 1p/19q loss from one t(1;19) translocation; TERT promoter mutation; CIC (about 70%) and FUBP1 mutations	Extra copy-number changes; CDKN2A/B loss in a few	Most chemosensitive glioma (hypermethylation silences MGMT and other repair genes); survival measured in decades
Glioblastoma, IDH-wildtype	Low-level drivers (often TERT promoter) in subventricular-zone stem cells	Chromosome +7/-10 (PTEN), EGFR amplification ± vlll, CDKN2A/B or CDK4/RB changes, NF1, PDGFRA, MET	Early changes are kept at relapse; hypermutation after temozolomide in a minority	Rapid, infiltrative, angiogenic; most relapse within 2 cm; no single-pathway drug has worked

Tumour	Starting event	Co-operating events	Progression and recurrence	What it means in clinic
Paediatric-type diffuse high-grade glioma	Histone H3 K27M (midline) or G34R/V (hemispheric); or H3/IDH-wildtype with PDGFRA, EGFR or MYCN	ACVR1 (H3.1 DIPG), TP53, ATRX–DAXX, PDGFRA	Usually rapid	Different diseases from adult glioblastoma: diagnose by H3 status and methylation; trials target the epigenome (for example dordaviprone)
Paediatric-type low-grade glioma	One MAPK-pathway driver: KIAA1549–BRAF fusion, BRAF V600E, FGFR1, NF1 loss, MYB/MYBL1	Usually none (genetically simple)	Rarely transforms (more with BRAF V600E + CDKN2A loss)	Matched MAPK inhibitors work; oncogene-induced senescence explains slow growth

RTK / RAS / PI3K growth signalling

- EGFR amplification (~40%), EGFRvIII
- PDGFRA, MET amplification; FGFR–TACC fusion
- PTEN loss (chromosome 10 loss 60–85%)
- NF1 loss; PI3K mutation
- → proliferation and survival

p53 pathway

- TP53 mutation (most IDH-mutant astrocytomas)
- MDM2/MDM4 amplification
- CDKN2A loss removes p14ARF
- → escape from apoptosis
- → genomic instability

RB / cell-cycle pathway

- CDKN2A/B deletion (p16, p15)
- CDK4 or CDK6 amplification (10–15%)
- RB1 loss (13q loss in about a third)
- Usually only one of these per tumour
- → unchecked G1 → S entry

Children and young adults: the histone route (epigenetic “oncohistones”)

H3 K27M (H3.3 or H3.1 genes; EZHIP mimics it) blocks the PRC2 complex → global loss of H3K27 trimethylation → developmental genes stay switched on.

Midline (pons, thalamus, spinal cord); DIPG often adds ACVR1 (H3.1) and TP53/PDGFRA changes. H3 G34R/V acts in hemispheric tumours of teenagers.

H3 mutations are mutually exclusive with IDH mutation: each defines a separate disease (Sturm 2012). Paediatric LGG instead has a single MAPK driver (BRAF, FGFR1, NF1, MYB).

Figure 10. The three core pathways defined by TCGA (2008): nearly every glioblastoma breaks each of them somewhere. Children's high-grade gliomas are driven mainly by histone mutations that rewire the epigenome rather than by the adult pattern.

Cell of origin

- **IDH-wildtype glioblastoma:** deep sequencing of tumour, normal cortex and subventricular-zone (SVZ) tissue showed astrocyte-like neural stem cells in the SVZ carrying low-level driver mutations, which then migrate and acquire further mutations ([Lee 2018](#)^[6]). This fits the frequent periventricular location and the de novo presentation.
- **IDH-mutant gliomas:** sampling of tumour and adjacent cortex points to cortical glial progenitors (oligodendrocyte-precursor-like cells) that already carry the IDH mutation. This fits their cortical, frontal-lobe location and their tendency to cause seizures.

How an IDH mutation makes a glioma

- IDH mutations were discovered in 12% of glioblastomas in 2008 ([Parsons 2008](#)^[7]) and then found in most lower-grade gliomas ([Yan 2009](#)^[8]). They are heterozygous, hit the active site (IDH1 R132, IDH2 R172) and occur first; every tumour cell carries them.
- **A new function, not a lost one:** the mutant enzyme converts alpha-ketoglutarate into the oncometabolite R-2-hydroxyglutarate (2-HG) ([Dang 2009](#)^[9]). 2-HG competitively blocks alpha-ketoglutarate-dependent enzymes: TET DNA demethylases and histone demethylases.
- **Hypermethylation (G-CIMP):** the result is a CpG-island methylator phenotype across the genome ([Noushmehr 2010](#)^[10]); an IDH1 mutation alone is enough to create it ([Turcan 2012](#)^[11]). Differentiation genes

are silenced, cells stay progenitor-like, and MGMT is methylated in almost every IDH-mutant glioma.

- **Insulator failure:** methylation stops CTCF from binding chromatin boundaries, so an enhancer reaches and switches on the PDGFRA oncogene ([Flavahan 2016](#)^[12]).
- **Immune escape:** 2-HG released by tumour cells suppresses T-cell activation in the microenvironment ([Bunse 2018](#)^[13]), one reason IDH-mutant gliomas are immunologically "cold".
- **Why this matters:** (1) IDH inhibitors such as vorasidenib lower 2-HG and slowed growth of grade 2 tumours in INDIGO; the effect is greatest early, before additional drivers accumulate. (2) The hypermethylated state silences DNA repair, which helps explain the chemosensitivity of oligodendroglioma. (3) 2-HG can be measured by MR spectroscopy.

The IDH-mutant astrocytoma route

- After IDH, the tumour inactivates **TP53** (usually a missense mutation in the DNA-binding domain, hotspots at codons 175, 248 and 273, with loss of the other allele) and **ATRX** (over 70% of grade 2–3 tumours). ATRX loss lets cells keep their telomeres by alternative lengthening (ALT) instead of telomerase.
- Progression is driven by **CDKN2A/B deletion**, RTK/PI3K activation (PDGFRA amplification, PIK3CA mutations), genome-wide copy-number instability and, at recurrence after temozolomide, hypermutation. These tumours were previously called "secondary glioblastoma" when they reached grade 4.
- Longitudinal cohorts show that recurrent tumours lose methylation as the cell cycle speeds up, which is now being used to refine grading.

The oligodendroglioma route

- After IDH, a single unbalanced translocation between chromosomes 1 and 19 is followed by loss of the derivative chromosome, deleting the whole of 1p and 19q in one step ([Jenkins 2006](#)^[14]).
- The remaining copies of tumour-suppressor genes on the lost arms are then mutated: **CIC** on 19q (about 70%) and **FUBP1** on 1p ([Bettegowda 2011](#)^[15]). Their exact roles are still unclear.
- Telomeres are maintained by **TERT promoter mutation** rather than ATRX loss, so TERT and ATRX alterations are mutually exclusive. A small TERT-wildtype subset in young patients may behave even more favourably.

The IDH-wildtype glioblastoma route

- **Telomerase:** TERT promoter mutations (55–80%) are among the earliest events.
- **Three core pathways** ([TCGA 2008](#)^[3]): growth signalling through RTK/RAS/PI3K (EGFR amplification in about 40%, a third of these with the constitutively active EGFRvIII; PDGFRA, MET; PTEN loss with chromosome 10 loss in 60–85%; NF1 loss); the p53 pathway (TP53, MDM2/MDM4, p14ARF); and the RB cell-cycle pathway (CDKN2A/B deletion, CDK4 amplification in 10–15%, RB1 loss). Within the RB pathway, tumours usually carry only one of these hits.
- **Autocrine loops and rare fusions:** tumour cells often make both a growth factor and its receptor (PDGF, EGF, HGF/MET, FGF). Rare FGFR3–TACC3 fusions ([Singh 2012](#)^[16]) are mutually exclusive with EGFR, PDGFR and MET amplification and are trial targets.
- **Angiogenesis and necrosis:** microthrombosis and hypoxia trigger HIF, which drives VEGF; hypoxic cells migrate away from necrotic zones, forming pseudopalisades around necrosis and microvascular proliferation. This explains the ring of enhancement, why bevacizumab reduces oedema and enhancement so quickly, and why that imaging response does not prolong survival.

- **Heterogeneity:** expression profiling defined proneural, neural, classical and mesenchymal subtypes ([Verhaak 2010^{\[17\]}](#)), but single-cell sequencing found several subtypes inside one tumour ([Patel 2014^{\[18\]}](#)). One tumour, many clones: a key reason single-pathway drugs (EGFR, mTOR, PDGFR inhibitors) have failed.

Treatment shapes the tumour

- After temozolomide, about a quarter to a half of recurrent gliomas become **hypermuted**, usually through loss of mismatch-repair genes such as MSH6 ([Cahill 2007^{\[19\]}](#)); this is much rarer after nitrosoureas or radiotherapy alone. MSH6 loss makes the tumour resistant to further temozolomide.
- Unlike germline mismatch-repair deficiency, treatment-induced hypermutation has not translated into responses to checkpoint inhibitors ([Touat 2020^{\[20\]}](#)).
- Founder events (IDH, 1p/19q, TERT) persist at relapse; progression events (CDKN2A/B loss, PDGFRA, PI3K, hypermutation) are often new, which is why re-biopsy at recurrence can change the grade and the options ([GLASS 2019^{\[5\]}](#)).

Paediatric gliomas: a different biology

- **Oncohistones:** recurrent mutations in histone H3 genes are found in about 30% of paediatric high-grade gliomas ([Schwartzentruber 2012^{\[21\]}](#)). K27M blocks the PRC2 methyltransferase, wiping out H3K27 trimethylation across the genome and locking cells in a developmental state; G34R/V changes a different histone mark in hemispheric tumours.
- H3 and IDH mutations are mutually exclusive and define separate epigenetic and clinical groups ([Sturm 2012^{\[22\]}](#)). DIPG often adds ACVR1 mutations (with H3.1 K27M), TP53 or PDGFRA changes.
- The H3-wildtype, IDH-wildtype paediatric-type high-grade glioma (PDGFRA, EGFR or MYCN amplification) is best diagnosed by DNA methylation profiling, and the same profile has been found in adults up to 70.
- **Low-grade gliomas of childhood** are genetically simple: one MAPK-pathway driver (KIAA1549-BRAF fusion, BRAF V600E, FGFR1 duplication or fusion, NF1 loss, MYB/MYBL1). This explains their excellent survival, their responses to RAF and MEK inhibitors and their rare transformation.

From biology to the clinic

- The route sets the name and the grade: IDH and 1p/19q split three adult diseases; CDKN2A/B loss signals a late, aggressive stage; TERT, EGFR and +7/-10 identify an early glioblastoma that looks low grade.
- Founding events make the best targets: IDH (vorasidenib), BRAF V600E (dabrafenib + trametinib), NTRK fusions (TRK inhibitors), H3 K27M (dordaviprone, under study). Late, subclonal or redundant pathways (EGFR, PI3K/mTOR, CDK4/6) have not yielded effective drugs.
- Epigenetic state predicts chemotherapy: MGMT methylation (glioblastoma) and the hypermethylated IDH-mutant state (especially oligodendroglioma) mean alkylating drugs work.
- Tumour biology, not location alone, now drives trial eligibility; keep tissue and request molecular profiling at diagnosis and at recurrence.

Molecular markers in gliomas: what each one means

Since 2021 the name and grade of a diffuse glioma depend on its molecular profile, and several markers also predict which treatment will work. A marker can be **diagnostic** (defines the tumour type), **prognostic** (tells you

how it will behave, whatever the treatment) or **predictive** (tells you whether a specific treatment will help). Most important markers do more than one job.

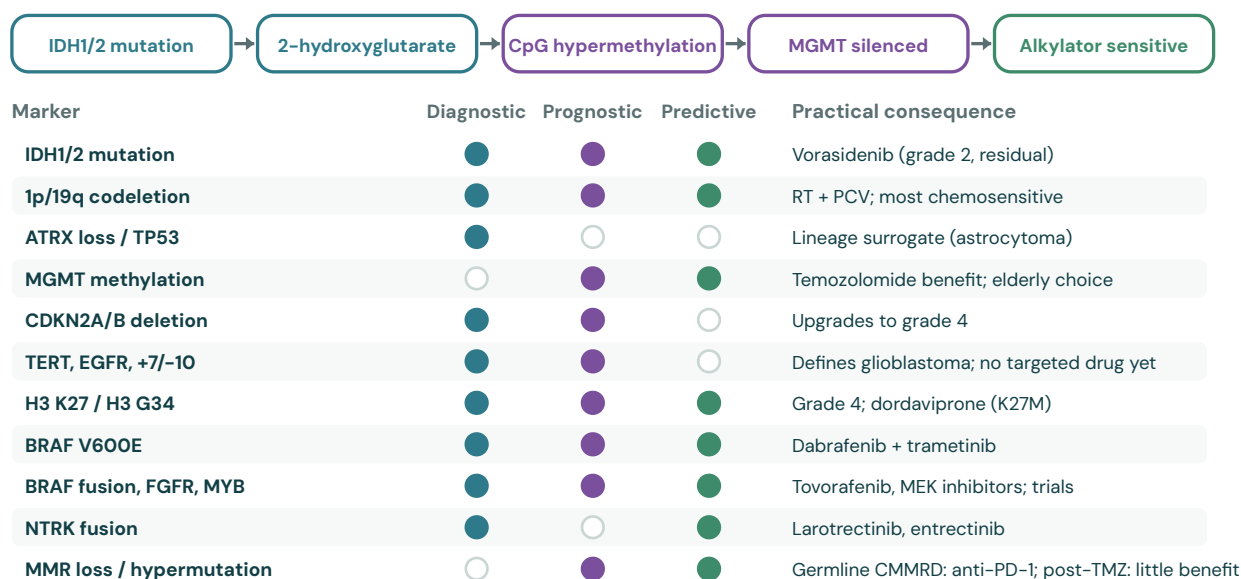


Figure 11. What each marker is for. Top: why IDH-mutant gliomas are chemosensitive (the oncometabolite 2-hydroxyglutarate blocks DNA demethylation, so MGMT is silenced). Filled circles mark established diagnostic, prognostic and predictive roles; a predictive role means the result changes which treatment works.

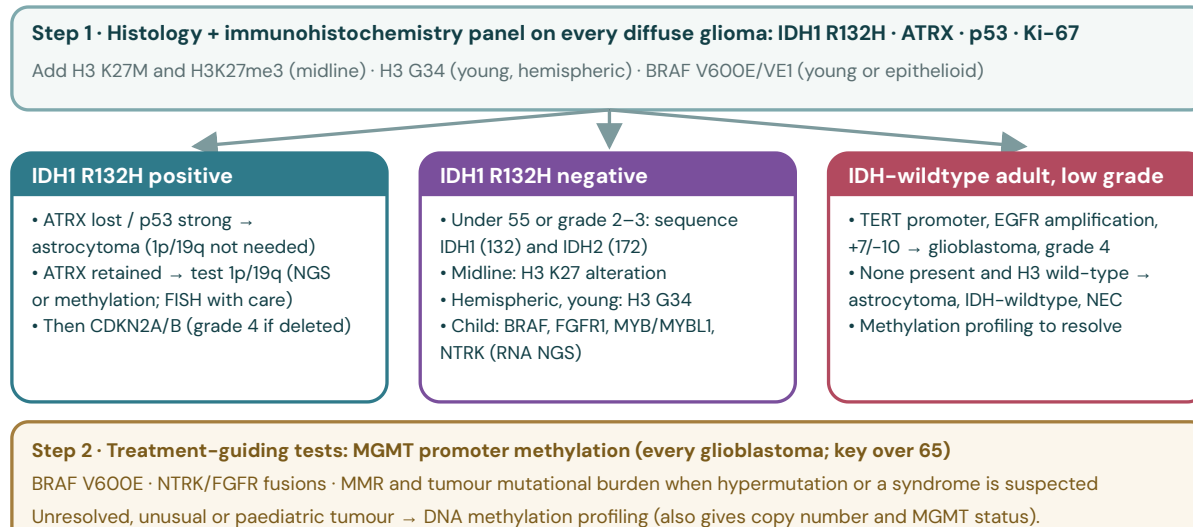


Figure 12. A stepwise testing pathway. Cheap immunohistochemistry answers most questions; sequencing, copy-number testing and methylation profiling are added only where the answer would change the diagnosis or the treatment.

Adult-type diffuse gliomas: marker by marker

Marker	What it is · where it is found	How it is tested	Clinical relevance	Pitfalls
IDH1 / IDH2 mutation	Hotspot mutation in a Krebs–cycle enzyme (IDH1 R132, IDH2 R172). The mutant enzyme makes 2–hydroxyglutarate, which blocks DNA and histone demethylases and causes a CpG-island hypermethylated state. It is the earliest (truncal) event in these tumours. <i>Found in:</i> Most adult grade 2–3 diffuse gliomas; nearly all are under 55 (Yan 2009^[8])	IHC for IDH1 R132H finds about 90%; sequence IDH1 codon 132 and IDH2 codon 172 if IHC is negative (10–20% are non-canonical). 2–HG can be seen on MR spectroscopy.	Diagnostic: splits astrocytoma/oligodendroglioma from glioblastoma. Prognostic: much longer survival. Predictive: vorasidenib for residual grade 2 (INDIGO^[23]).	A negative IHC is not IDH-wildtype in young or lower-grade tumours. IDH1 R132C suggests Li-Fraumeni: consider germline TP53.
1p/19q codeletion	Loss of the whole short arm of chromosome 1 and long arm of 19 after an unbalanced t(1;19) translocation. CIC (19q, about 70%) and FUBP1 (1p) mutations often accompany it. <i>Found in:</i> Defines oligodendroglioma; always with IDH mutation, usually with TERT promoter mutation	NGS or methylation-array copy number (whole-arm). FISH is widely used but cannot prove whole-arm loss.	Diagnostic for oligodendroglioma. Prognostic: median survival 15–20 years. Predictive: marked benefit from PCV with RT (EORTC 26951/RTOG 9402^[24]).	"Codeletion" without IDH mutation means partial deletions: look for glioblastoma features. Not needed when ATRX loss or p53 overexpression already shows an astrocytoma.
ATRX loss	Chromatin remodeller; loss allows alternative lengthening of telomeres (ALT). <i>Found in:</i> More than 70% of grade 2–3 IDH-mutant astrocytomas; mutually exclusive with 1p/19q codeletion and TERT mutation	IHC: loss of nuclear staining in tumour cells, retained in vessels (internal control)	Diagnostic surrogate: IDH-mutant + ATRX lost = astrocytoma.	Also lost in H3 G34-mutant gliomas, which are IDH-wildtype: do not call these IDH-mutant astrocytoma without IDH proof.
TP53 mutation	Tumour suppressor; mutation of one copy plus loss of the other. <i>Found in:</i> Most IDH-mutant astrocytomas; also many glioblastomas	IHC (strong, diffuse nuclear p53) as surrogate; sequencing	Diagnostic support for astrocytic lineage with ATRX loss.	Young patient, family cancers or IDH1 R132C: think Li-Fraumeni.
MGMT promoter methylation	Epigenetic silencing of the DNA-repair enzyme that removes the methyl lesion made by temozolomide and lomustine. <i>Found in:</i> 40–50% of glioblastomas (30–60% depending on assay); almost all IDH-mutant gliomas (part of the hypermethylated state)	Methylation-specific PCR, pyrosequencing or methylation array; no universal cut-off, and a "grey zone" exists	Prognostic and predictive in glioblastoma: median 21.7 vs 15.3 months with temozolomide if methylated, little gain if not (Hegi 2005^[2]). Decides temozolomide alone vs RT alone in older or frail patients. Predicts pseudoprogression.	Unknown or failed test: still give temozolomide to fit patients. Not routinely needed in oligodendroglioma. Small biopsies often fail.
CDKN2A/B homozygous deletion	Loss of both copies of the 9p21 cell-cycle brakes (p16, p14ARF, p15). <i>Found in:</i> Subset of IDH-mutant astrocytomas (more at recurrence); about 7% of grade 3 oligodendrogliomas; many glioblastomas	FISH, NGS or methylation-array copy number	Grading: IDH-mutant astrocytoma becomes grade 4 regardless of histology (cIMPACT-NOW update 5^[25], Shirahata 2018^[26]). Prognostic: CATNON median 3 vs 9.6 years.	Hemizygous loss or mutation does not upgrade by itself. Biopsy can miss a deleted subclone.

Marker	What it is · where it is found	How it is tested	Clinical relevance	Pitfalls
TERT promoter mutation	Hotspot mutations (C228T, C250T) that switch on telomerase. <i>Found in:</i> Most oligodendrogliomas; 55–80% of IDH-wildtype glioblastomas	Targeted sequencing (make sure the panel covers the promoter)	Diagnostic: in an IDH-wildtype adult astrocytoma it establishes glioblastoma, grade 4 (cIMPACT-NOW update 3 ^[27]). Prognostic depends on context (Eckel-Passow 2015 ^[28]).	A small group of "TERT-only", non-enhancing IDH-wildtype tumours may behave better than glioblastoma: discuss at MDT before maximal treatment in frail patients.
EGFR amplification (± EGFRvIII)	Many extra copies of the EGFR gene; about a third also carry the truncated, constitutively active variant III. <i>Found in:</i> About 40% of glioblastomas	FISH or NGS copy number	Diagnostic of glioblastoma in IDH-wildtype astrocytoma.	No effective EGFR-targeted drug or vaccine in glioma so far; trials only.
Chromosome +7 / -10	Whole-chromosome 7 gain with 10 loss (10 carries PTEN). <i>Found in:</i> Chromosome 10 loss in 60–85% of glioblastomas	Methylation array, NGS or FISH copy number	Diagnostic of glioblastoma in IDH-wildtype astrocytoma.	Must be whole-chromosome; partial changes do not count.
PDGFRA, CDK4, MET amplification; PI3K mutations	Growth-signal and cell-cycle drivers <i>Found in:</i> Glioblastoma; aggressive or recurrent IDH-mutant astrocytoma	NGS	Prognostic: PDGFRA amplification may imply grade 4 behaviour in IDH-mutant astrocytoma.	No standard targeted therapy; trials. MET fusions and FGFR3-TACC3 fusions are rare trial targets.
MMR deficiency / hypermutation	Loss of MLH1, MSH2, MSH6 or PMS2 → thousands of mutations <i>Found in:</i> Germline Lynch or constitutional MMR deficiency (young, IDH-wildtype); acquired after temozolomide in 25–50% of recurrences (often MSH6)	MMR IHC; tumour mutational burden on NGS; germline testing	Predictive: checkpoint inhibitors can work in germline CMMRD (Bouffet 2016 ^[29]); temozolomide-induced hypermutation does not predict benefit (Touat 2020 ^[20]). MSH6 loss → temozolomide resistance.	Always ask whether hypermutation is germline or treatment-induced; refer families for genetics.

Paediatric-type gliomas and glioneuronal tumours: marker by marker

Marker	Typical tumour	How tested	Clinical relevance
H3 K27M / H3K27me3 loss (H3-3A, H3C2/3; EZHIP)	Diffuse midline glioma: pons (DIPG), thalamus, spinal cord; children and young adults	IHC for K27M plus loss of K27me3; sequencing	Grade 4 regardless of histology; survival usually under 1–2 years; dordaviprone at recurrence (pooled response 20% ^[30]). ACVR1 mutation often accompanies H3.1-mutant DIPG.
H3 G34R/V	Diffuse hemispheric glioma, adolescents and young adults	Mutation-specific IHC; sequencing	Grade 4. Shares ATRX loss and p53 with IDH-mutant astrocytoma, so IDH must be checked.
KIAA1549-BRAF fusion	Pilocytic astrocytoma (60–80%, especially cerebellar)	RNA NGS, FISH or RT-PCR	Good prognosis after resection; tovorafenib or MEK inhibitors when progressive (FIREFLY-1 ^[31]). First-generation BRAF inhibitors can paradoxically drive fusion-positive tumours: avoid them.
BRAF V600E	Paediatric LGG (about 15–20%), ganglioglioma (up to 60%), PXA, epithelioid glioblastoma	IHC (VE1) or sequencing	Dabrafenib + trametinib first line in paediatric LGG (Bouffet 2023 ^[32]) and at recurrence in adults (ROAR ^[33]). With CDKN2A deletion: higher risk of transformation.
FGFR1/2/3 alterations	Paediatric-type diffuse LGG (FGFR1 duplication about a quarter), DNET, rosette-forming glioneuronal tumour	NGS (DNA + RNA)	Usually indolent; FGFR inhibitors in trials.

Marker	Typical tumour	How tested	Clinical relevance
MYB / MYBL1 alterations	Diffuse astrocytoma MYB/MYBL1-altered, angiocentric glioma	RNA NGS, methylation	CNS WHO grade 1: surgery is usually enough.
NF1 loss	Optic pathway glioma in NF1; some sporadic LGG	Germline testing / NGS	Selumetinib or other MEK inhibitors (PBTC^[34]); avoid RT in NF1 (second tumours, vasculopathy).
NTRK, ALK, ROS1, MET fusions	Infant-type hemispheric glioma and some paediatric HGG	RNA NGS	Highly responsive to matched TRK or ALK inhibitors: test every infant glioma.
PDGFRA, EGFR, MYCN amplification	Diffuse paediatric-type HGG, H3-wildtype and IDH-wildtype	NGS; methylation profiling is the reference test	Poor prognosis; trials. Also reported in adults up to 70 years.

Important points

- **Read the layered report:** integrated diagnosis (for example "Astrocytoma, IDH-mutant, CNS WHO grade 3"), then histology, then grade (Arabic numerals, assigned within the tumour type), then the molecular results. Plan treatment from the integrated line, not from histology alone.
- **Molecular results outrank appearance:** TERT, EGFR or +7/-10 make an IDH-wildtype adult astrocytoma a glioblastoma; CDKN2A/B deletion makes an IDH-mutant astrocytoma grade 4; oligodendroglioma needs both IDH mutation and 1p/19q codeletion, whatever it looks like.
- **NOS versus NEC:** "not otherwise specified" means the test was not done or failed (ask for it); "not elsewhere classified" means it was done and the tumour does not fit a defined type (consider methylation profiling and MDT review).
- **Prognostic order** of the adult groups: oligodendroglioma (median 15–20 years) > IDH-mutant astrocytoma (grade 2 >10 years, grade 3 7–9, grade 4 3–6) > IDH-wildtype glioblastoma (about 15 months in trials) ([TCGA 2015^{\[4\]}](#), [Eckel-Passow 2015^{\[28\]}](#)).
- **Markers that change treatment today:** MGMT (temozolomide), 1p/19q (PCV with RT), IDH (vorasidenib), BRAF V600E (dabrafenib + trametinib), NTRK fusion (TRK inhibitors), H3 K27M (dordaviprone at recurrence), germline MMR deficiency (checkpoint inhibitors). EGFR, PTEN, CDKN2A and TERT are diagnostic and prognostic but not yet drug targets.
- **Imaging can hint, not decide:** the T2–FLAIR mismatch sign is almost specific for IDH-mutant, 1p/19q-intact astrocytoma ([Jain 2020^{\[35\]}](#)); calcification and cortical spread suggest oligodendroglioma; 2-HG on MR spectroscopy suggests an IDH mutation. Tissue is still required.
- **Germline clues:** IDH1 R132C (Li-Fraumeni), MMR loss or hypermutation without prior temozolomide in a young patient (Lynch or constitutional MMR deficiency), NF1 features with optic pathway or pilocytic tumours, SHH medulloblastoma (TP53, SUFU, PTCH1). Refer for genetic counselling.
- **Common laboratory pitfalls:** small or necrotic biopsies with low tumour content (undergrading, failed MGMT); FISH "codeletion" from partial losses; IDH IHC negative but sequencing positive; ATRX loss in H3 G34 tumours; H3 K27M also occurs in some non-diffuse tumours (ganglioglioma, ependymoma), so it defines diffuse midline glioma only in an infiltrative midline glioma.
- **Re-test at recurrence** when it could change care: transformation (new CDKN2A/B deletion, PDGFRA amplification), hypermutation after temozolomide, or a new target. CSF or blood "liquid biopsy" is promising but not yet standard outside DIPG research.
- **A practical panel for Indian centres:** on every diffuse glioma, IHC for IDH1 R132H, ATRX, p53 and Ki-67 (add H3 K27M for midline, BRAF VE1 for young or epithelioid tumours); 1p/19q by FISH or NGS when ATRX is

retained; MGMT for every glioblastoma, above all in patients over 65; IDH sequencing when IHC is negative under 55; TERT/EGFR/CDKN2A by a targeted NGS panel when an IDH-wildtype tumour looks low grade; methylation profiling through a reference laboratory for paediatric, unusual or NEC tumours. Keep paraffin blocks and request molecular tests at the first MDT so results are ready when RT planning starts.

- Guidance: WHO CNS5 ([Louis 2021](#)^[36]), [CAP/ASCO/SNO molecular testing guideline \(2022\)](#)^[37], [EANO molecular testing guideline \(2023\)](#)^[38], [EANO diffuse glioma guideline \(2021\)](#)^[39].

05 Local therapy: surgery & radiotherapy

Surgery

- **Glioma:** maximal safe resection is the first step for every accessible diffuse glioma. More complete resection predicts longer survival in all molecular groups, most clearly in IDH-mutant astrocytoma, where even small residual volumes matter. Use awake mapping or tractography near eloquent cortex.
- **Biopsy** (stereotactic or open) for deep, multifocal or bihemispheric tumours and when lymphoma is suspected. Take enough for molecular testing.
- **Single metastasis:** resection plus radiotherapy beat radiotherapy alone in fit patients with controlled extracranial disease ([Patchell 1990](#)^[40]: survival 40 vs 15 weeks, local recurrence 20 vs 52%; [Vecht 1993](#)^[41]). Resect large (>3 cm), symptomatic or posterior fossa lesions with mass effect, or when the diagnosis is uncertain. Permanent weakness after surgery is about 8–9%.
- **Children:** maximal safe resection, ideally in a paediatric neuro-oncology centre; gross total resection cures most pilocytic astrocytomas and is the strongest prognostic factor in ependymoma. Hydrocephalus: tumour removal, endoscopic third ventriculostomy or a shunt.

Radiotherapy

Setting	Usual schedule (dose per course, no drug doses)
Glioblastoma, ≤70 y, fit	60 Gy in 30 fractions + daily temozolomide
Grade 3 glioma	59.4 Gy in 33 fractions (or 60/30)
Grade 2 glioma (when RT chosen)	50.4–54 Gy in 28–30 fractions
Older or frail glioblastoma	40 Gy in 15 fractions (or 25 Gy in 5)
1–4 (up to ~10–15) small metastases	Stereotactic radiosurgery, single or 3–5 fractions
Resected metastasis cavity	Cavity SRS rather than whole brain
Many metastases, no SRS option	WBRT 30 Gy in 10 (hippocampal avoidance + memantine)
Medulloblastoma, ependymoma (spread)	Craniospinal irradiation + boost
DIPG	54–59.4 Gy, or 39–45 Gy hypofractionated

Involved-field RT: tumour (enhancement, cavity ± FLAIR) plus a margin; 80–90% of high-grade gliomas recur within 2 cm of the original site.

Figure 13. Radiotherapy schedules in common use (NRG, EORTC, ASTRO, EANO). Dose escalation above 60 Gy has not improved survival in glioblastoma; SRS has replaced whole-brain RT for most patients with limited metastases.

- **High-grade glioma:** involved-field RT to the cavity and enhancing tumour (± FLAIR) with a margin. Dose escalation above 60 Gy (conventional, stereotactic boost, brachytherapy) has not improved survival; IMRT/VMAT spares normal brain and optic structures. Proton dose escalation is under study.
- **Older or frail glioblastoma:** 40 Gy in 15 fractions is as effective as 60 Gy in 30 and spares 3 weeks of travel (Roa 2004); RT beat supportive care in patients over 70 ([ANOCEF](#)^[42]).
- **Stereotactic radiosurgery (SRS)** for up to 4, and in practice up to about 15–20, small metastases. Adding an SRS boost to WBRT improved survival for a single unresectable metastasis ([RTOG 9508](#)^[43]). Adding whole-brain RT halves new intracranial relapse but does not prolong survival and worsens memory: [EORTC 22952–26001](#)^[44], [JROSG 99–1](#)^[45], [NO574](#)^[46] (cognitive decline 92 vs 64% at 3 months). For 5–20

metastases, SRS gave better symptom scores than hippocampal-avoidance WBRT with similar survival ([Aizer 2026](#)^[47]).

- **After resection:** cavity SRS halves local recurrence compared with observation ([Mahajan 2017](#)^[48]) and preserves cognition better than WBRT ([N107C](#)^[49]). Large cavities (>2.5–3 cm) do better with fractionated SRS (3–5 fractions).
- **WBRT** when SRS is not possible and prognosis is reasonable: hippocampal avoidance plus memantine ([NRG CCOO1](#)^[50], [RTOG 0614](#)^[51]). In poor-prognosis lung cancer patients WBRT added nothing to dexamethasone and supportive care ([QUARTZ](#)^[52]).
- **Children:** avoid RT under 3 years where possible (chemotherapy to delay it); focal conformal or proton RT for ependymoma and LGG; craniospinal RT plus boost for medulloblastoma (dose by risk group). Late effects: IQ decline (worse with younger age and larger fields), endocrine failure, hearing loss, second tumours, vasculopathy.
- Reirradiation is reasonable for a focal relapse after a long interval; radiation-induced gliomas can be reirradiated after about 5 years. Re-RT plus bevacizumab improved PFS but not survival over bevacizumab alone in recurrent glioblastoma ([RTOG 1205](#)^[53]).

SHARE WITH PATIENTS: SURGERY AND RADIOTHERAPY

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[A brain biopsy or surgery makes cancer spread faster?](#)

[Every brain tumour needs open brain surgery?](#)

[Radiotherapy to the brain always causes permanent memory loss?](#)

[Gamma Knife or CyberKnife treatment means cutting open the skull?](#)

[A brain tumour that can't be completely removed is automatically incurable?](#)

o6 Systemic therapy: indications & options

Indications and options only; no doses. Benefits are given in absolute terms where possible. Trial names link to the primary publications.

Glioblastoma, IDH-wildtype

IDH-wildtype glioblastoma after maximal safe resection or biopsy

≤70 years, KPS ≥70

- RT 60 Gy + daily temozolomide, then 6 monthly cycles
- MGMT methylated: lomustine–temozolomide an option for young, fit patients
- Add tumour-treating fields if the patient accepts
- Unmethylated: same standard; consider trials

>70 years, KPS ≥70

- Short-course RT (40/15) + temozolomide
- Methylated and frail: temozolomide alone
- Unmethylated: short-course RT alone
- Decide with the family; function first

KPS <70 (any age)

- Methylated: temozolomide alone or short RT
- Unmethylated: short RT or best supportive care
- Early palliative care
- Steroids at the lowest dose that works

Not recommended first line: bevacizumab (no survival gain: AVAglio, RTOG 0825), nivolumab (CheckMate 498), more than 6 adjuvant cycles (GEINO 14-01).

Figure 14. Glioblastoma: age, function and MGMT decide the plan. MGMT methylation (40–50% of tumours) doubles 2-year survival with temozolomide; in unmethylated tumours the gain is small but no better option exists.

- **Standard (≤70, fit):** RT with daily temozolomide, then 6 monthly cycles ([EORTC/NCIC^{\[54\]}](#)): median survival 14.6 vs 12.1 months; 2-year survival 27 vs 11% and 5-year 10 vs 2% ([5-year update^{\[55\]}](#)). Benefit concentrated in MGMT-methylated tumours.
- **Lomustine plus temozolomide** for younger, fit patients with methylated tumours ([CeTeG/NOA-09^{\[56\]}](#)): median 48 vs 31 months in the prespecified analysis, but only 141 patients and more toxicity; a reasonable option, not a mandate.
- **Tumour-treating fields** with adjuvant temozolomide ([EF-14^{\[57\]}](#)): median survival 20.9 vs 16.0 months from randomisation; worn ≥18 hours a day on a shaved scalp; unblinded. Availability and cost limit use in India.
- **What does not help first line:** bevacizumab (PFS gain only; [AVAglio^{\[58\]}](#), [RTOG 0825^{\[59\]}](#)), nivolumab in unmethylated tumours (worse survival, [CheckMate 498^{\[60\]}](#)), nivolumab–ipilimumab ([NRG BN007^{\[61\]}](#)), dose-dense temozolomide ([RTOG 0525^{\[62\]}](#)), continuing temozolomide beyond 6 cycles ([GEINO 14-01^{\[63\]}](#)).
- **Older adults:** short-course RT with temozolomide improved survival over short RT alone ([Perry 2017^{\[64\]}](#), greatest if methylated); temozolomide alone is as good as RT in methylated tumours ([Nordic^{\[65\]}](#), [NOA-08^{\[66\]}](#)).
- **Practical points:** weekly counts during RT (thrombocytopenia 10–20%, worse in women); PJP prophylaxis for patients on steroids or with lymphopenia; avoid routine PPIs (survival association in a pooled analysis); contraception and fertility counselling.

IDH-mutant astrocytoma and oligodendroglioma

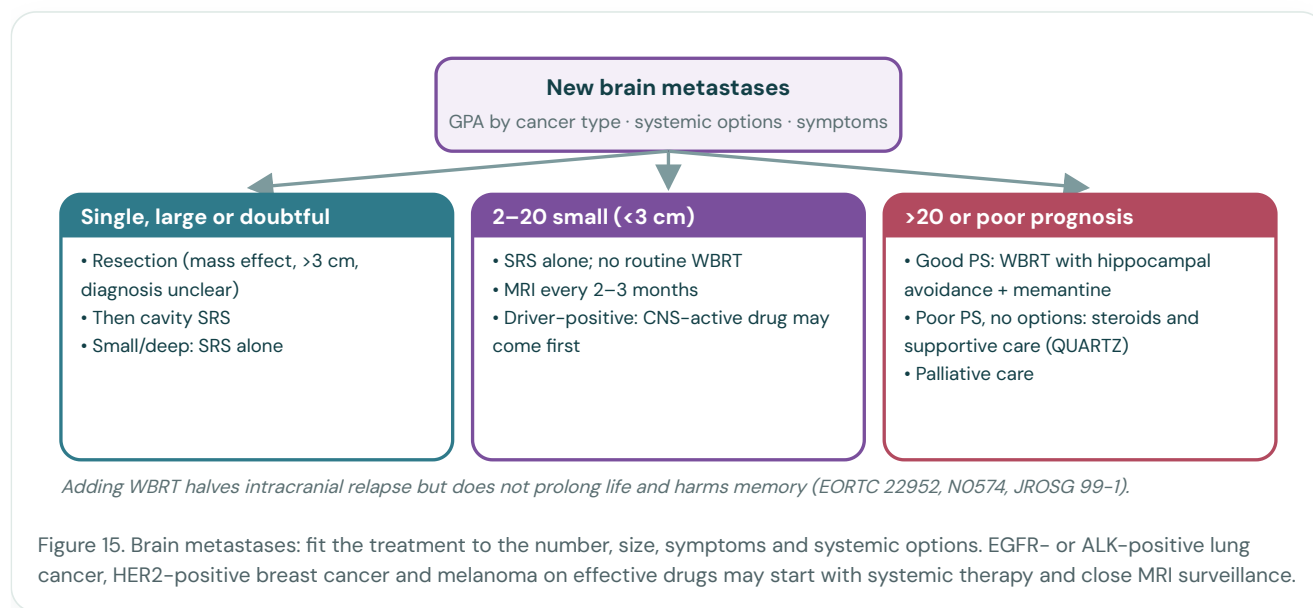
- **Grade 2, residual tumour, no uncontrolled symptoms:** vorasidenib, an oral IDH1/2 inhibitor, more than doubled PFS (27.7 vs 11.1 months) and delayed next intervention ([INDIGO^{\[23\]}](#)); overall survival unknown; ALT rise in about 10%. After gross total resection, watchful waiting or vorasidenib by shared decision.

- **Grade 2 needing treatment, and all grade 3:** RT plus chemotherapy, not RT alone. [RTOG 9802](#)^[67]: RT + PCV median survival 13.3 vs 7.8 years. [CATNON final](#)^[68]: 12 cycles of adjuvant temozolomide after RT in IDH-mutant grade 3 astrocytoma, median about 12.5 vs 6.8 years; concurrent temozolomide added little (consistent with the earlier [interim report](#)^[69]).
- **Oligodendroglioma:** RT + PCV doubled median survival in codeleted grade 3 tumours ([RTOG 9402](#)^[70]: 13.2 vs 7.3 years; [EORTC 26951](#)^[71]: 14.2 vs 9.3 years; [joint final report](#)^[24]). Temozolomide is a reasonable, better-tolerated alternative; the CODEL trial compares them. Chemotherapy alone is inferior ([EORTC 22033](#)^[72]) except for very large fields.
- **Grade 4 IDH-mutant astrocytoma:** RT with temozolomide, glioblastoma-style or with 12 adjuvant cycles.

Recurrent high-grade glioma

- No therapy has been shown to prolong survival over another at recurrence; median survival about 8–9 months for glioblastoma. Choose by prior treatment, steroid dependence, oedema and goals.
- **Lomustine:** lomustine + bevacizumab improved PFS (4.2 vs 1.5 months) but not survival (9.1 vs 8.6) ([EORTC 26101](#)^[73], [BELOB](#)^[74]). **Bevacizumab** is best used for symptomatic oedema and steroid toxicity. **Temozolomide rechallenge** for late relapse of a methylated tumour.
- Nivolumab did not beat bevacizumab ([CheckMate 143](#)^[75]). Genotype-directed: dabrafenib + trametinib for BRAF V600E ([ROAR](#)^[33]), TRK inhibitors for NTRK fusions, dordaviprone for H3 K27M-mutant diffuse midline glioma ([response rate 20%](#)^[30]).
- Re-resection helps selected focal relapses and distinguishes necrosis from tumour; offer palliative care alongside.

Brain metastases



- **CNS-active targeted drugs** (osimertinib, alectinib, lorlatinib, tucatinib-based HER2 regimens, BRAF/MEK in melanoma) can be used first for small, asymptomatic metastases with MRI every 6–8 weeks; SRS for symptomatic, large or progressing lesions.
- **Immunotherapy** with ipilimumab–nivolumab controls asymptomatic melanoma brain metastases in about half of patients; steroids blunt the effect, so avoid unnecessary dexamethasone.

- Guidance: [EANO–ESMO brain metastasis guideline \(2021\)](#)^[76] and ASCO–SNO–ASTRO guidelines; treatment is planned by cancer type and genotype at a multidisciplinary meeting.
- Leptomeningeal disease: MRI brain and spine, CSF cytology; focal RT to symptomatic sites, systemic drugs that cross the CSF, intrathecal therapy in selected cases; prognosis is generally weeks to months.

Children

- Low-grade glioma**, unresectable and progressive: carboplatin–vincristine or weekly vinblastine ([COG A9952](#)^[77]; 5-year OS 86–87% with either chemotherapy arm). BRAF V600E: dabrafenib + trametinib first line, response 47 vs 11% and PFS 20.1 vs 7.4 months versus chemotherapy ([Bouffet 2023](#)^[32]). BRAF fusion/other RAF alterations: tovorafenib ([FIREFLY-1](#)^[31], response 67%). NF1 and BRAF–altered: selumetinib ([PBTC](#)^[34]). About half progress after first-line therapy; overall survival at 20 years is close to 90%.
- High-grade glioma (>3 years)**: focal RT with temozolomide and adjuvant lomustine ([ACNS0423](#)^[78]); bevacizumab added nothing ([HERBY](#)^[79]). BRAF V600E: dabrafenib + trametinib after RT ([Hargrave 2023](#)^[80]). Constitutional MMR deficiency: anti-PD-1 ([Bouffet 2016](#)^[29]). Five-year survival 15–35%.
- DIPG**: RT is the only proven treatment; hypofractionation (39–45 Gy) is non-inferior and spares anaesthesia and travel ([Zaghloul 2022](#)^[81]). No chemotherapy has improved survival; median survival under a year.
- Ependymoma**: maximal resection then focal RT; post-RT maintenance chemotherapy did not improve outcomes ([ACNS0831](#)^[82]). Observation after complete resection of a supratentorial grade 2 tumour is an option.
- Medulloblastoma**: surgery, risk-adapted craniospinal RT and cisplatin-based chemotherapy; 5-year survival about 70–80% for average risk (higher for WNT). Infants: chemotherapy-based approaches to delay or avoid RT.

SHARE WITH PATIENTS: TREATMENT MYTHS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[Telugu–English handout: seizures and steroid tablets at home \(తెలుగు–English\)](#)

[Chemotherapy can't work against brain tumours because of the blood–brain barrier?](#)

[Brain cancer always means death within a few months?](#)

[If a brain tumour is benign, it never needs treatment?](#)

Steroids (dexamethasone)

- Only for symptomatic oedema; none if asymptomatic
- Load then 8–16 mg/day for severe, 2–4 mg/day for mild
- Taper to the lowest dose; watch glucose, myopathy
- Avoid before biopsy if lymphoma possible

Seizures

- No prophylaxis if never had a seizure
- After a seizure: levetiracetam (non-enzyme-inducing)
- Avoid phenytoin/carbamazepine with chemo, TKIs
- Rescue benzodiazepine at home near end of life

Venous thrombosis

- No routine prophylaxis except after surgery
- Treat DVT/PE: DOAC preferred, else LMWH
- Higher bleed risk: melanoma, RCC, thyroid, choriocarcinoma
- Non-contrast CT before starting

Infection and stomach

- PJP prophylaxis if steroids or lymphopenia on temozolomide
- H2 blocker rather than PPI with glioblastoma
- Vaccinate; check sugar on steroids
- Early palliative and rehabilitation input

Figure 16. Supportive care that changes everyday outcomes. Steroids are for symptoms, not for the scan; antiseizure drugs are for patients who have had a seizure; DOACs caused less intracranial bleeding than LMWH in glioma cohorts.

Quick-reference tables (also printable as one PDF from the Printable Teaching Resources page). No chemotherapy doses; check current approvals and product information.

Table A. Molecular tests and what they change

Test	Where it matters	How tested	What it changes	Key evidence
IDH1/IDH2 mutation	Every adult diffuse glioma	IHC for IDH1 R132H; sequence codons 132/172 if negative (especially under 55)	IDH-mutant: astrocytoma or oligodendroglioma, better prognosis; residual grade 2 → vorasidenib option	INDIGO^[23] , WHO 2021^[36]
1p/19q codeletion	Every IDH-mutant glioma	NGS, methylation array or LOH (FISH alone is imperfect); ATRX retained/p53 negative suggests it	Defines oligodendroglioma; RT + PCV (or temozolomide); chemotherapy alone for very large fields	EORTC 26951/RTOG 9402^[24]
MGMT promoter methylation	Glioblastoma (all ages)	Methylation-specific PCR or pyrosequencing; methylated in 40–50%	Predicts temozolomide benefit; temozolomide alone is reasonable in frail methylated patients	Hegi 2005^[2]
CDKN2A/B homozygous deletion	IDH-mutant astrocytoma (and oligodendroglioma)	NGS or FISH/copy number	Grade 4 regardless of histology; poor prognosis	CATNON final^[68]
TERT promoter, EGFR amplification, +7/–10	IDH-wildtype astrocytoma without necrosis	NGS / copy number	Diagnose glioblastoma; treat as grade 4	WHO 2021
H3 K27 alteration	Midline glioma (thalamus, pons, spinal cord), children and young adults	IHC for H3 K27M and loss of H3K27me3	Diffuse midline glioma grade 4; dordaviprone at recurrence; trials	ONC201 pooled analysis^[30]
H3 G34 mutation	Hemispheric high-grade glioma, teens and young adults	IHC / sequencing	Diffuse hemispheric glioma grade 4	WHO 2021
BRAF V600E / BRAF fusion	Paediatric LGG, ganglioglioma, PXA, some adult gliomas	IHC (VE1) or NGS; KIAA1549–BRAF fusion by NGS/FISH	V600E: dabrafenib + trametinib; fusions: tovorafenib, MEK inhibitors	Bouffet 2023^[32] , ROAR^[33] , FIREFLY-1^[31]
MMR deficiency / hypermutation	Glioma in young people with café-au-lait spots or family cancers; recurrence after temozolomide	IHC for MMR proteins, TMB on NGS; germline testing	CMMRD/Lynch counselling; checkpoint inhibitor in selected cases	Bouffet 2016^[29]
Medulloblastoma group (WNT, SHH, group 3, group 4)	All medulloblastomas	IHC panel ± methylation; TP53 status in SHH	Risk-adapted craniospinal dose and chemotherapy; germline testing in SHH (TP53, SUFU, PTCH1)	WHO 2021, COG/SIOP protocols
Ependymoma group (ZFTA, YAP1, PFA/PFB)	All intracranial ependymomas	IHC (H3K27me3 loss = PFA), fusion testing; 1q gain	PFA with 1q gain/6q loss: high risk; drives trial eligibility	ACNS0831^[82]

Table B. Systemic and radiation therapy by setting (no doses)

Setting	Standard	Alternatives / notes	Evidence
Glioblastoma, ≤70 y, fit	RT 60 Gy/30 + daily temozolomide → 6 adjuvant cycles	Lomustine–temozolomide (methylated, young, fit); tumour–treating fields with adjuvant phase	EORTC/NCIC^[54] , CeTeG/NOA-09^[56] , EF-14^[57]
Glioblastoma, >70 y or frail	Short-course RT (40/15) + temozolomide	Methylated: temozolomide alone; unmethylated: short RT alone; KPS <50: supportive care	Perry 2017^[64] , Nordic^[65] , NOA-08^[66]
Astrocytoma, IDH–mutant grade 2, residual, no uncontrolled symptoms	Vorasidenib, or watchful waiting	Uncontrolled symptoms/growth: RT + temozolomide (12 cycles) or PCV	INDIGO^[23] , RTOG 9802^[67]
Astrocytoma, IDH–mutant grade 3	RT 59.4 Gy + 12 cycles adjuvant temozolomide	Concurrent temozolomide adds little; PCV alternative	CATNON final^[68]
Astrocytoma, IDH–mutant grade 4	RT + temozolomide (glioblastoma–style or 12 adjuvant cycles)	Trials	Extrapolated from CATNON, EORTC/NCIC
Oligodendroglioma grade 2 (residual) or 3	Grade 3: RT + PCV (or temozolomide); grade 2 residual: vorasidenib option	Very large field: chemotherapy first	EORTC 26951/RTOG 9402^[24] , RTOG 9802^[67] , INDIGO^[23]
Recurrent glioblastoma	Single agent: lomustine, bevacizumab or temozolomide rechallenge (late, methylated)	Re–resection or re–irradiation for focal relapse; trials; palliative care	EORTC 26101^[73] , BELOB^[74] , RTOG 1205^[53]
BRAF V600E glioma (any age)	Dabrafenib + trametinib	Children with LGG: first line instead of chemotherapy	ROAR^[33] , Bouffet 2023^[32]
Paediatric LGG, progressive, no V600E	Carboplatin–vincristine or weekly vinblastine	BRAF fusion: tovorafenib; NF1: selumetinib/MEK; RT for older children when needed	COG A9952^[77] , FIREFLY-1^[31] , PBTC selumetinib^[34]
Paediatric HGG (>3 y)	Focal RT + temozolomide → lomustine	BRAF V600E: dabrafenib–trametinib after RT; CMMRD: anti–PD–1	ACNSO423^[78] , Hargrave 2023^[80]
DIPG	Focal RT (conventional or hypofractionated)	No proven systemic therapy; trials; re–irradiation at progression	Zaghloul 2022^[81]
Ependymoma, child, gross total resection	Focal conformal RT	Supratentorial grade 2 GTR: observation possible; post–RT chemotherapy did not help	ACNSO831^[82] , Merchant 2009^[83]
Brain metastases, driver–positive	CNS–active targeted therapy (osimertinib, alectinib/lorlatinib, tucatinib–based HER2 regimens)	SRS for symptomatic or progressing lesions	See lung and breast modules
Brain metastases, 1–20 small, no CNS–active drug	SRS alone	Cavity SRS after resection; WBRT with hippocampal avoidance + memantine only if SRS not possible	N0574^[46] , N107C^[49] , NRG CCO01^[50]

Table C. Supportive care essentials

Problem	Do	Avoid	Evidence / note
Vasogenic oedema	Dexamethasone only if symptomatic: about 10 mg load then 8–16 mg/day (severe) or 2–4 mg/day (mild); taper to the lowest dose	Steroids for asymptomatic oedema; steroids before biopsy if lymphoma possible	Vecht 1994^[84] , bevacizumab for refractory oedema

Problem	Do	Avoid	Evidence / note
Raised ICP, impending herniation	Head up, IV dexamethasone, mannitol or hypertonic saline, urgent neurosurgery (shunt/ETV/resection)	Lumbar puncture with mass effect	Emergency
First seizure	Levetiracetam monotherapy; check levels before switching; driving advice	Prophylaxis in seizure-free patients; enzyme inducers (phenytoin, carbamazepine) with chemotherapy or TKIs	SNO/EANO 2021 ^[85]
Stopping antiseizure drugs	Consider only after long seizure freedom and stable tumour; shared decision	Abrupt withdrawal	About 1 in 4 glioma patients relapse after withdrawal
DVT / PE	Non-contrast CT first; DOAC preferred, LMWH if DOAC unsuitable; long-term for glioblastoma	IVC filter routinely; anticoagulation within 48 h of a bleed	Carney 2019 ^[86] , Leader 2020 ^[87]
VTE prevention	Mechanical + pharmacological prophylaxis after surgery; mobilise	Routine outpatient prophylaxis	PRODIGE ^[88]
Infection on temozolomide	PJP prophylaxis with steroids or lymphopenia; weekly counts during RT	Live vaccines	NNT ~288 without risk factors (Canadian cohort)
Gastric protection on steroids	H2 blocker when needed	Routine PPIs with glioblastoma (survival association)	Le Rhun 2025 pooled analysis
Cognition, mood, fatigue	Screen each visit; rehabilitation, school/work plans; memantine with WBRT	Ignoring carer burden	RTOG 0614 ^[51]
End of life	Home seizure rescue plan (buccal/nasal benzodiazepine), dysphagia plan, palliative care	Late referral	EANO palliative care guideline

Table D. Managing common treatment side effects

Side effect	Usual cause	Prevent / monitor	When to stop or refer
Thrombocytopenia, neutropenia	Temozolomide (2–3× more in women), lomustine, PCV	Weekly counts during RT; day 22/29 counts in cycles	Hold TMZ if platelets <100 or ANC <1.5 ×10 ⁹ /L in the concurrent phase; aplastic anaemia is rare but serious
Nausea, constipation	Temozolomide, lomustine, ondansetron	Antiemetic before doses; bowel regimen	Persistent vomiting; check ICP, hyponatraemia
Raised liver enzymes	Temozolomide, vorasidenib (ALT rise ~10% grade ≥3)	LFTs monthly early on	Hold for grade ≥3; restart lower or stop
Pulmonary fibrosis	Lomustine (cumulative)	PFTs with long courses	New breathlessness: stop and investigate
Hypertension, proteinuria, wound problems	Bevacizumab	BP each visit, urine protein	Stop before surgery; stop for bleeding, perforation, arterial clot
Fever, rash	Dabrafenib + trametinib	Pause at fever onset; restart when settled	Persistent fever, ejection fraction fall, eye symptoms
Skin irritation under arrays	Tumour-treating fields	Rotate array position, skin care	Ulceration or infection

Side effect	Usual cause	Prevent / monitor	When to stop or refer
Fatigue, hair loss, scalp dermatitis	Cranial RT	Explain early; gentle scalp care	Somnolence weeks after RT is usually self-limited
Steroid myopathy, diabetes, insomnia, infection	Dexamethasone	Lowest dose; morning dosing; glucose checks	Proximal weakness: taper; consider bevacizumab for steroid dependence
Cognitive decline	WBRT, large-field RT, tumour	SRS where possible; hippocampal avoidance; memantine	Neuropsychology and rehabilitation
Endocrine, hearing, growth (children)	Cranial/craniospinal RT, cisplatin	Yearly endocrine review; audiology	Hormone replacement; school support

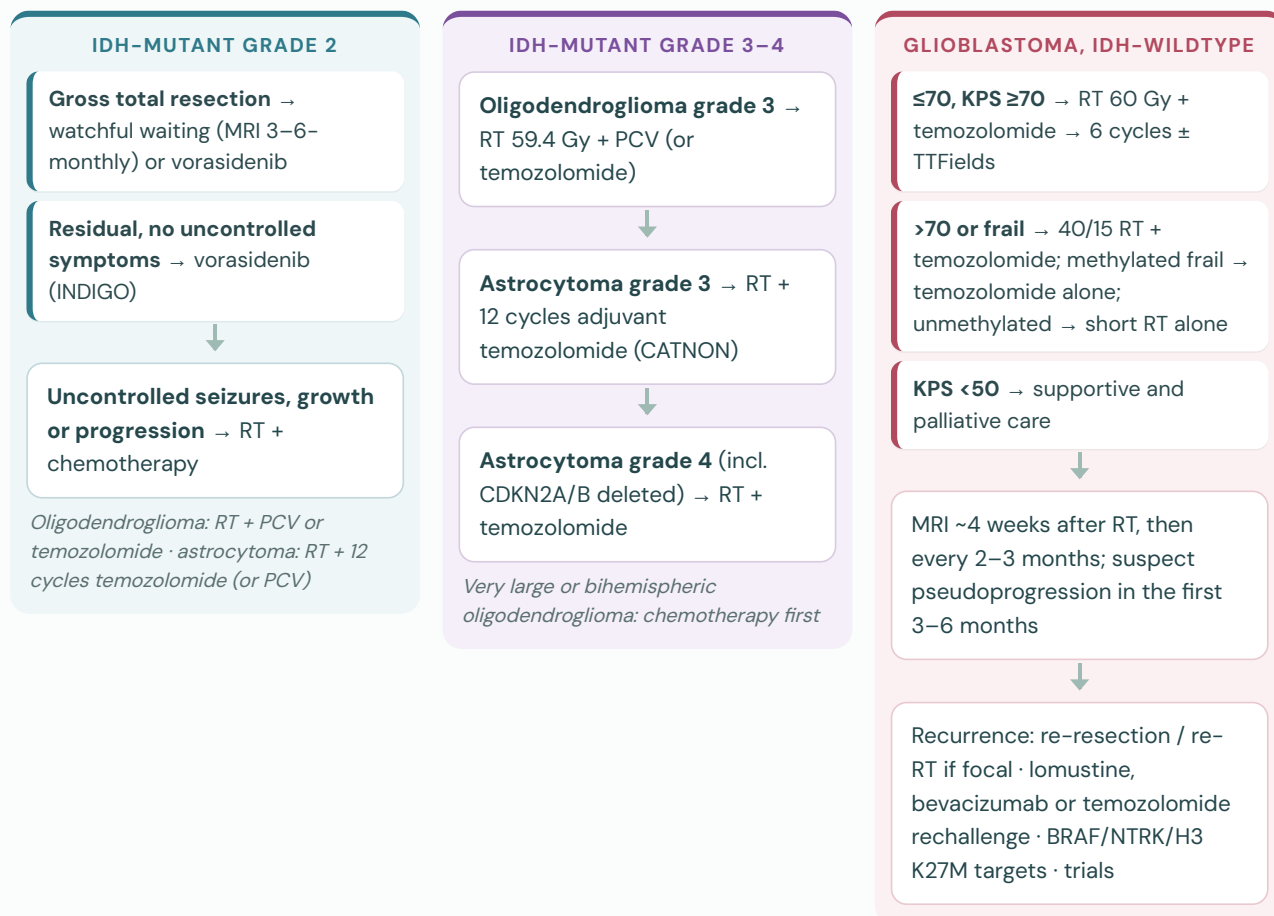
07 Management algorithms

These decision paths pull together sections 02–06. Colours: teal for favourable paths, purple for intermediate, rose for high-risk paths.

ALGORITHM 1

Adult diffuse glioma

Suspected glioma on MRI: neuro-oncology MDT · steroids only if symptomatic · antiseizure drug only after a seizure · **maximal safe resection** (biopsy if deep or diffuse) · MRI in 24–48 h · integrated diagnosis: IDH, 1p/19q, CDKN2A/B, MGMT

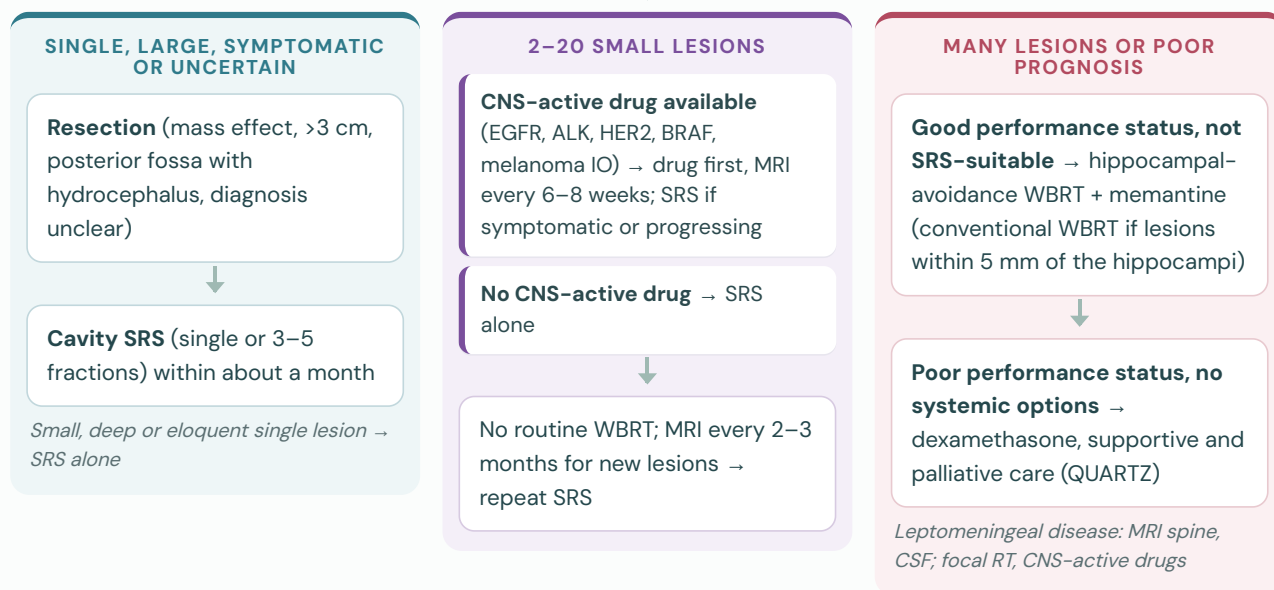


All patients: shared decisions about goals · driving and work advice after seizures · fertility and contraception · weekly counts and PJP prophylaxis (if steroids/lymphopenia) on daily temozolomide · avoid routine PPIs · rehabilitation and carer support · palliative care alongside, not instead.

ALGORITHM 2

Brain metastases

New brain metastases: MRI with contrast (count and size) · systemic staging · tumour genotype · GPA · steroids only if symptomatic · neurosurgery and radiation oncology at the first MDT

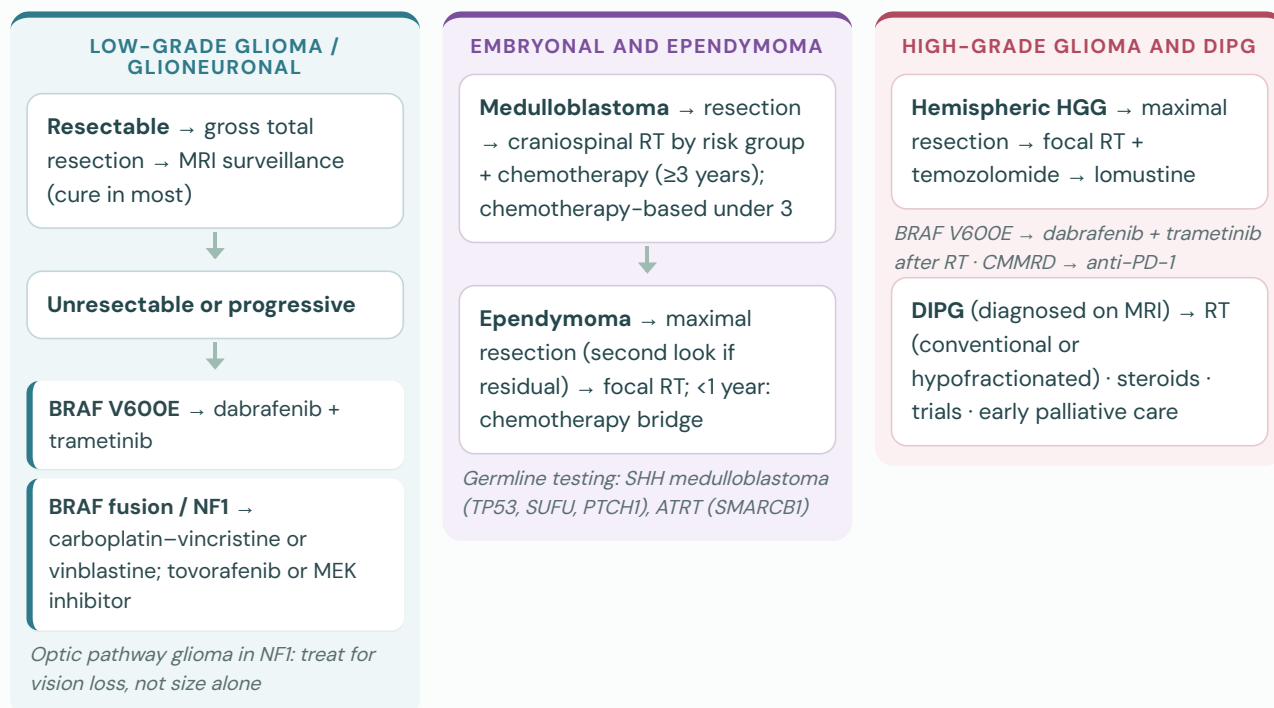


All patients: no prophylactic antiseizure drugs · DOAC or LMWH for VTE (individualise in melanoma, RCC, thyroid, choriocarcinoma) · taper steroids early, especially before immunotherapy · driving advice · discuss goals of care.

ALGORITHM 3

Children with a brain tumour

Red flags (morning vomiting, ataxia, squint, head tilt, regression, headache ≤ 6 years) → urgent MRI (CT if unavailable)
 → paediatric neurosurgery the same day if hydrocephalus · steroids for oedema · staging: spine MRI, CSF, AFP/ β -hCG where relevant · tissue + molecular (BRAF, H3, groups)



All children: paediatric neuro-oncology centre · fertility preservation where possible · school and neurocognitive support · lifelong late-effects clinic (endocrine, hearing, growth, second tumours) · family genetic counselling when a syndrome is suspected.



For neurosurgeons: primary brain tumours

Referral to oncology and adjuvant treatment by integrated diagnosis: specific indications, timing, what to send

Almost every patient with a malignant primary brain tumour needs radiotherapy, chemotherapy or both after surgery, and several decisions depend on what is done (and saved) at the operation. Final plans are made at the neuro-oncology MDT.

1 Before and at surgery: discuss with oncology when

1 Lymphoma is possible

Periventricular, homogeneous, diffusion-restricting, or immunosuppressed patient: stereotactic biopsy only, and hold steroids if the patient is stable.

2 A metastasis is likely

Known cancer, multiple lesions, or a smoker over 40: stage the body first; resect only large, symptomatic or diagnostic lesions.

3 Pineal or suprasellar mass

Serum and CSF AFP and β -hCG and a spine MRI before any operation: germ cell tumours may need no resection.

4 Deep, multifocal or frail

Agree biopsy versus resection, and the questions the tissue must answer (IDH, MGMT, H3).

5 Spine staging needed

Children, medulloblastoma, ependymoma, germ cell tumours: spine MRI before

6 After the operation

MRI within 24–48 hours; keep enough tissue and the paraffin

surgery avoids post-operative artefact.

blocks for the full integrated diagnosis.

2 Adjuvant management by integrated diagnosis: specific indications

Always / urgent refer every patient, usually before definitive treatment · **Yes** refer when the situation applies · **Usually no** specialist follow-up only

Glioblastoma, IDH-wildtype, age ≤70, KPS ≥70

Always

PLAN RT 60 Gy in 30 fractions with daily temozolomide, then 6 monthly cycles (EORTC/NCIC^[54]); tumour-treating fields optional (EF-14^[57]); lomustine–temozolomide for selected young, fit, MGMT-methylated patients (CeTeG/NOA-09^[56])

POINTS **Referral:** As soon as histology is known (do not wait for all molecular results. Start RT about 3–6 weeks after surgery once the wound has healed (common practice). Send MGMT. Weekly counts; PJP prophylaxis if on steroids.

Glioblastoma, age >70 or KPS 50–70

Always

PLAN Short-course RT (40 Gy/15 or 25 Gy/5) with temozolomide if fit (Perry 2017^[64]); MGMT-methylated and frail: temozolomide alone (Nordic^[65], NOA-08^[66]); unmethylated: short-course RT alone

POINTS **Referral:** Choice depends on MGMT and function. Biopsy is enough when resection is unsafe; ask for MGMT on the biopsy. KPS <50: supportive and palliative care; discuss before surgery.

Astrocytoma, IDH-mutant, grade 2 — gross total resection

Yes

PLAN Watchful waiting (MRI every 3–6 months) or vorasidenib

POINTS **Referral:** For a shared decision. IDH sequencing if IHC negative and age <55; CDKN2A/B status needed.

IDH-mutant glioma, grade 2 (astrocytoma or oligodendroglioma) — residual tumour, seizures controlled, no mass effect

Yes

PLAN Vorasidenib to delay RT and chemotherapy (INDIGO^[23]; PFS 27.7 vs 11.1 months)

POINTS INDIGO patients had non-enhancing measurable disease, no steroids, KPS ≥80. Monthly LFTs at first.

IDH-mutant glioma, grade 2 — uncontrolled seizures, growth, mass effect or enhancement

Yes

PLAN RT (50.4–54 Gy) plus chemotherapy: PCV (RTOG 9802^[67], median survival 13.3 vs 7.8 years) or 12 cycles of temozolomide

POINTS **Referral:** Promptly. Chemotherapy alone only when the RT field would be very large (bihemispheric oligodendroglioma).

Astrocytoma, IDH-mutant, grade 3

Always

PLAN RT 59.4 Gy, then 12 cycles of adjuvant temozolomide (CATNON final^[68]); concurrent temozolomide adds little

POINTS No role for vorasidenib outside trials at grade 3.

Astrocytoma, IDH-mutant, grade 4 (including CDKN2A/B-deleted)

Always

PLAN RT with temozolomide (glioblastoma-style, or 12 adjuvant cycles)

POINTS Report CDKN2A/B status: it changes the grade even without necrosis.

Oligodendroglioma, IDH-mutant, 1p/19q-codeleted, grade 3

Always

PLAN RT 59.4 Gy plus PCV (or temozolomide if PCV cannot be given) (EORTC 26951/RTOG 9402^[24]; survival about doubled)

POINTS Whole-arm 1p/19q by NGS/methylation preferred to FISH alone.

Diffuse midline glioma, H3 K27-altered (thalamus, brainstem, cord)**Always**

PLAN Focal RT (about 54–60 Gy); clinical trials; dordaviprone at progression ([ONC201](#)^[30])

POINTS Resection usually not possible; stereotactic biopsy in an experienced centre.

Ependymoma, adult**Yes**

PLAN Grade 3, or grade 2 with residual: focal RT. Grade 2 after gross total resection: RT or observation, individualised

POINTS Stage with MRI of the whole spine (ideally before surgery) and CSF cytology about 2 weeks after surgery.

Meningioma, grade 1**Usually no**

PLAN Gross total resection: observe. Subtotal: observe, or RT/radiosurgery if growing or symptomatic

POINTS **Referral:** Neurosurgical follow-up. MRI at 3–6 months, then yearly; per EANO meningioma guidance.

Meningioma, grade 2 (atypical)**Yes**

PLAN Subtotal resection: adjuvant RT. Gross total resection: RT or close MRI surveillance (randomised trials ongoing)

POINTS **Referral:** Radiation oncology. Discuss at MDT; no proven chemotherapy.

Meningioma, grade 3 (anaplastic)**Always**

PLAN Adjuvant RT (about 60 Gy) whatever the extent of resection

POINTS High recurrence risk; trials for recurrence.

Circumscribed gliomas: pilocytic astrocytoma, PXA, ganglioglioma**If residual or recurrent**

PLAN Gross total resection: observe. Residual or progressive: re-resection, RT, or targeted therapy if BRAF V600E ([ROAR](#)^[33])

POINTS Ask for BRAF V600E (VE1) and BRAF fusion testing.

Primary CNS lymphoma (suspected)**Urgent**

PLAN Stereotactic biopsy only; then methotrexate-based chemotherapy and consolidation (autologous transplant or RT) under haemato-oncology

POINTS **Referral:** Before definitive surgery. Withhold steroids before biopsy if the patient is stable; resection does not help. HIV test, eye (slit-lamp) and CSF studies.

Medulloblastoma or other embryonal tumour (adult or child)**Always**

PLAN Craniospinal RT with boost plus cisplatin-based chemotherapy (risk-adapted); infants: chemotherapy to delay RT

POINTS Spine MRI and CSF staging; molecular group (WNT, SHH, group 3/4); germline testing for SHH.

Pineal or suprasellar mass (possible germ cell tumour)**Before surgery**

PLAN Germinoma: chemotherapy and/or RT, no radical resection; raised serum/CSF AFP or markedly raised β -hCG: chemotherapy first without biopsy

POINTS Check serum and CSF AFP and β -hCG and spine MRI before any operation.

Resected brain metastasis**Always**

PLAN Cavity SRS rather than whole-brain RT ([Mahajan](#)^[48], [N107C](#)^[49]), plus systemic therapy for the primary

POINTS **Referral:** Radiation and medical oncology. Cavity SRS within about a month of surgery (3–4 weeks may lower side effects). Send tissue for EGFR/ALK/HER2/BRAF as relevant.

Any brain tumour in a child**Always**

- PLAN** By type: focal or craniospinal RT, chemotherapy, BRAF/MEK inhibitors for BRAF-altered LGG ([Bouffet 2023^{\[32\]}](#))
- POINTS** **Referral:** To a paediatric neuro-oncology team. Avoid RT under 3 years where possible; fertility, endocrine and school planning.

3 What to send with the referral

- ✓ Integrated pathology report: histology, CNS WHO grade, IDH (sequencing if IHC negative and under 55), ATRX, p53, 1p/19q, CDKN2A/B, Ki-67
- ✓ Pre-operative MRI and post-operative MRI within 24–48 hours (images, not just reports) for radiotherapy planning
- ✓ KPS or ECOG, deficits, seizures and the current antiseizure drug, steroid dose and taper plan, VTE prophylaxis or events
- ✓ MGMT for every glioblastoma; H3 K27M (midline), H3 G34 (young, hemispheric), BRAF V600E where relevant; blocks kept available
- ✓ Operation note: extent of resection, residual tumour and its location, eloquent areas, CSF leak or wound concerns
- ✓ What the patient and family understand; for young adults, whether fertility has been discussed

Do

- Refer high-grade tumours the same week the diagnosis is known; molecular results can follow.
- Taper dexamethasone to the lowest dose that controls symptoms; H2-blocker rather than routine PPI.
- Use levetiracetam for patients who have had seizures; stop perioperative prophylaxis if there were none ([SNO/EANO^{\[85\]}](#)).
- Give post-operative VTE prophylaxis; treat clots with a DOAC or LMWH after CT excludes bleeding.
- Start radiotherapy about 3–6 weeks after surgery once the wound has healed (common practice).
- Write driving advice after any seizure.

Avoid

- Steroids before biopsy when lymphoma is possible and the patient is stable.
- Enzyme-inducing antiseizure drugs (phenytoin, carbamazepine, phenobarbital): they lower temozolomide, targeted drug and dexamethasone levels.
- A late post-operative MRI (after about 72 hours): surgical enhancement hides residual tumour.
- Reporting "glioma grade 2" without IDH and 1p/19q, or using up all tissue on frozen section.
- Re-operating for early new enhancement within 3–6 months of chemoradiation without MDT review: often pseudoprogression.

Refer back, or re-discuss at the MDT, when

- New or enlarging enhancement after treatment (pseudoprogression, recurrence or radiation necrosis).
- Recurrence that may be resectable: re-resection, re-irradiation and systemic options are planned together.
- Growth or new enhancement of a low-grade glioma under surveillance or on vorasidenib.
- Steroid dependence or refractory oedema (bevacizumab option), uncontrolled seizures, or new VTE.
- Hydrocephalus or a wound problem during radiotherapy.

o8 Survivorship, follow-up & reducing recurrence

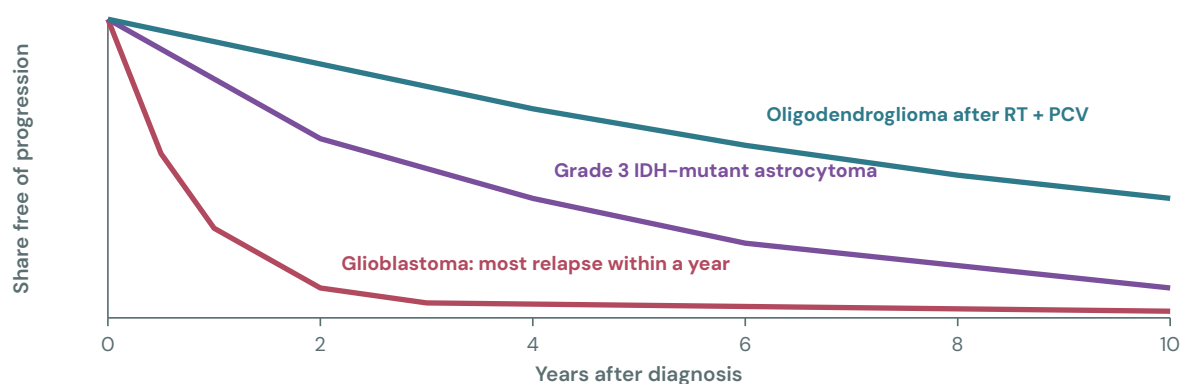


Figure 17. When relapses happen (illustrative shapes from trial medians, not to scale). The pace differs tenfold between glioma types, so follow-up intensity and the meaning of a “stable” scan differ too.

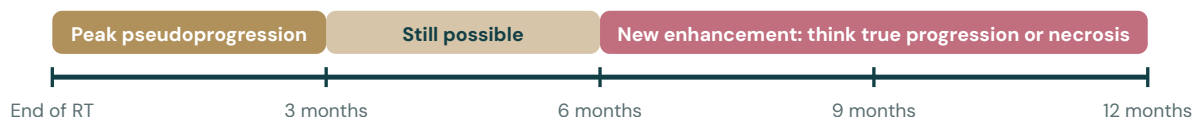
High-grade: MRI ~4 weeks after RT, then every 2–3 months for 2–3 years



- High-grade glioma: MRI + clinic (steroid dose, seizures, cognition, mood, blood counts on temozolomide)
- Low-grade glioma: MRI every 3–6 months for 5 years, then 6–12-monthly for life (more often on vorasidenib early)

Metastases after SRS: MRI every 2–3 months for a year. Children: MRI per protocol; endocrine, hearing, growth, school and fertility review. Treat the person: driving and work advice, epilepsy safety, carer support, advance-care planning when appropriate.

Figure 18. A simple follow-up rhythm (NCCN, EANO). MRI drives follow-up; interpret early changes after chemoradiation with pseudoprogression in mind.



Favours pseudoprogression

- Within 3–6 months of chemoradiation
- Inside the high-dose field
- MGMT methylated; patient well
- Low perfusion (rCBV) on MRI

Favours true progression

- New lesion outside the field
- Clinical decline off steroids
- High rCBV; growth on serial MRI
- Confirm with tissue if it changes care

Figure 19. Pseudoprogression. New enhancement soon after chemoradiation is often treatment effect; continue adjuvant temozolomide and repeat MRI in 4–8 weeks rather than abandoning effective therapy.

Follow-up protocol (NCCN, EANO)

Tumour	Imaging	Also
Glioblastoma and other high-grade gliomas	MRI about 4 weeks after RT, every 2–3 months during adjuvant therapy and for 2–3 years, then every 3–6 months	Blood counts and LFTs on temozolomide; steroid taper; seizure review; cognition and mood
Low-grade glioma (grade 2), oligodendroglioma	MRI every 3–6 months for 5 years, then at least yearly for life (monthly LFTs and 3-monthly MRI early on vorasidenib)	Late effects of RT: cognition, endocrine (if field near hypothalamus/pituitary)
Brain metastases after SRS or surgery	MRI every 2–3 months in year 1, then every 3–6 months	Radiation necrosis in 10–25%, more with immunotherapy or targeted therapy; perfusion MRI or tissue to separate from relapse
Children	MRI per protocol (often 3-monthly in year 1); spine MRI for medulloblastoma/ependymoma	Growth, puberty, thyroid, cortisol, hearing (cisplatin), vision, IQ and school, second tumours, stroke risk after RT

- **Pseudoprogression** (new enhancement within 3–6 months of chemoradiation, commoner when MGMT is methylated) settles without a change of therapy; continue temozolomide and repeat MRI in 4–8 weeks unless the patient deteriorates.
- **Seizures and driving:** patients should not drive until seizure-free for the period required by local rules (commonly 6–12 months) and should be told so in writing. Antiseizure drugs may be tapered after long seizure freedom with stable disease, but about 1 in 4 glioma patients relapse.
- **Steroids:** plan the taper at every visit; long-term dexamethasone causes myopathy, diabetes, infections, insomnia and Cushingoid change.
- **Rehabilitation and return to work or school:** early physiotherapy, occupational and speech therapy; neuropsychology for cognitive complaints; written plans for teachers.
- **Carers and goals:** carers of people with high-grade glioma carry a heavy load; discuss goals and preferred place of care early, and leave a home seizure-rescue plan near the end of life.

SHARE WITH PATIENTS: FOLLOW-UP

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[📄 Telugu–English handout: seizures and steroid tablets at home \(తెలుగు · English\)](#)

[After successful treatment, follow-up MRI scans aren't needed?](#)

[Brain cancer always means death within a few months?](#)

09 Landmark trials

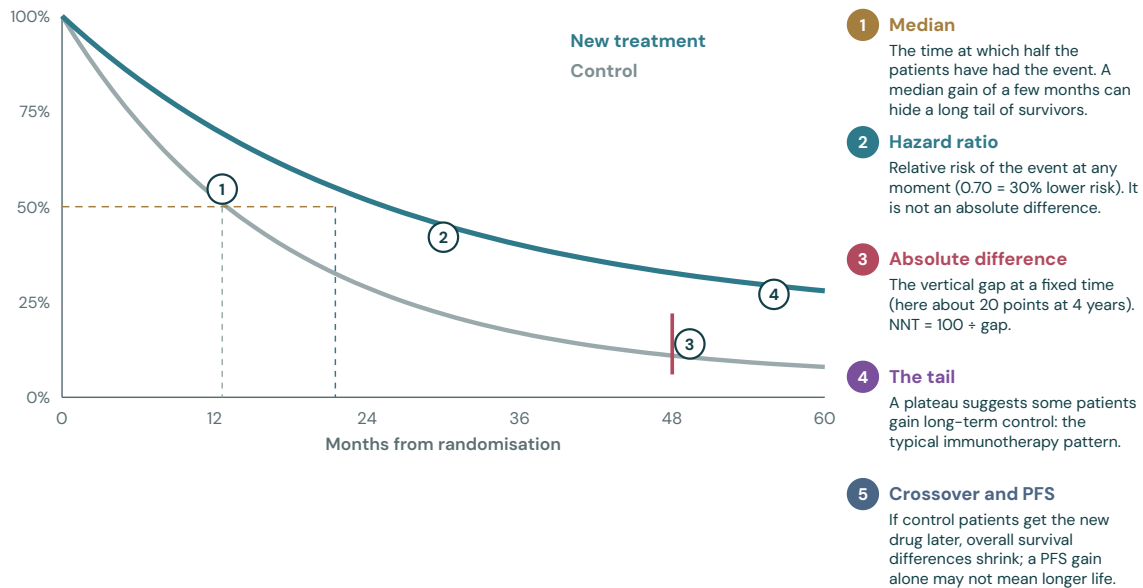


Figure 20. How to read a survival curve (illustrative). Use the absolute gap at a fixed time and overall survival, not the median or PFS alone, when weighing benefit against toxicity and cost.

- [EORTC/NCIC \(2005\)](#)^[54]: RT ± temozolomide in glioblastoma → median 14.6 vs 12.1 months, 5-year 10 vs 2% → the standard of care for fit adults ≤70.
- [Hegi \(2005\)](#)^[2]: the same trial by MGMT status → benefit mostly when methylated → MGMT testing guides older and frail patients.
- [EF-14](#)^[57]: tumour-treating fields with adjuvant temozolomide → median survival 20.9 vs 16.0 months → an option for willing patients; not sham-controlled.
- [AVAglio](#)^[58] / [RTOG 0825](#)^[59]: bevacizumab first line → longer PFS, no survival gain, more toxicity → a lesson in PFS versus OS.
- [Perry \(2017\)](#)^[64]: 40/15 RT ± temozolomide over 65 → median 9.3 vs 7.6 months, larger if methylated → standard for older fit patients.
- [RTOG 9802](#)^[67]: RT ± PCV in high-risk low-grade glioma → median 13.3 vs 7.8 years → chemotherapy belongs with RT.
- [CATNON final](#)^[68]: adjuvant temozolomide after RT in non-codeleted grade 3 glioma → benefit confined to IDH-mutant tumours (HR 0.54) → 12 adjuvant cycles; concurrent adds little.
- [EORTC 26951 / RTOG 9402](#)^[24]: RT ± PCV in anaplastic oligodendroglioma → median survival about doubled in codeleted tumours with 20-year follow-up.
- [INDIGO](#)^[23]: vorasidenib vs placebo in residual grade 2 IDH-mutant glioma → PFS 27.7 vs 11.1 months → first targeted drug for glioma; survival unknown.
- [EORTC 26101](#)^[73]: lomustine ± bevacizumab at first recurrence → PFS gain, no survival gain.
- [Patchell \(1990\)](#)^[40]: surgery + WBRT vs WBRT for a single metastasis → survival 40 vs 15 weeks → resection for fit patients with a single lesion.

- [N0574](#)^[46]: SRS ± WBRT for 1–3 metastases → better control but more cognitive decline (92 vs 64%) and no survival gain → SRS alone.
- [N107C](#)^[49]: cavity SRS vs WBRT after resection → less cognitive decline, similar survival.
- [QUARTZ](#)^[52]: WBRT vs supportive care in poor-prognosis lung cancer → no difference in survival or quality-adjusted life → spare WBRT when life expectancy is short.
- [Bouffet \(2023\)](#)^[32]: dabrafenib–trametinib vs carboplatin–vincristine in BRAF V600E paediatric LGG → response 47 vs 11%, PFS 20.1 vs 7.4 months, fewer severe side effects → first-line targeted therapy.
- [ACNS0831](#)^[82]: post-RT chemotherapy in childhood ependymoma → no gain → focal RT alone after resection.
- [Zaghloul \(2022\)](#)^[81]: 39–45 Gy hypofractionated vs 54 Gy in 253 children with DIPG → non-inferior survival → shorter course for families.

10 Practice pearls & pitfalls

- A first seizure in an adult is an indication for MRI with contrast, not just an EEG and a prescription.
- Do not start dexamethasone "to be safe" before a biopsy when lymphoma is on the list; if the patient is stable, wait for tissue.
- Weakness that melts on steroids is oedema; plan the taper on the day you start.
- Patients who have never had a seizure do not need antiseizure prophylaxis; if a drug is needed, levetiracetam avoids interactions with chemotherapy and TKIs (phenytoin and carbamazepine induce their metabolism).
- Ask the pathologist for an **integrated diagnosis**; "glioma, grade 2" without IDH and 1p/19q is not enough to plan treatment in 2026.
- MGMT methylation is the best single guide to treatment in older or frail patients with glioblastoma; send it with the first block.
- Early new enhancement after chemoradiation is often pseudoprogression: confirm before stopping effective therapy.
- Hypofractionated RT (40 Gy in 15) shortens the course for older patients who travel long distances, without losing efficacy.
- Procarbazine supply can be unreliable; temozolomide is a reasonable partner for RT in oligodendroglioma when PCV cannot be completed.
- Most brain metastases need neither WBRT nor prophylactic antiseizure drugs; SRS and the right systemic drug do more with less harm.
- An EGFR- or ALK-positive patient with small, asymptomatic brain metastases may start the TKI and have MRI in 6–8 weeks.
- Anticoagulation is usually safe with brain tumours; DOACs caused less intracranial bleeding than LMWH in glioma cohorts. Individualise in melanoma, RCC, thyroid cancer and choriocarcinoma metastases.
- In a child, persistent morning vomiting, a new squint or head tilt is a brain MRI question, not a gastric one.
- Test BRAF in every paediatric low-grade glioma; V600E changes first-line therapy.
- Diagnose DIPG on MRI; biopsy only in a specialised centre, for atypical features or a trial.
- Neurocysticercosis and tuberculoma are common in India, but a growing lesion on treatment is a biopsy question.

11 Case vignettes: lines of management

Eight cases, written for postgraduates and practising clinicians. Read the presentation, decide on diagnosis, workup and plan, then open the line of management. No doses are given.

CASE 1 Oligodendroglioma · grade 2 · residual

A first seizure in a 34-year-old engineer

34 years, man

Right frontal, non-enhancing

IDH1 R132H, 1p/19q codeleted

A 34-year-old software engineer has a generalised seizure at work. He recalls brief episodes of a strange smell for a year. Examination is normal. MRI: a 5 cm right frontal T2/FLAIR-bright mass with indistinct borders and no enhancement; CT shows small calcifications.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1 SEIZURE CARE

Levetiracetam; no driving (written advice); steroids not needed with no symptomatic oedema.

2 SURGERY

Awake craniotomy with mapping; near-total resection, 6 cm³ residual near the motor strip. MRI at 24 hours confirms the residual.

3 INTEGRATED DIAGNOSIS

IDH1 R132H mutant, 1p/19q whole-arm codeleted, CDKN2A/B intact, no anaplasia: oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 2.

4 POSTOPERATIVE PLAN

Residual disease and controlled seizures: options are vorasidenib (INDIGO; delays progression and next intervention) or watchful waiting with 3-monthly MRI. He chooses vorasidenib; monthly LFTs at first.

5 IF IT GROWS OR SEIZURES BECOME UNCONTROLLED

RT (54 Gy) plus PCV or temozolomide; expected median survival is well over a decade. Fertility and work counselling.

TEACHING POINTS

- A seizure with a non-enhancing frontal mass in a young adult is a low-grade glioma until proven otherwise.
- IDH and 1p/19q decide the name, the prognosis and the drug.
- Vorasidenib postpones RT; it has not yet been shown to prolong life.

See: Sections 02–06 · Algorithm 1 · [INDIGO](#)^[23], [RTOG 9802](#)^[67]

CASE 2 Glioblastoma · MGMT methylated

Word-finding difficulty in a 58-year-old teacher

58 years, woman

Left temporal ring-enhancing

IDH-wildtype, MGMT methylated

A 58-year-old teacher has 3 weeks of word-finding difficulty and headache. MRI: a 4 cm left temporal mass with an irregular enhancing rim, central necrosis and surrounding oedema. CT chest-abdomen is not needed; there is no history of cancer.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1 BEFORE SURGERY

Dexamethasone for symptomatic oedema, tapered after surgery; no seizure prophylaxis.

2

SURGERY

Awake craniotomy, gross total resection of the enhancing tumour; speech preserved.

3

DIAGNOSIS

Glioblastoma, IDH-wildtype, CNS WHO grade 4; TERT promoter mutant; MGMT promoter methylated.

4

ADJUVANT THERAPY

RT 60 Gy in 30 fractions with daily temozolomide (weekly counts; PJP prophylaxis while on steroids), then 6 monthly cycles. Tumour-treating fields discussed. Lomustine-temozolomide is an option for her as fit and methylated, with more toxicity.

5

AT 2 MONTHS

New enhancement at the cavity rim, she is well: likely pseudoprogression. Continue temozolomide; MRI in 6 weeks shows improvement.

TEACHING POINTS

- Methylated glioblastoma treated with standard chemoradiation has a median survival near 2 years.
- Early new enhancement within the RT field is often pseudoprogression.
- Avoid routine PPIs; use H2 blockers if needed.

See: Sections 04, 06, 08 · Algorithm 1 · [EORTC/NCIC](#)^[54], [Hegi](#)^[2], [EF-14](#)^[57], [CeTeG/NOA-09](#)^[56]

CASE 3 Glioblastoma · older adult · unmethylated**Confusion in a 76-year-old farmer**

76 years, man

KPS 70

MGMT unmethylated

A 76-year-old farmer from a village 120 km away has 6 weeks of confusion and left-sided weakness. MRI: a butterfly mass crossing the corpus callosum. He is diabetic and lives with his son.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

TISSUE

Stereotactic biopsy (resection not possible): glioblastoma, IDH-wildtype; MGMT unmethylated.

2

GOALS CONVERSATION

Median survival is under a year; the family wants treatment that keeps him at home as long as possible.

3

PLAN

Unmethylated, over 70, KPS 70: short-course RT (40 Gy in 15, or 25 Gy in 5) alone; temozolomide adds little when unmethylated. If methylated, temozolomide alone or short RT with temozolomide would be options.

4

SUPPORTIVE CARE

Lowest effective dexamethasone with glucose monitoring; physiotherapy; early palliative care; home seizure plan if seizures occur.

TEACHING POINTS

- Age, performance status and MGMT decide treatment in older adults.
- Shorter RT courses reduce travel without losing benefit.
- Palliative care belongs at diagnosis.

See: Sections 05–06 · Algorithm 1 · [Perry 2017](#)^[64], [Nordic](#)^[65], [ANOCEF](#)^[42]

CASE 4 Ring lesion · India trap · lymphoma**Four months of treatment for a "tuberculoma"**

48 years, woman

Periventricular, solid

Steroids already started

A 48-year-old woman was started on antituberculous drugs and dexamethasone 4 months ago for a left periventricular enhancing lesion. She improved briefly, then became drowsy and unsteady. Repeat MRI: two homogeneously enhancing periventricular masses with restricted diffusion. HIV negative.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**RECOGNISE THE PATTERN**

Homogeneous, diffusion-restricting periventricular masses suggest primary CNS lymphoma; the transient response to steroids fits.

2**PREPARE FOR BIOPSY**

Taper dexamethasone if she is stable (steroids can make the biopsy non-diagnostic); stereotactic biopsy, not resection.

3**STAGING**

Slit-lamp eye examination, CSF cytology and flow cytometry, CT or PET body, testicular/bone marrow per protocol.

4**TREATMENT**

High-dose methotrexate-based induction in a centre experienced with it, then consolidation by fitness. Stop antituberculous treatment once TB is excluded.

TEACHING POINTS

- A growing lesion on antituberculous treatment needs tissue.
- Steroids before biopsy can hide lymphoma.
- Lymphoma is treated with chemotherapy, not resection.

See: Sections 02–03 · [WHO 2021](#)^[36]

CASE 5 Brain metastases · EGFR lung cancer**Three small brain metastases at diagnosis**

52 years, woman, never-smoker

EGFR exon 19 deletion

3 lesions, largest 9 mm

A 52-year-old never-smoker has stage IV lung adenocarcinoma with an EGFR exon 19 deletion. Staging MRI shows three asymptomatic metastases, the largest 9 mm, with minimal oedema.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**STERIODS AND SEIZURES**

None: asymptomatic, no seizures.

2**FIRST TREATMENT**

Osimertinib, which penetrates the CNS well; MRI at 6–8 weeks and then every 2–3 months.

3**IF A LESION GROWS OR CAUSES SYMPTOMS**

SRS to that lesion while continuing the TKI.

4**WHAT TO AVOID**

Upfront whole-brain RT: no survival gain, cognitive harm, and it may limit future options.

TEACHING POINTS

- Genotype changes the brain plan as well as the body plan.
- Small, asymptomatic metastases can be watched on a CNS-active drug with close MRI.
- Keep SRS in reserve.

See: Sections 05–06 · Algorithm 2 · [N0574](#)^[46], [GPA](#)^[1]

CASE 6 Brain metastasis · surgery + SRS · VTE**Vomiting and unsteadiness after breast cancer**

61 years, woman

Triple-negative breast cancer

3.5 cm cerebellar lesion

A 61-year-old woman treated for triple-negative breast cancer 2 years ago has a week of vomiting and unsteadiness. MRI: a single 3.5 cm right cerebellar metastasis compressing the fourth ventricle with early hydrocephalus. Body CT: two small lung nodules.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**URGENT CARE**

Dexamethasone; same-day neurosurgical review.

2**SURGERY**

Resection of the cerebellar metastasis relieves hydrocephalus and confirms the diagnosis.

3**AFTER SURGERY**

Cavity SRS (fractionated for a large cavity) within about a month rather than WBRT (N107C, Mahajan); taper dexamethasone; systemic therapy for the lung disease.

4**TWO WEEKS LATER: CALF DVT**

Non-contrast CT shows no haemorrhage; start a DOAC (or LMWH), continued while cancer is active.

TEACHING POINTS

- Large posterior fossa metastases with mass effect go to the surgeon.
- Cavity SRS beats WBRT for cognition and observation for local control.
- Anticoagulation is usually safe after a brain metastasis is treated.

See: Sections 05, 06, 08 · Algorithm 2 · [Patchell](#)^[40], [N107C](#)^[49], [Mahajan 2017](#)^[48], [Leader 2020](#)^[87]

CASE 7 Child · posterior fossa · pilocytic**A 6-year-old treated for worms**

6 years, girl

Cerebellar cystic mass

KIAA1549-BRAF fusion

A 6-year-old girl has 2 months of early-morning vomiting, treated twice for worms and acidity. Her mother notices she walks unsteadily and tilts her head. Fundi show papilloedema.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**IMAGE NOW**

Urgent MRI (CT if MRI unavailable): a cystic left cerebellar mass with an enhancing mural nodule and obstructive hydrocephalus.

2**SAME-DAY NEUROSURGERY**

Dexamethasone; relieve hydrocephalus; gross total resection.

3

DIAGNOSIS

Pilocytic astrocytoma, CNS WHO grade 1, KIAA1549–BRAF fusion.

4

AFTER SURGERY

No further treatment after gross total resection; MRI surveillance; late-effects follow-up is light. If it had been incomplete and progressive: chemotherapy or a RAF/MEK inhibitor.

TEACHING POINTS

- Morning vomiting with ataxia in a child is a brain tumour until proven otherwise.
- A cyst with a mural nodule in the cerebellum is classically pilocytic astrocytoma.
- Complete resection cures most cerebellar pilocytic astrocytomas.

See: Sections 02, 05 · Algorithm 3 · [COG A9952](#)^[77]

CASE 8 Child · hypothalamic LGG · BRAF V600E**Vision loss and weight loss in a 9-year-old**

9 years, boy

Suprasellar mass

BRAF V600E

A 9-year-old boy has 6 months of falling school marks, bumping into doors and weight loss. MRI: a large suprasellar/hypothalamic enhancing mass; visual fields show bitemporal loss. Endocrine tests: low free T4 and cortisol.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

STABILISE

Hydrocortisone before thyroxine; ophthalmology baseline.

2

TISSUE

Partial resection/biopsy (radical resection would injure the hypothalamus): low-grade glioma with BRAF V600E.

3

TREATMENT

Dabrafenib + trametinib first line (response 47 vs 11% and longer PFS than carboplatin–vincristine); monitor for fever, skin, eyes and heart function.

4

LONG TERM

Vision, endocrine replacement, school support; RT reserved for later and avoided where possible.

TEACHING POINTS

- Replace cortisol before thyroxine.
- BRAF testing changes first-line therapy in paediatric LGG.
- Function (vision, hormones, learning) is the goal as much as tumour control.

See: Sections 04, 06 · Algorithm 3 · [Bouffet 2023](#)^[32]

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Educational summary for health professionals, written in our own words from current guidelines and primary trials. No chemotherapy doses are given. Verify current guidelines, Indian regulatory approvals and individual patient factors before treatment decisions.