Protocol Support Committee (PSC) Discuss with Us Series

Brain Cancer: Fundamentals

Anatomy · Classification & Grading · Diagnostic Workup

With a preview of treatment modalities and outcomes

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Disclosures

No Disclosures

The presenter has no relevant financial relationships to disclose.

SESSION OVERVIEW

Learning objectives & roadmap

By the end of this session, you will be able to:

- Find the brain's major regions, grooves (sulci), and "eloquent" zones where damage hits hardest
- Name the normal cell types that primary brain tumors grow from
- Read the 2021 WHO classification, which blends microscope findings with genetics
- Explain how tumors are graded 1–4, using both how they look and their genetics
- Tell grading apart from cancer "staging" — and the cases where spread via spinal fluid is staged
- Walk the initial workup, from first scan to a final, combined diagnosis

Today's agenda

01 Epidemiology & context

02 Brain anatomy & landmarks

03 Classification & molecular markers

04 WHO grading & staging (expanded)

05 Diagnostic workup & imaging

06 Treatment & outcomes (preview)

EPIDEMIOLOGY

How common — and why context matters

~24

per 100,000/yr

New primary brain & CNS tumors each year

~7

per 100,000/yr

Of those, the cancerous (malignant) ones

~10×

more common

Cancer spreading to the brain vs. starting there

~7%

5-year survival

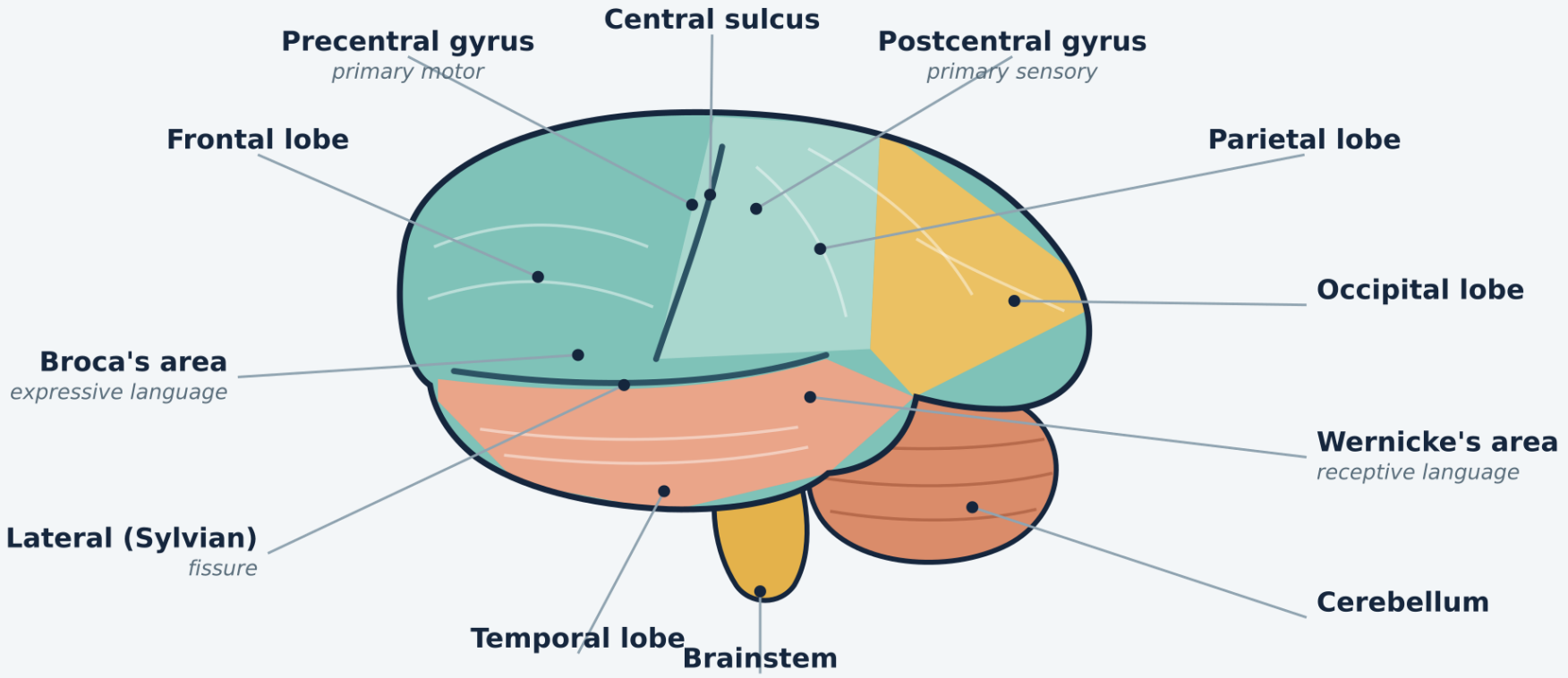
Glioblastoma — the most common malignant primary

Primary CNS tumors by type (approx. distribution)

Clinical context

- Tumors that spread from cancer elsewhere (metastases) are the most common brain tumors of all
- They most often come from lung, breast, melanoma (skin), kidney, and colon cancers
- Meningiomas are the most common tumor starting in the brain — but usually benign (non-cancerous)
- Gliomas drive most malignant primary disease; glioblastoma (GBM) is the most common and most aggressive

The brain at a glance: lobes & landmarks



Schematic for teaching; not to anatomical scale.

Lateral view

left hemisphere

- Four cerebral lobes, each with its own main jobs
- A groove called the central sulcus separates the movement and touch areas
- The Sylvian fissure is the deep cleft above the temporal lobe
- Broca's area = producing speech; Wernicke's area = understanding it
- Cerebellum & brainstem sit in the lower-rear compartment (posterior fossa)

Functional anatomy: major divisions

Frontal lobe

Decision-making, planning, voluntary movement, personality, and producing speech (Broca's area)

Parietal lobe

Processes touch and body sensation; spatial awareness; numbers and calculation

Temporal lobe

Hearing, memory, and understanding language (Wernicke's area)

Occipital lobe

The brain's main vision-processing center

Cerebellum

Coordination, balance, and fine-tuning of movement

Brainstem

Relays nerves to the face; controls consciousness and automatic survival functions (breathing, heart rate)

Eloquent cortex & why location drives risk

Eloquent areas

"Eloquent" areas are regions where even small damage causes an outsized, often permanent loss of function.

- The surgical goal is the most tumor that can be removed safely — not simply the most tumor
- These zones are mapped before and during surgery (functional MRI, fiber-tract imaging, and even operating while the patient is awake)
- How much is removed is always balanced against protecting function

1

Primary motor cortex

Controls movement — damage causes weakness on the opposite side of the body

2

Primary sensory cortex

Registers touch — damage causes numbness on the opposite side

3

Broca's area

Damage makes speech effortful and halting (expressive aphasia)

4

Wernicke's area

Damage garbles comprehension — fluent but nonsensical speech (receptive aphasia)

Supporting structures & cells of origin

Meninges

The brain's protective wrapping layers. Meningiomas grow from them; they're also a path tumors use to spread.

Ventricles & CSF

Fluid-filled spaces and the cushioning fluid (CSF). A mass can block flow and cause fluid buildup (hydrocephalus).

Blood–brain barrier

A filter that shields the brain — it blocks many drugs, and where it breaks, MRI contrast leaks in and lights up.

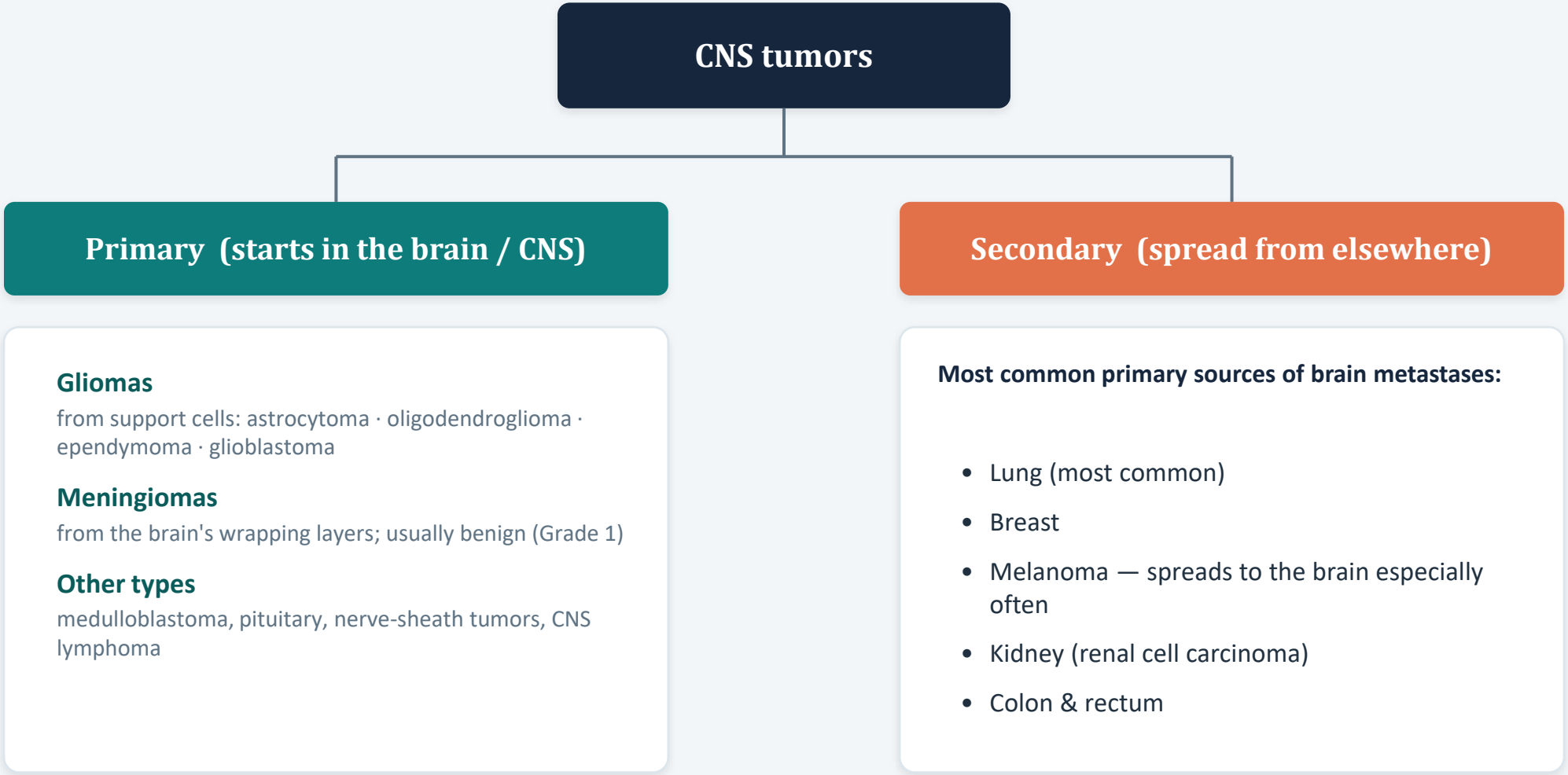
Glial cells

The brain's support cells (astrocytes, oligodendrocytes, ependymal cells) — the starting point for gliomas.

Where the names come from: gliomas are named after the support cell they resemble (astrocytoma, oligodendroglioma, ependymoma). Today that naming is refined by genetic testing, not just appearance under the microscope.

CLASSIFICATION

Primary vs. secondary CNS tumors



CLASSIFICATION

Evolution toward integrated diagnosis

How the basis for classification shifted from what a tumor looks like to what it is, molecularly.

2007

By appearance

Tumors were sorted mainly by how they looked under the microscope. Grade came from that appearance alone.

2016

Genetics added

A few genetic markers (such as IDH) joined the diagnosis — appearance plus genetics for the first time.

2021

Fully blended (CNS5)

Genetics now help define the tumor type and set its grade. Grades use plain numbers 1–4, with new categories added.

Why it matters: a diagnosis based on appearance alone can be incomplete — or wrong — by today's standards. Genetic testing is now part of the diagnosis itself.

The 2021 WHO classification (CNS5)

Integrated diagnosis

Appearance
how cells look

+

Genetics
key DNA markers

=

Dx
final diagnosis + grade

- Genetic markers can outweigh how a tumor looks
- A tumor that looks low-grade can still be called Grade 4 if it carries certain genetic changes
- Tumor types are now defined by their cell family plus their defining genetic features

Layered reporting format

Layer 1	Final integrated diagnosis
Layer 2	Tumor type by appearance
Layer 3	WHO grade (1–4)
Layer 4	Genetic findings

CLASSIFICATION

WHO grading: a spectrum of behavior

GRADE 1

Well-defined and slow-growing; often cured by surgery alone

e.g. pilocytic astrocytoma, most meningiomas

GRADE 2

Slow-growing but invades nearby tissue; tends to return over time

e.g. diffuse astrocytoma, IDH-mutant

GRADE 3

Clearly abnormal cells dividing more actively

e.g. astrocytoma, IDH-mutant, Grade 3

GRADE 4

Aggressive; zones of dead tissue and abnormal new blood vessels

e.g. glioblastoma, IDH-wildtype

Increasing malignancy, decreasing survival →

What sets the grade: what pathologists look for

Cell division

How many tumor cells are actively splitting — measured by a marker called Ki-67. ("Mitotic activity")

Abnormal nuclei

Cell control-centers that look irregular — varying in size, shape, and darkness. ("Nuclear atypia")

New blood vessels

Disordered growth of tiny new vessels feeding the tumor. ("Microvascular proliferation")

Dead tissue

Patches of dead tumor where it outgrows its blood supply — a hallmark of the worst tumors. ("Necrosis")

For the common gliomas: abnormal nuclei → **G2** + faster division → **G3** + new vessels and / or dead tissue → **G4**

Genetic findings can raise the grade on their own, even when these features aren't seen — see next slide.

Grading in the molecular era

Sometimes a single genetic change tells us a tumor is Grade 4 — even if it looks milder under the microscope. Three examples:

CDKN2A / B deletion

Loss of a protective "brake" gene. In an IDH-mutant astrocytoma, this alone makes it Grade 4 — no dead tissue or new vessels required.

IDH-wildtype + TERT, EGFR, or +7 / −10 changes

These DNA features define a glioblastoma (Grade 4), even when the tumor looks lower-grade under the microscope.

H3 K27M alteration

This single change defines a diffuse midline glioma — automatically Grade 4, regardless of appearance.

Bottom line: grade is set within a tumor type, and certain genetic changes are a shortcut to Grade 4 that the microscope alone would miss.

Grading across CNS tumor families

Tumor family	WHO grade	Typical basis for grade
Astrocytoma, IDH-mutant	**2 – 4**	Reaches Grade 4 via a key gene loss or aggressive features
Oligodendroglioma (IDH-mut, 1p/19q)	**2 – 3**	Best outlook among the infiltrating gliomas
Glioblastoma, IDH-wildtype	**4**	Always Grade 4 — there is no lower grade
Meningioma	**1 – 3**	About 80% are benign Grade 1
Ependymoma	**2 – 3**	Grouped by location in the brain and by genetics
Pilocytic astrocytoma	**1**	Well-defined; often cured by surgery
Medulloblastoma	**4**	High-grade; risk scored separately (see staging)

Tumors that spread to the brain, and CNS lymphoma, aren't given a 1–4 grade here. "IDH" and "1p/19q" are genetic markers used to define glioma types.

What the grade means in practice

GRADE 1

Well-defined

Surgery to remove it completely is often a cure; then periodic scans. Extra treatment is rarely needed.

GRADE 2

Slow but invasive

Remove as much as is safe, then radiation and/or chemotherapy tuned to risk; watch long-term for return.

GRADE 3 – 4

Aggressive

Remove as much as is safe, then combined chemo + radiation; genetics guide the drugs; clinical trials are an option.

Grade is one input. The plan combines grade + genetics + location and how safely it can be removed + the patient's age and overall health.

MOLECULAR PATHOLOGY

Key genetic markers — and what they tell us

A handful of DNA findings now do most of the diagnostic work. The essentials:

IDH mutation

The master switch — its presence marks the better-outlook gliomas

1p/19q co-deletion

Loss of two chromosome pieces; with IDH, defines oligodendroglioma (often chemo-responsive)

MGMT methylation

A chemical "off-switch" on a repair gene; predicts who benefits from the chemo drug temozolomide

ATRX & TP53

When altered, point toward the astrocytoma family of gliomas

TERT, EGFR, +7/−10

In an IDH-normal tumor, these mark a glioblastoma (Grade 4)

CDKN2A/B · H3 K27M

Push a tumor to Grade 4; H3 K27M defines a diffuse midline glioma

The takeaway: genetic testing is no longer optional. Markers like IDH (and, for oligodendroglioma, 1p/19q) are needed for a complete, modern diagnosis — and they change both outlook and treatment.

COMMON MISCONCEPTION

Why brain tumors aren't TNM-staged

Most systemic cancers

- **Staged with the TNM system**
  - T — size / extent of the main tumor
  - N — spread to nearby lymph nodes
  - M — spread to distant organs
- Based on how far the cancer has traveled through the body

≠

Primary CNS tumors

- **Classified and graded — not TNM-staged**
- Almost never spread outside the brain & spine — so "N" and "M" add little
- Outlook depends on: grade, genetics, location and how safely it can be removed, plus age and overall health
- Instead of spreading far, it creeps along the brain's wiring (white-matter tracts)

These tumors creep locally through the brain rather than spreading to lymph nodes or distant organs.

STAGING · THE EXCEPTION

When "staging" does matter: spread through spinal fluid

A few brain tumors can shed cells into the cerebrospinal fluid (CSF) — the fluid bathing the brain and spinal cord. For these, we map how far it has spread, which changes risk group and treatment.

Tumors that tend to spread this way

- Medulloblastoma & other embryonal tumors
- Ependymoma (especially in the lower-rear brain)
- Germ cell tumors and CNS lymphoma
- Cancer coating the brain's linings (from elsewhere)

How the spread is checked

- MRI of the whole brain and spine, with contrast dye
- A sample of spinal fluid checked for tumor cells — taken ≥ 2 weeks after surgery to avoid false alarms
- A spread score (called the Chang M-stage, M0–M4)
- Sets the risk group (e.g. average- vs high-risk medulloblastoma)

≠

Still not TNM. There's no lymph-node or distant-organ category here — the spread stays within the brain and spinal cord, carried by the CSF. Think of it as the brain's own version of staging, used only for tumors that travel this way.

Clinical presentation

General signs (rising pressure)

- Headache — classically worse in the morning or when bearing down
- Nausea and vomiting
- Swelling at the back of the eye (papilledema); blurred vision
- Drowsiness or slowed thinking
- **A new seizure — often the very first sign**

Focal signs (point to a location)

- Weakness or numbness, usually on the opposite side of the body
- Trouble producing or understanding speech (aphasia)
- Loss of part of the field of vision
- Personality or decision-making changes (frontal lobe)
- Loss of balance and coordination (cerebellum)
- Double vision or facial weakness (brainstem nerves)

DIAGNOSTIC WORKUP

First-line imaging: MRI with contrast

MRI with and without contrast dye (gadolinium) is the standard test; CT is mainly for emergencies. ▸ ***In slide-show mode, click any sequence to see an example.***

T1 + contrast

Dye lights up where the blood–brain barrier has broken down — a sign of active, often higher-grade tumor

MP-RAGE (3-D T1)

A fast, high-resolution 3-D scan (the "RAGE" sequence); crisp anatomy for surgical navigation, often the post-contrast workhorse

T2 / FLAIR

Shows non-enhancing tumor and the surrounding brain swelling (edema), revealing the infiltrating edges

DWI / ADC

Tracks how freely water moves; helps tell dense tumor from an abscess or a stroke

T1 (no contrast)

Baseline anatomy; picks up blood, fat, and bright signal before any dye is given

SWI / GRE

Especially sensitive to tiny bleeds and calcium deposits inside a lesion

Post-op MRI < 48 h

Early scan to measure how much tumor was removed, before healing changes set in

Important limit: scans can show where a tumor is and what it looks like, but they can't give a final diagnosis. Bright enhancement points toward — but doesn't prove — a high grade. That still takes a tissue sample and genetic testing.

DIAGNOSTIC WORKUP

Advanced & functional imaging

MR perfusion

Measures blood flow in the tumor — high flow suggests a higher grade, and helps tell regrowth from radiation damage

MR spectroscopy

Reads the tumor's chemical fingerprint to help separate true tumor from normal or scarred tissue

Amino-acid PET

A nuclear scan using labeled amino acids; sharpens grading, biopsy targeting, and spotting regrowth

Functional MRI & fiber mapping

Maps the critical function areas and the brain's wiring to plan the safest possible surgery

DIAGNOSTIC WORKUP

Tissue diagnosis: the definitive step

Needle biopsy

- For tumors too deep or risky to remove safely
- Only a tiny sample — can miss the most aggressive part

Surgical removal

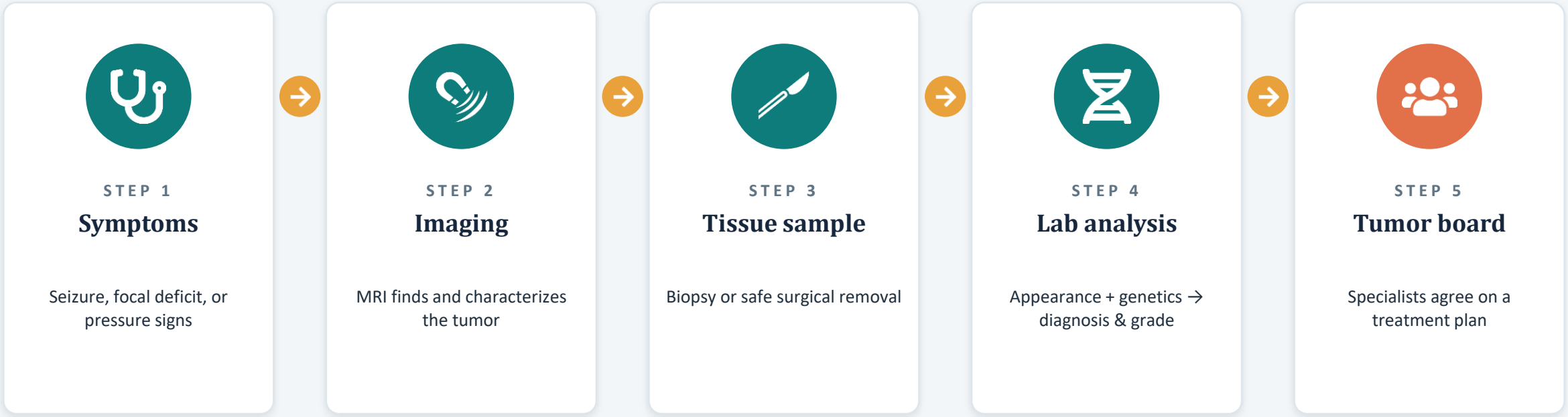
- Both diagnoses and treats — takes out as much as is safe
- A bigger sample means more reliable genetic testing

From specimen to integrated diagnosis

1. **Quick read during surgery** — a fast first look to guide the operation
2. **Microscope exam** — appearance, cell family, and grade clues
3. **Protein stains** — highlight telltale proteins (IDH, Ki-67…)
4. **Genetic testing** — DNA changes — IDH, 1p/19q, MGMT
5. **Final diagnosis** — all combined into tumor type + grade

PUTTING IT TOGETHER

The diagnostic pathway, end to end



PREVIEW · PART 2

Treatment modalities at a glance

Surgery

Removes as much as is safe; eases pressure and provides tissue

Radiation

Targeted radiation, usually in small daily doses after surgery

Chemotherapy

Drugs like temozolomide; the standard combo with radiation in GBM

Targeted therapy

Drugs aimed at a tumor's specific genetic changes; many in trials

Tumor-treating fields

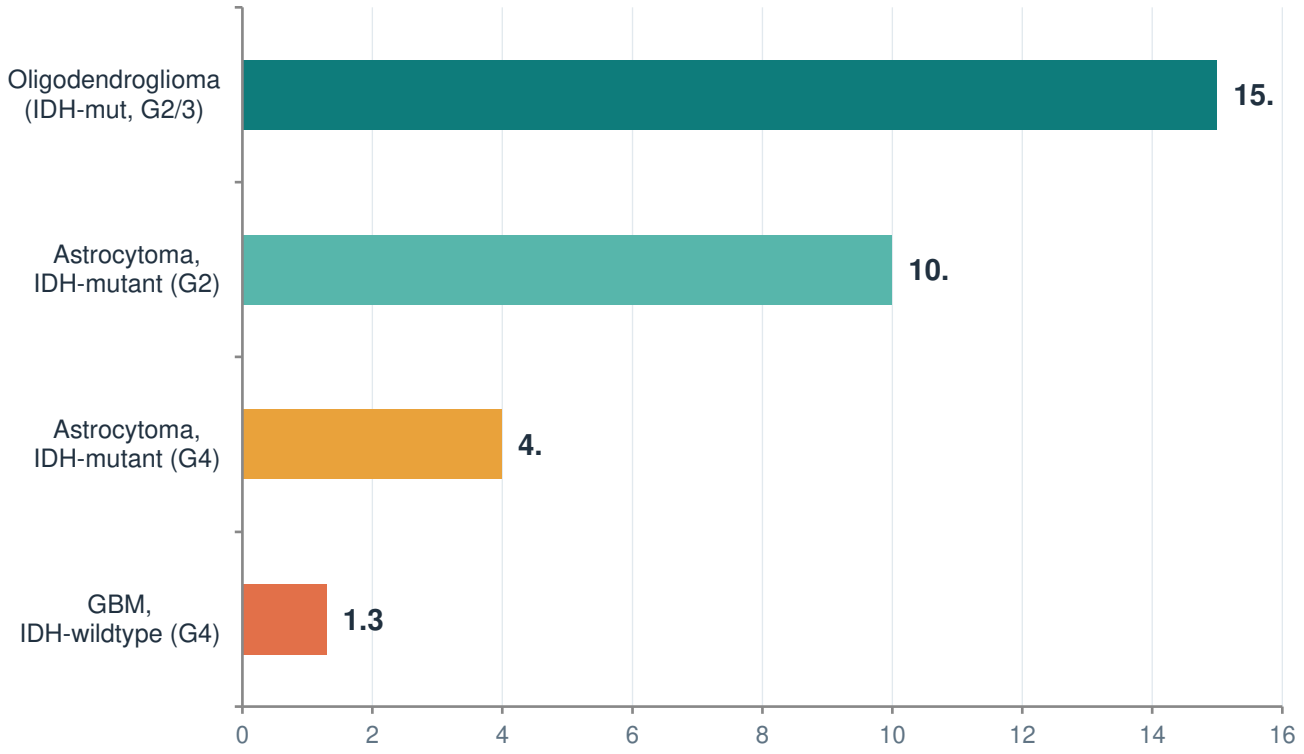
A wearable device using electric fields, added in glioblastoma

Supportive care

Steroids, anti-seizure meds, rehab, and symptom support

A team effort: surgeons, radiation and medical oncologists, pathologists, radiologists, and supportive-care specialists plan together at a tumor board. Part 2 digs into the specific drugs, timing, and trials.

Outlook: genetics change everything



What shapes the outlook

- Tumor grade and genetics
- IDH and 1p/19q markers
- MGMT marker (predicts chemo benefit)
- How much tumor was removed
- The patient's age and overall health

SUMMARY

Key takeaways

1	**Location is destiny**	Where a tumor sits predicts its symptoms and how risky surgery will be.
2	**Graded, not staged**	Brain tumors are graded 1–4 by how they behave — not staged like body cancers.
3	**Diagnosis is combined**	The modern diagnosis blends how a tumor looks with its genetics (IDH, 1p/19q, MGMT).
4	**Scans suggest, tissue confirms**	MRI shows where and what; a tissue sample plus genetics give the final answer.
5	**Genetics drive the outlook**	Subtype can shift survival from months to many years — and guides treatment.

Questions & discussion

Coming up — Part 2

- Surgical strategies and how much tumor to remove
- Radiation and chemotherapy regimens, and how they're sequenced
- Targeted therapy, immunotherapy, and the clinical-trial landscape

Selected references

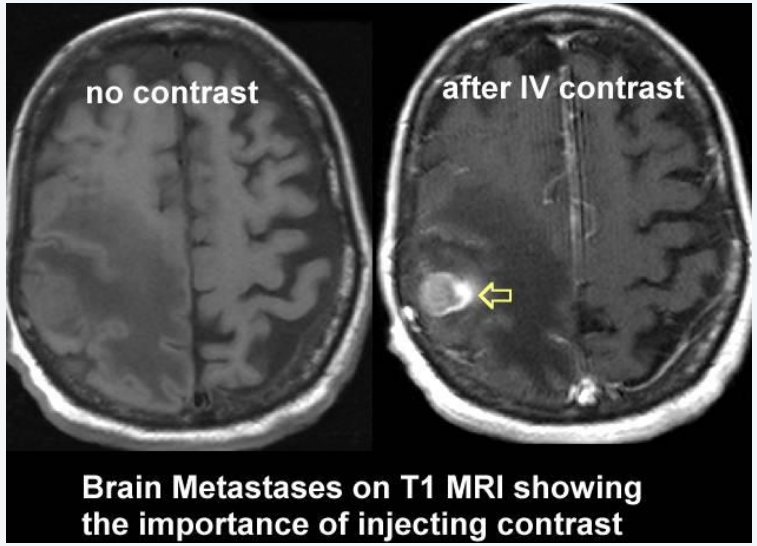
WHO Classification of Tumours of the CNS, 5th ed. (2021)

Louis DN et al. Neuro-Oncology, 2021 (cIMPACT-NOW updates)

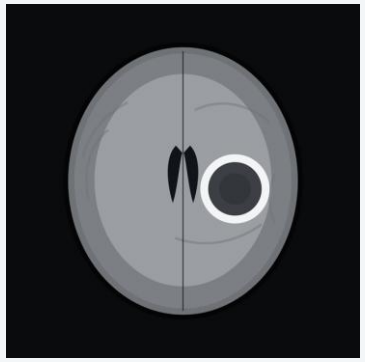
Stupp R et al. NEJM, 2005 — concurrent RT + temozolomide

CBTRUS Statistical Report (epidemiology)

T1 + contrast (post-gadolinium)



Brain Metastases on T1 MRI showing the importance of injecting contrast



What you're seeing

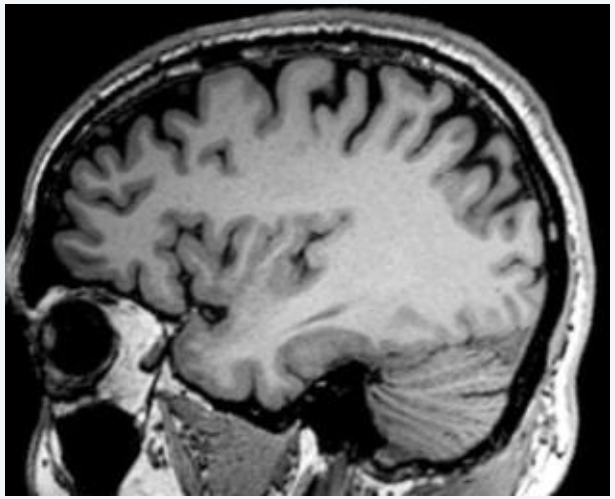
After contrast dye, areas where the blood–brain barrier has broken down light up bright. A bright ring with a darker center is the classic look of an aggressive tumor such as glioblastoma.

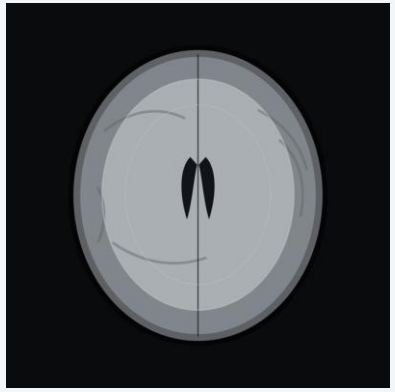
- Bright signal = dye leaking through a damaged barrier
- Ring = the active, growing tumor edge
- Dark center = dead tissue (necrosis)

‹ Back to imaging

Next example ›

MP-RAGE (fast 3-D T1)





What you're seeing

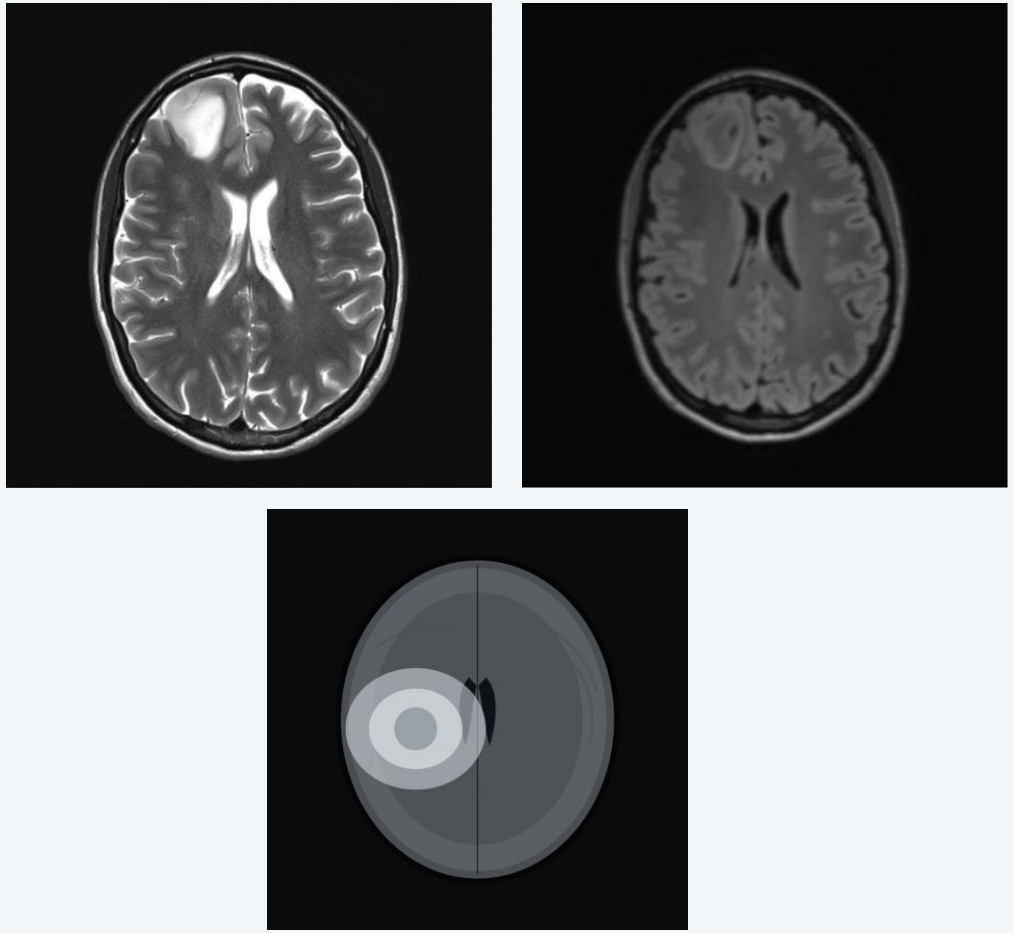
A fast, high-resolution 3-D T1 scan — the "RAGE" sequence. It gives crisp anatomy with clear gray–white separation, ideal for surgical navigation and 3-D planning, and is often the post-contrast series too.

- Very high spatial detail
- Whole brain captured in thin 3-D slices
- Used to guide neuro-navigation during surgery

‹ Back to imaging

Next example ›

T2 / FLAIR



What you're seeing

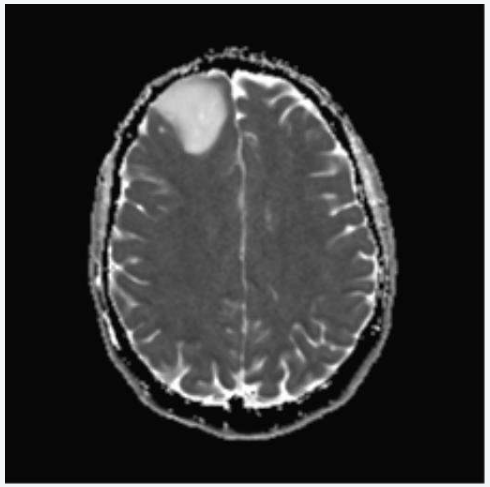
These sequences highlight water. The non-enhancing tumor and the swelling (edema) around it appear bright. FLAIR darkens normal fluid so the abnormal area stands out — showing how far the tumor has spread.

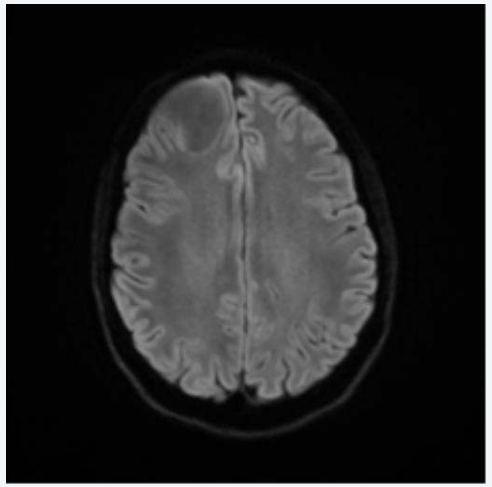
- Bright = swelling and infiltrating tumor
- Usually extends beyond the enhancing core
- Maps the tumor's true footprint

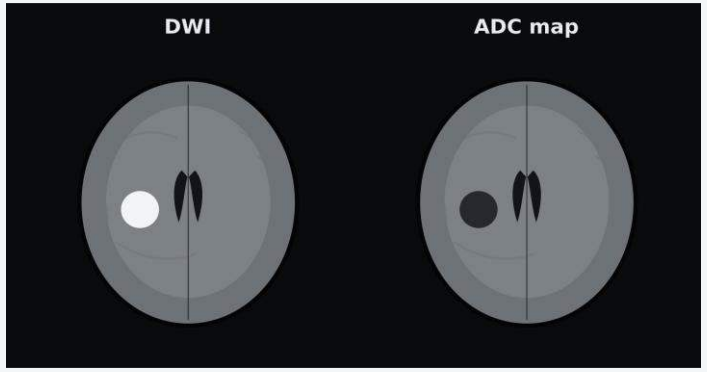
‹ Back to imaging

Next example ›

DWI / ADC







What you're seeing

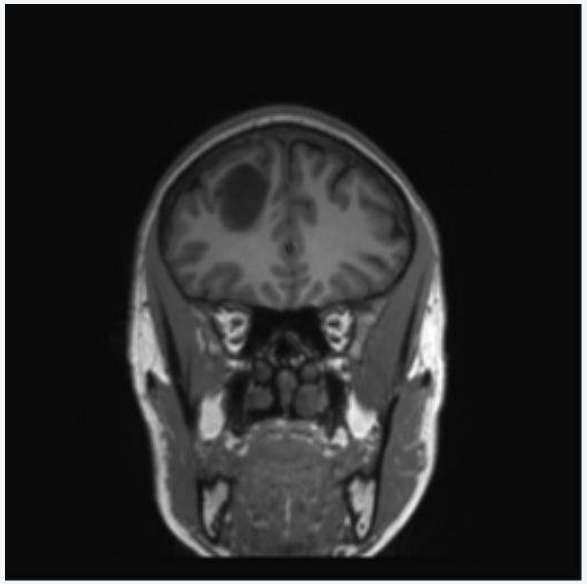
These measure how freely water moves. Densely packed tissue restricts water — appearing bright on DWI and dark on the matching ADC map. This pairing helps separate dense tumor or an abscess from normal brain, and flags a stroke.

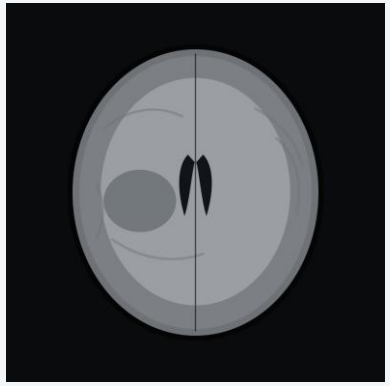
- Bright on DWI + dark on ADC = restricted
- Suggests dense tumor or an abscess
- Also flags a stroke after surgery

‹ Back to imaging

Next example ›

T1 (no contrast)





What you're seeing

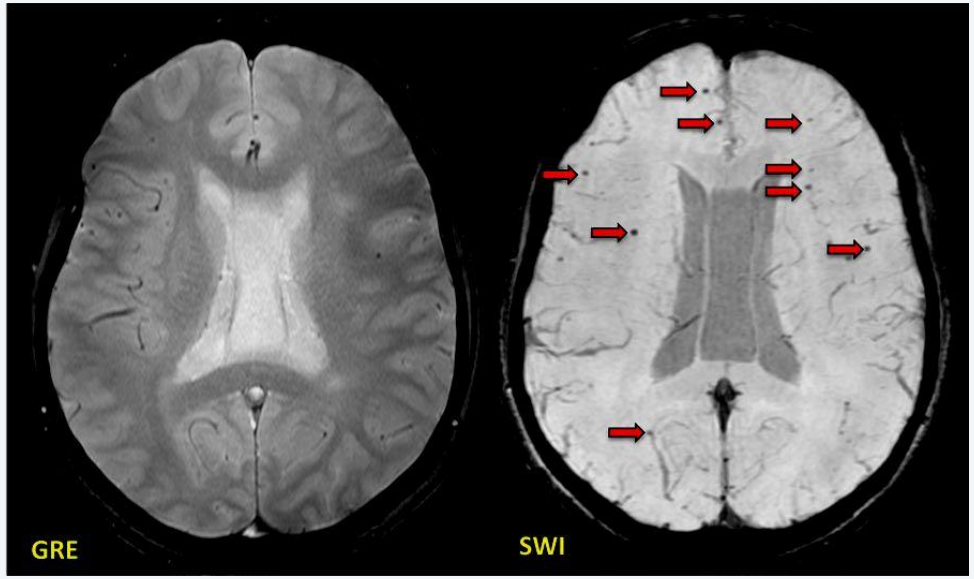
The baseline anatomy scan taken before any dye. Many tumors look slightly darker (hypointense) than normal brain. It also helps detect blood and fat, which have their own characteristic signal.

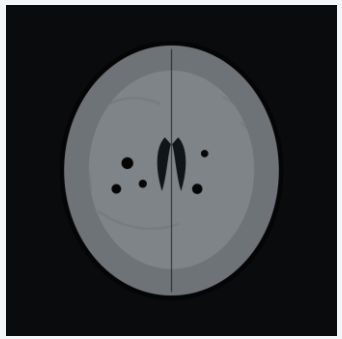
- Baseline taken before contrast
- Tumor often appears subtly dark
- Detects blood and fat by their signal

‹ Back to imaging

Next example ›

SWI / GRE





What you're seeing

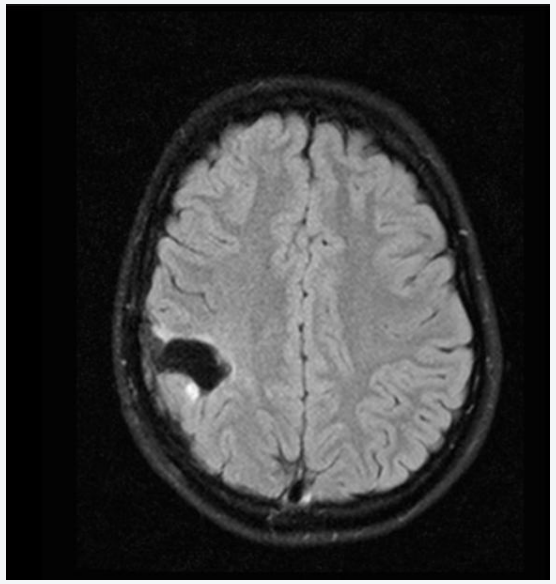
These are very sensitive to blood products and calcium, which "bloom" into dark spots. Useful for spotting tiny hemorrhages and calcification within a lesion that other sequences can miss.

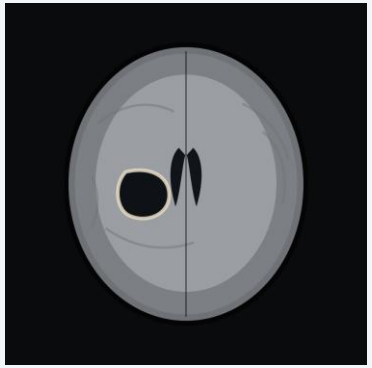
- Dark "blooming" spots
- Tiny areas of bleeding
- Calcium deposits within a lesion

‹ Back to imaging

Next example ›

Post-op MRI (< 48 hours)





What you're seeing

Done within about 48 hours of surgery to measure how much tumor was removed — before normal healing changes appear and make the picture harder to read. It sets the baseline for any further treatment.

- Establishes the extent-of-resection baseline
- Captured before healing changes set in
- Guides decisions about further therapy

‹ Back to imaging

Back to imaging ›