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JSRS 2026 · DAY 2 · 10:00–10:30

Imaging of Glioblastoma

An imaging-driven — but imaging-limited — disease

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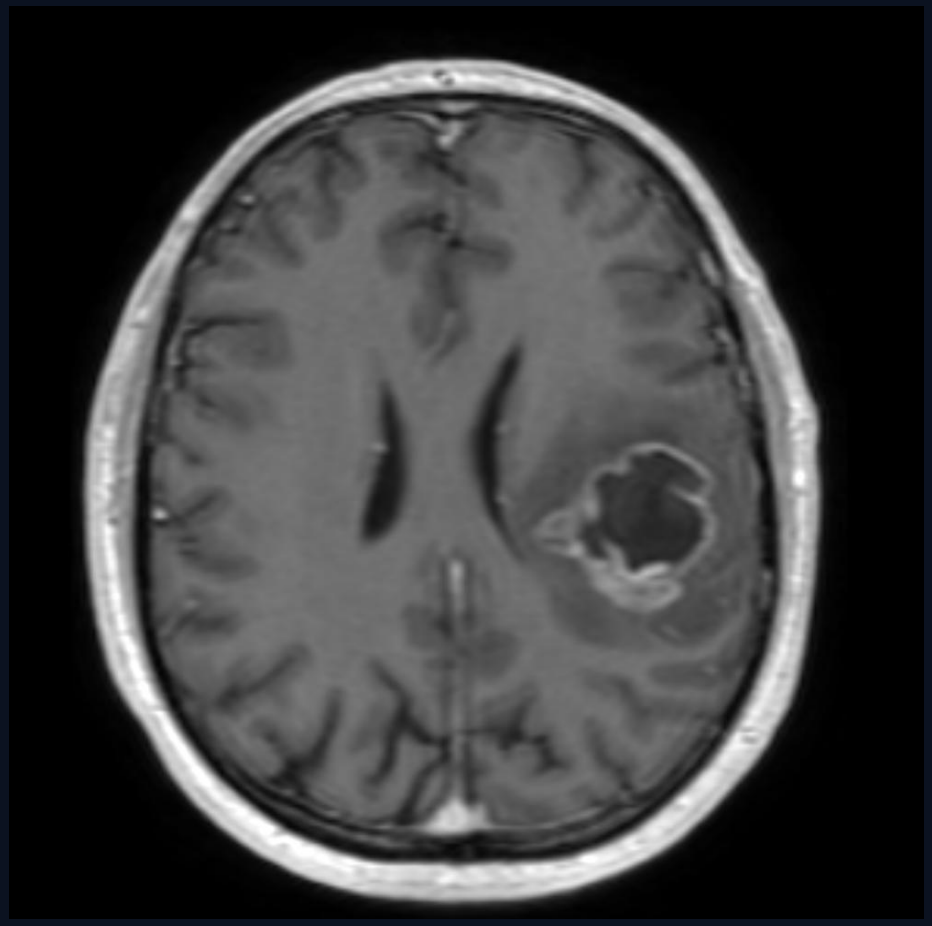

Pre-op T1 + contrast — the classic ring-enhancing GBM

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What this talk is about

1. **Setting the scene** — what GBM is, and what our job now is
2. **The molecular shift** — genetics, not the image, defines it
3. **Response assessment** — the genuinely hard problem
4. **Advanced imaging** — promise vs. delivery
5. **The AI paradox** — solving the wrong problem well

Glioblastoma is imaging-driven — but imaging-limited.

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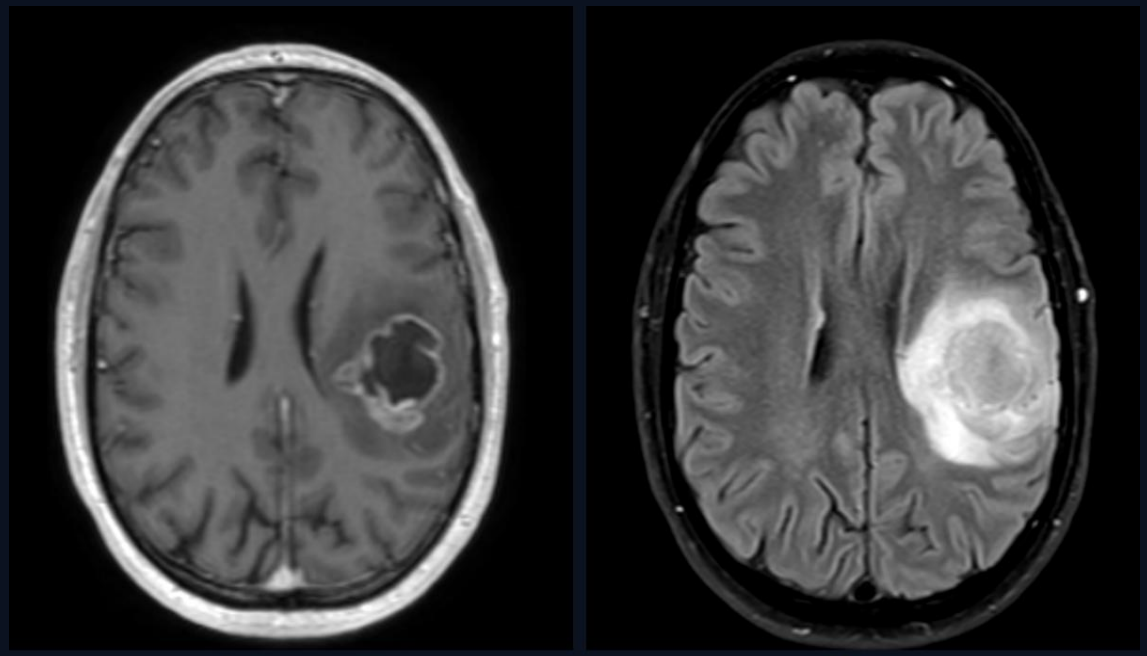


T1 + contrast

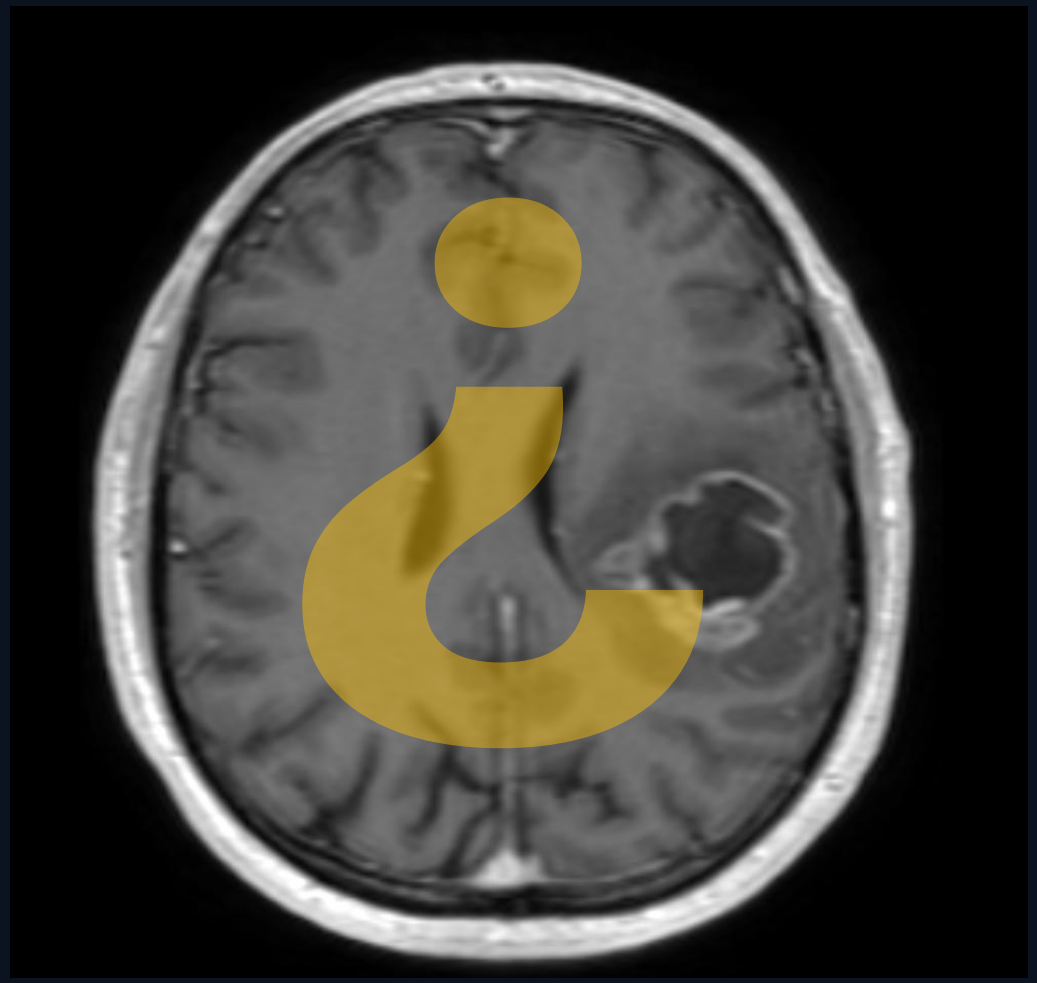
FLAIR

Typical GBM: irregular ring enhancement, central necrosis (T1+c); modest perilesional FLAIR.

Glioblastoma: the basics

- The most common malignant primary brain tumour
  - Incidence 3/100,000 per year
  - median survival 15 months; 5-year <7%
- Typical imaging
  - Intra-axial, supratentorial
  - Irregular ring enhancement with central necrosis
  - Variable on T2/FLAIR – both edema and infiltration
  - Diffusion restriction or haemorrhage may occur

Epidemiology: standard figures.



Molecular genetics has changed the radiological questions

WE USED TO ASK

"Is this a primary brain tumour?"

~~***"And what type and grade is it?"***~~

↓

What should we do to ascertain that this is a primary brain tumor?

Surgery? Biopsy? Full body CT / PET? Wait and scan?

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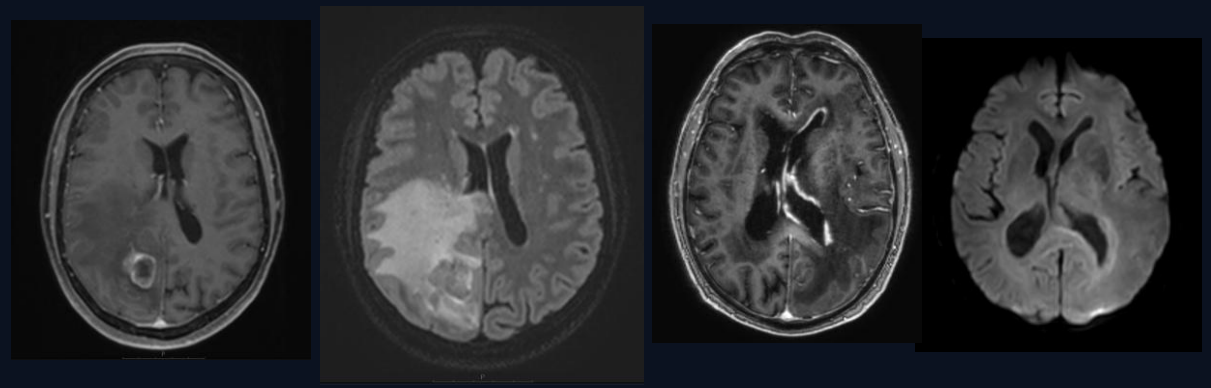
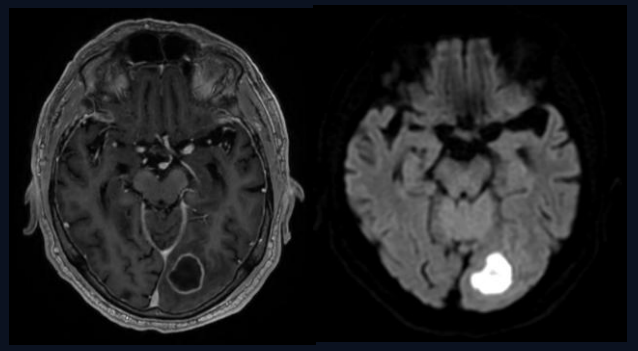
Metastasis
T1+C · FLAIR

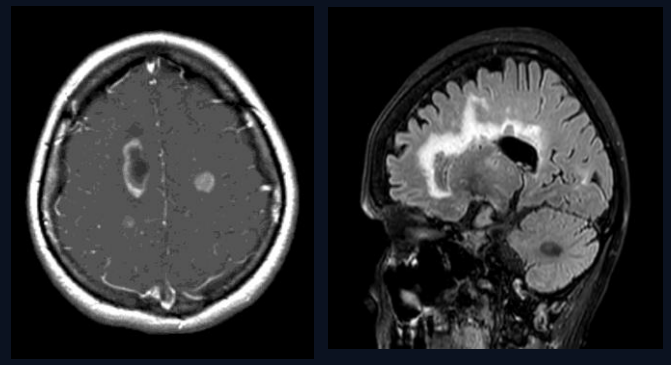


Lymphoma
T1+C · DWI b1000

Abscess
T1+C · DWI b1000



Tumefactive demyelination
T1+C · FLAIR

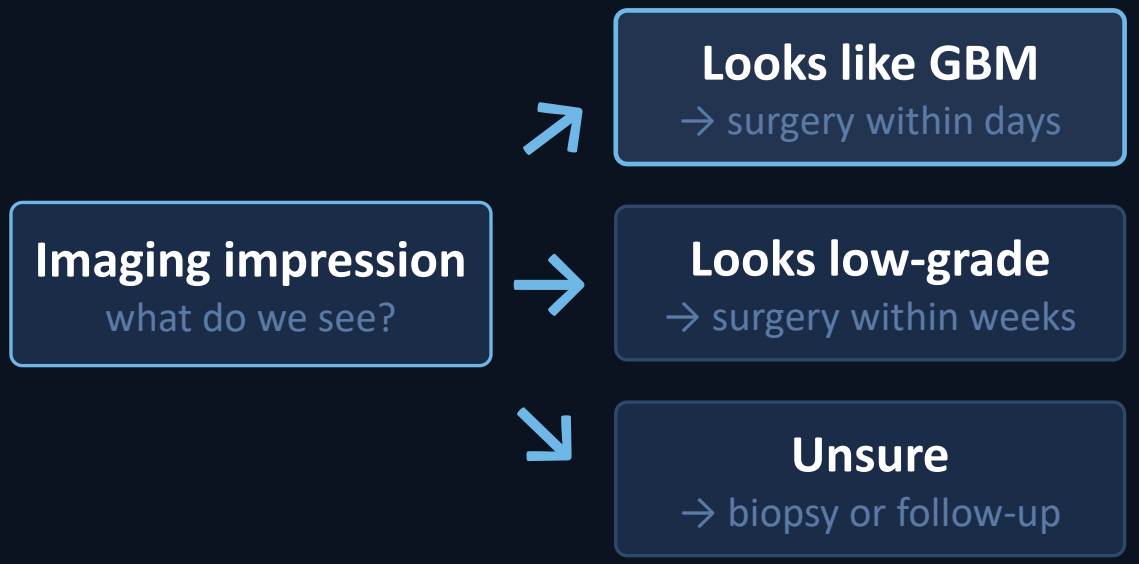


First: is it even a tumour?

Confirm it IS a tumour, and exclude the mimics

Key discriminators (vs the classic GBM on slide 3):

- Metastasis: solid/ring enhancement, often multiple, sharper brain interface
- Lymphoma: marked DWI restriction (low ADC), periventricular, dense pre-contrast
- Abscess: ring with central DWI restriction — nearly pathognomonic
- Tumefactive demyelination: incomplete “open” ring, little mass effect
- *Unsure? Short-interval MRI (weeks, not months) — OR biopsy OR alternative imaging OR Lumbar puncture*

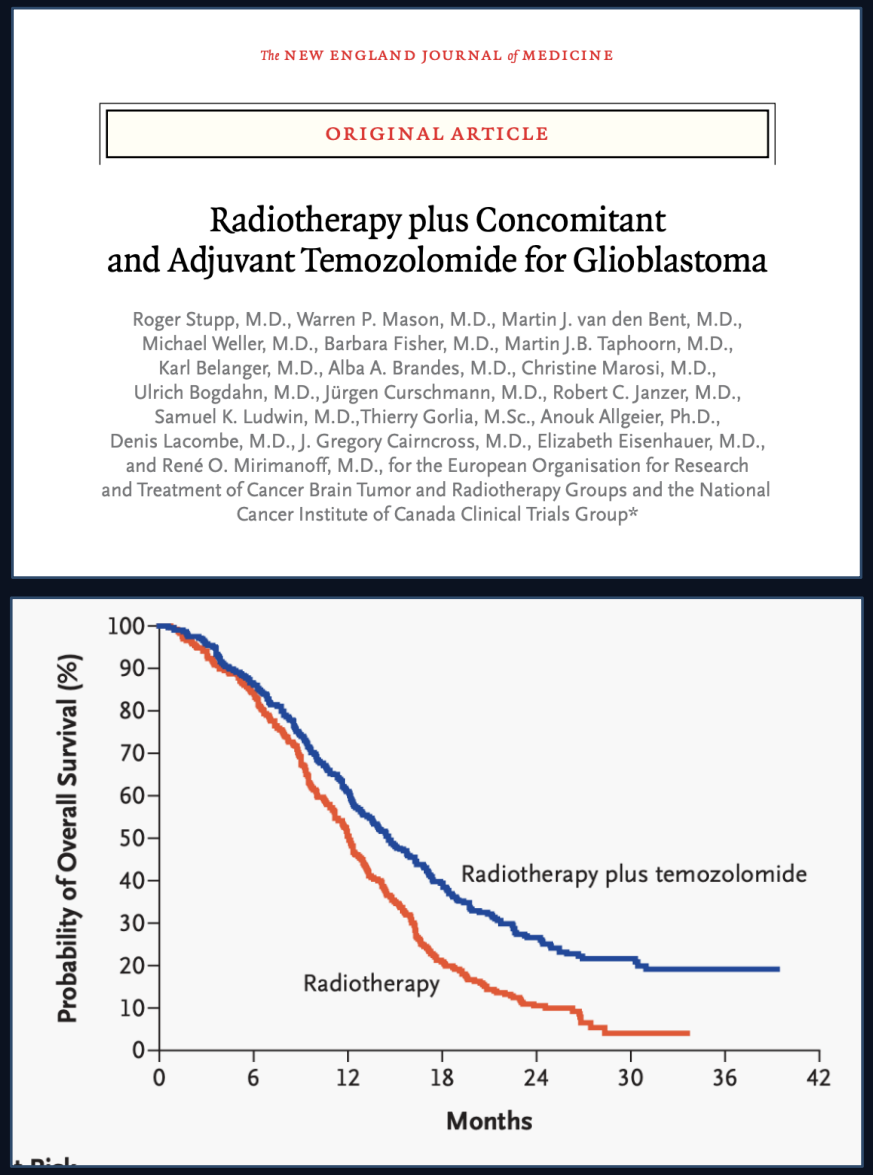


How urgent is surgery?

When it is a tumour: set the tempo

Our imaging impression sets the urgency — even though the final grade comes from tissue.

- Diagnosis is now molecular — tissue almost always needed
- Operability is a separate call: eloquent location or frail patient can make surgery too costly — even when the image looks obvious
- *Flagging where and how operable is part of our job - almost all tumors are surgically removed if feasible*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

Stupp et al., NEJM 2005

BACKGROUND FOR THE WHOLE TALK

Twenty years, unchanged survival

- Stupp protocol (2005): surgery + radiotherapy + temozolomide
- Median OS then ~15 months; in our own cohort today: 17.3 months
- Despite billions invested and hundreds of trials — the curve has hardly moved

≈ 15 months

median survival — then, and now

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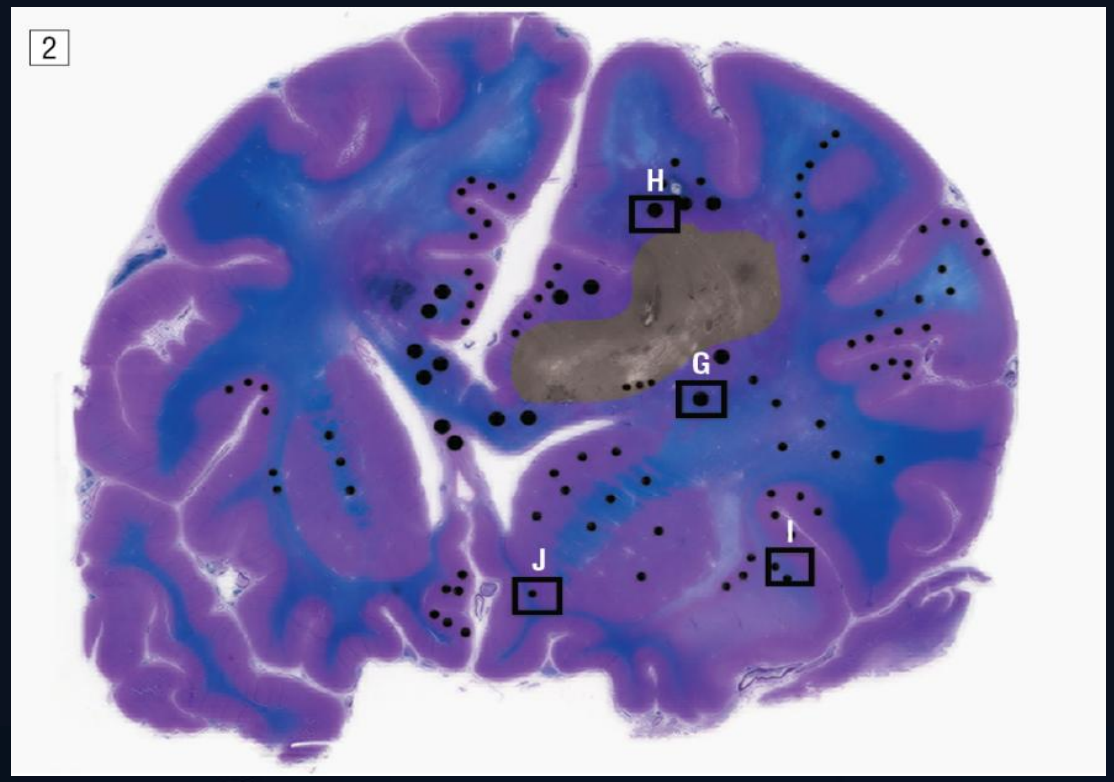

Whole-brain section: grey mass = visible tumour; black dots = individual tumour cells, in both hemispheres.

Sahm et al., Arch Neurol 2012 (IDH1-R132H single-cell staining)

BACKGROUND FOR THE WHOLE TALK

We see the tip of the iceberg

- GBM is a diffusely infiltrating disease
- The contrast-enhancing mass is only the tip
- Recurrence is almost always within 2 cm of the cavity — but cells extend far beyond
- We can only remove, measure, and segment what we see

PART 2

The molecular shift

Now we have the tissue — the genetics, not the image, define the treatment and the prognosis

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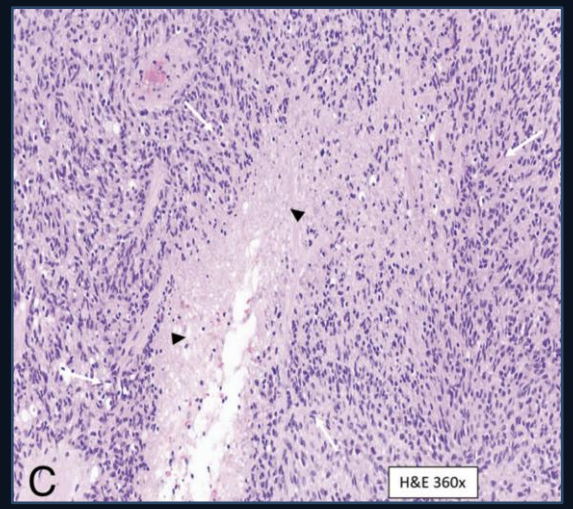
From histology to a molecular definition



Histology — H&E

H&E — necrosis & microvascular proliferation

DNA methylation profiling
genome-wide array

↓

Brain-tumour classifier
matches to reference classes

↓

METHYLATION MATCH

Glioblastoma, IDH-wildtype

0.99

calibrated score

- With tissue in hand, genetics — not the image — define the tumour
- GBM = IDH-wildtype, CNS WHO grade 4
- Diagnosable on molecular criteria alone — even without classic grade-4 histology (necrosis / microvascular proliferation)
- *So we guess grade far less — the diagnosis no longer rests on the picture*

"Molecularly, it is a glioblastoma." — the phrase you now hear from pathology.

Simplified from WHO 2021 (Louis et al., Neuro-Oncology 2021).

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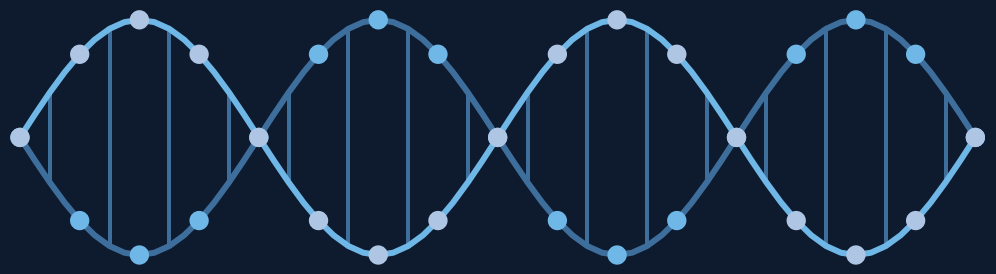

Imaging features often hint at IDH status — and AI can predict it (Part 5).

The markers worth knowing

IDH wild-type = glioblastoma; mutant = astrocytoma / oligodendroglioma

MGMT methylation predicts temozolomide response & prognosis

Targetable alterations e.g. vorasidenib for grade-2 IDH-mutant glioma (2024)

In our own cohort: methylated MGMT, HR 0.38 for overall survival.

Carlsen / Rykkje cohort (Sci Rep 2024).

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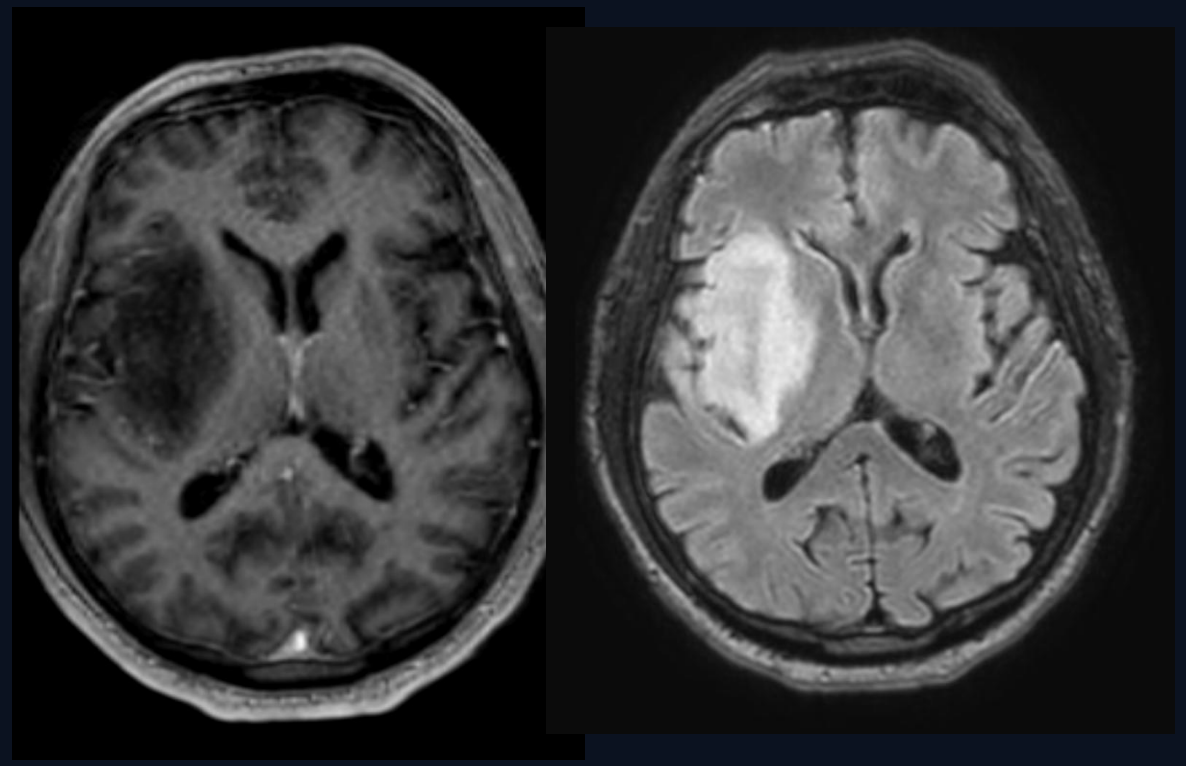

T1 + C , FLAIR

75Y M, Mistakable for low-grade — but it is not.

When a glioma does not enhance

> ⚠ *"No enhancement, therefore low grade."*

- <1% of histological GBM show little or no enhancement
- >10% of "molecular" GBM (IDH-wildtype) are non-enhancing
- Gliomatosis-like pattern: ~35% of molecular GBM vs ~8% of histological GBM
- ***The trap: a non-enhancing, infiltrative tumour in an older patient is NOT reassuringly low-grade***
- ***IDH-wild type >> IDH mutant***

Vollmuth et al., Korean J Radiol 2025.

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The treatment: the Stupp protocol

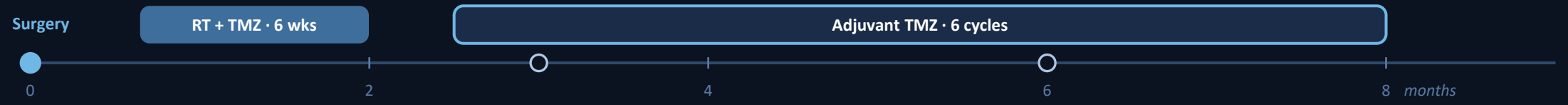
Surgery maximal safe resection

Radiotherapy + TMZ 60 Gy + concomitant TMZ

Adjuvant TMZ 6 cycles of temozolomide

Follow-up MRI every ~3 months

- One protocol since 2005 — largely unchanged
- Maximal safe resection, then chemoradiation, then adjuvant temozolomide
- MGMT methylation predicts how much benefit temozolomide gives
- ***Every step changes the brain — which is why follow-up is hard***



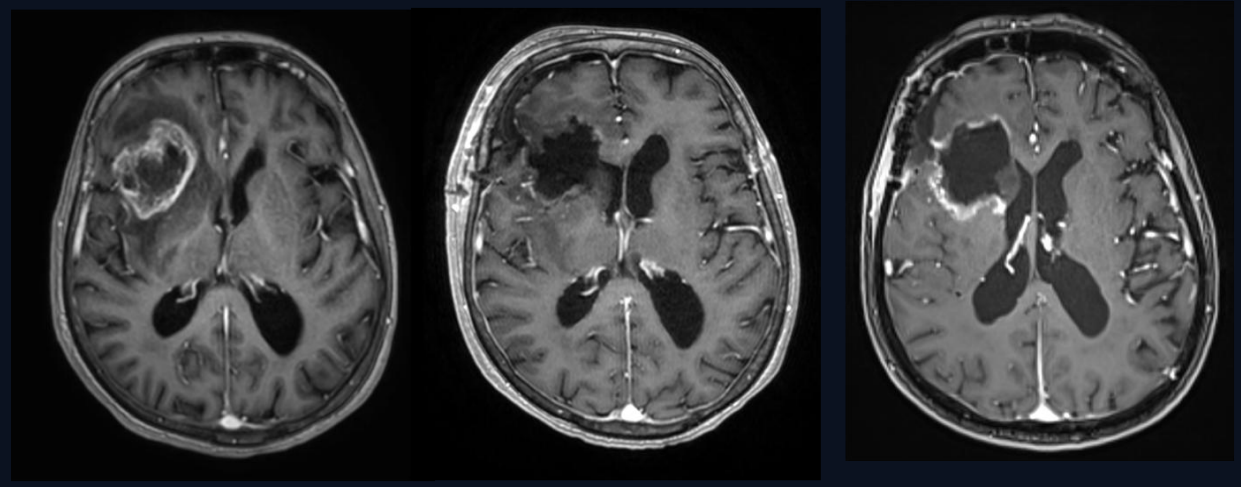
Stupp et al., NEJM 2005.

PART 3

Response: the hard problem

After treatment, the brain becomes much harder to read

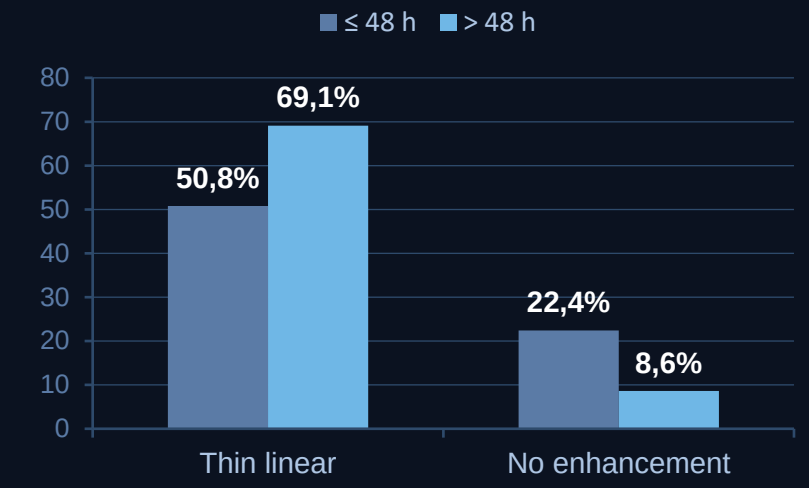
T1 + C x 3



Diagnosis | epMRI at 48h | Radiation at 2w

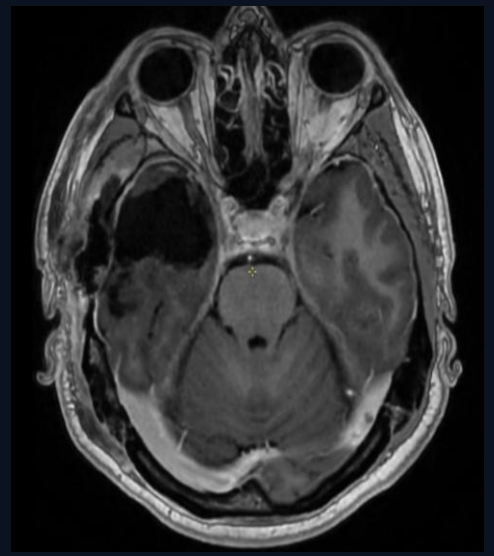
The post-treatment brain is a different beast

- Two questions after initial surgery: is the tumour removed — and when is it coming back?
- Why so early? To capture residual tumour and extent of resection — before surgical change sets in
- Surgery, radiation and chemotherapy all impact the image
- Reactive enhancement and pseudoprogression imitate real change
- ***This is where imaging is both indispensable and most easily fooled***

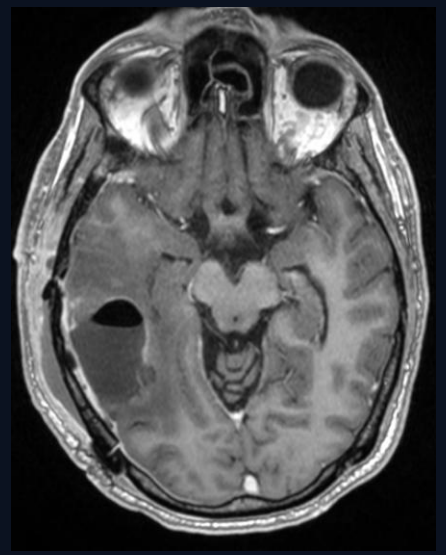


Rykkje et al., Diagnostics 2021 & 2023.

Clean cavity (≤48 h)



Thin linear (>48 h)

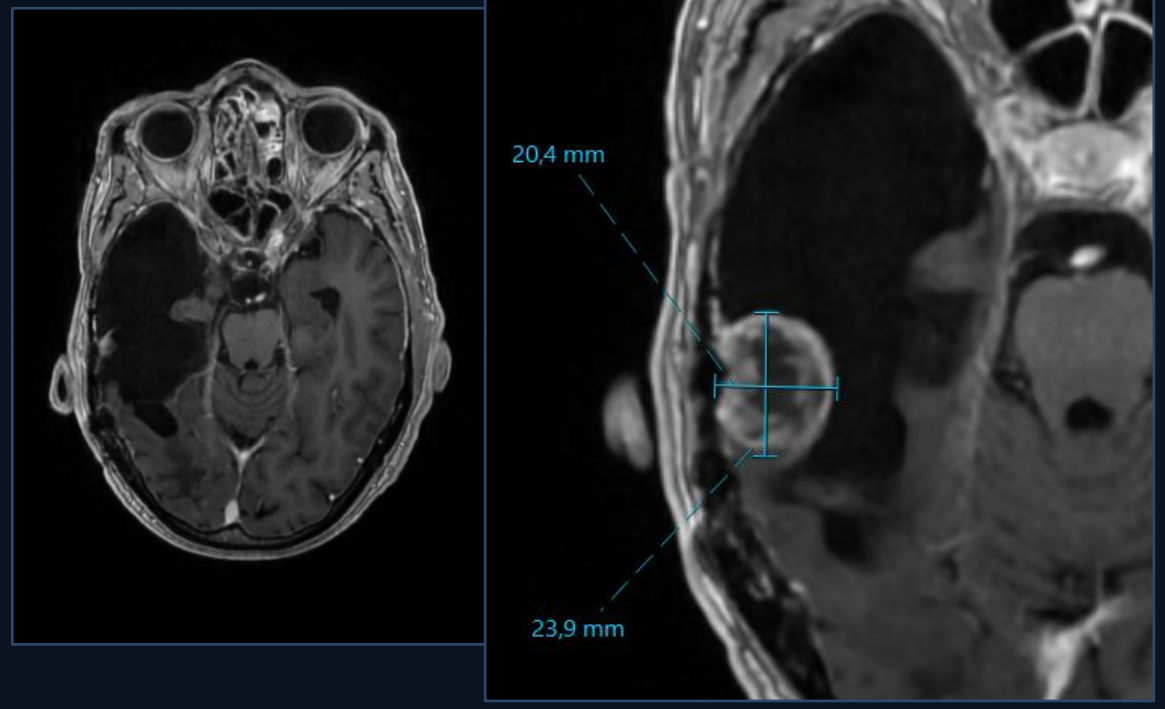


Surgery itself creates enhancement

The operation itself produces contrast enhancement

- **Thin linear enhancement around the cavity is usually surgically induced — and it grows with time**
- **Our data (n=311): thin linear rises 50.8% → 69.1% across 48 h; "no enhancement" falls 22.4% → 8.6%**
- ***So do the early post-op MRI within 48 hours — wait longer and surgery fools you***
- ***RANO 2.0 shortened the baseline window from 72 h to under 48 h — exactly for this reason***

CASE *Clean cavity → measurable recurrence at 3 mo · RANO 2.0: Progression*



epMRI 3 months FU

Complete Remission	Partial Remission	Stable Disease	Progression

RANO measures enhancing tumour, in 2D — by design.

How we report treatment response: RANO 2.0

- RANO is how we grade response — and decide when to change treatment; 2.0 is the 2023 update
- It still measures enhancing tumour in two dimensions — simple and reproducible
  - All new CE lesions are progression
  - Increase > 25% of sum of products is progression
- Advanced imaging is NOT part of the criteria
- *Reality gap: only ~27% of centres use RANO routinely — mainly a trials tool*

Wen et al., RANO 2.0, JCO 2023 · Thust et al. 2018.

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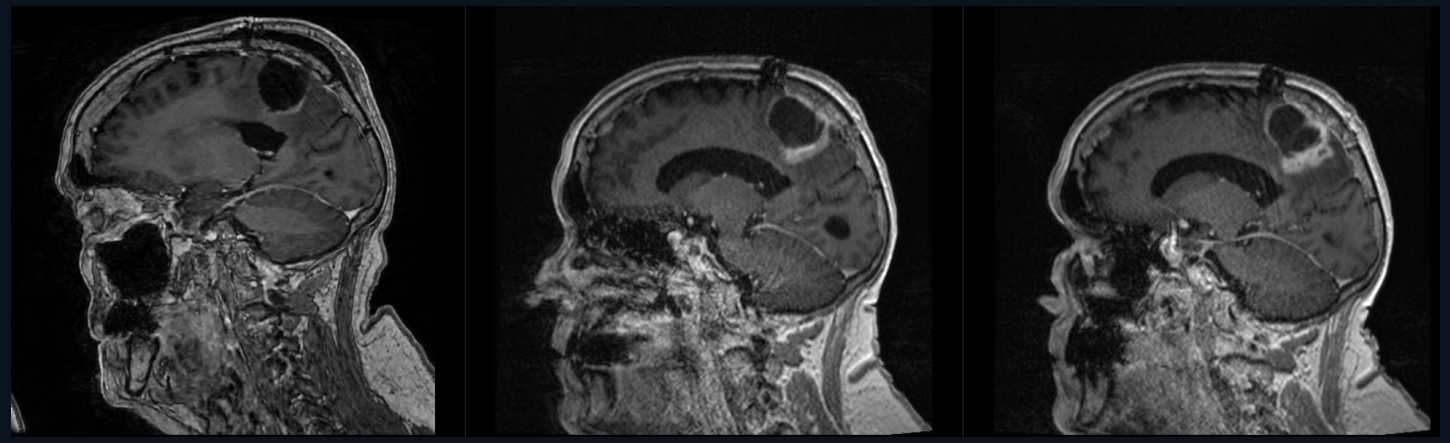
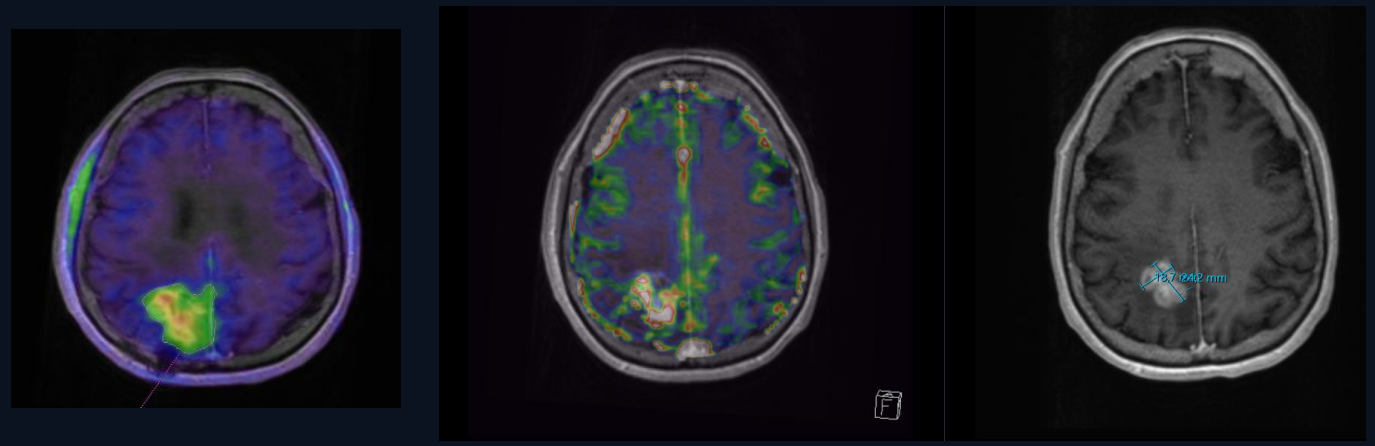
Pseudoprogression

SAGITTAL T1+C

Post-RT baseline → +3 mo → +6 mo



FET-PET · DCE perfusion · T1+C axial at +3 mo



Both "advanced" modalities were **false positive**. *This patient has now been operated 3 times for pseudoprogression — this was #2.*

- New/enlarging enhancement mimicking progression — but treatment effect
- Peaks <12 wks post-chemoRT: ~20% at 3 mo, ~8% at 6 mo
- Conventional MRI alone: often can't separate from true progression
- RANO 2.0 fix: baseline on post-RT scan; confirm before acting in first 12 wks
- Call it too early → you stop a working treatment
- ***Continuing TMZ when unsure: no clear survival cost — but needless reoperations still uncounted***

BRIDGE PET in CNS tumours: see Prof. Ian Law, Day 3.

PART 4

Advanced imaging

Is this the answer to the response problem?

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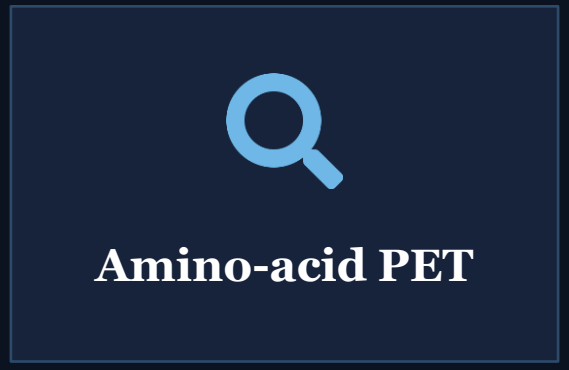
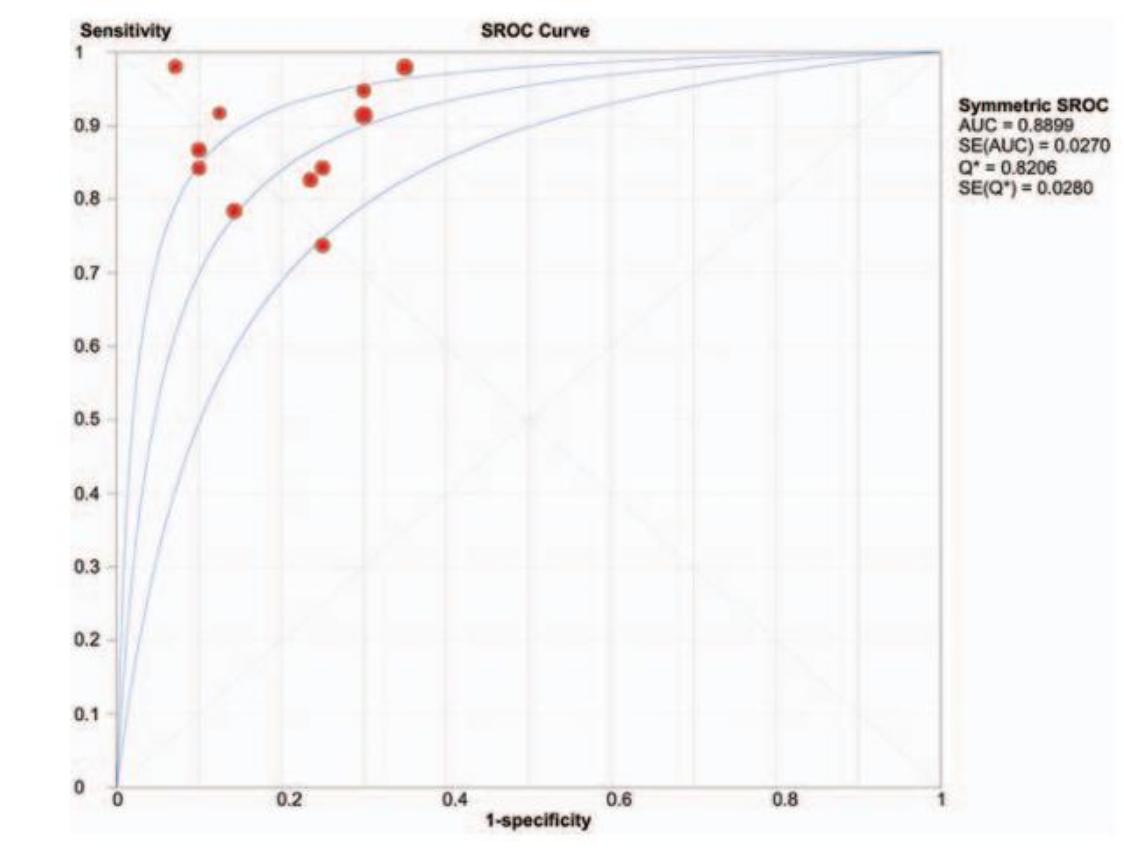


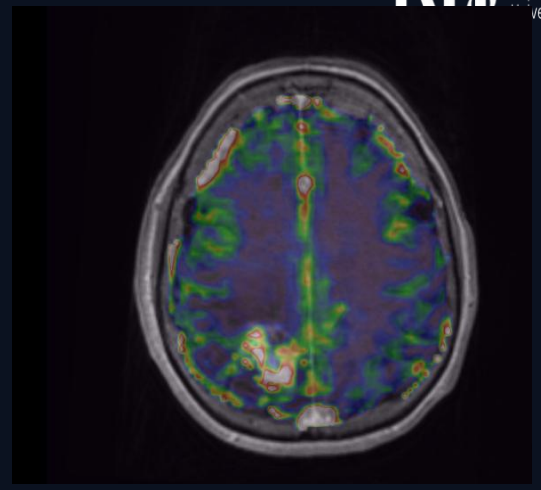
Beyond conventional MRI

- Three tools matter for the response problem — perfusion, spectroscopy, amino-acid PET
  - Perfusion and Spectroscopy are widely available
  - Amino-acid PET varied availability
- Pre-op: rarely decisive (surgery vs biopsy vs follow-up) — may help in doubtful cases, if experienced
- Post-op is the real test — and each tool has its own pitfalls (next slides)
- *The question for each: does it actually change what we do?*
- *Often we want advanced imaging for the difficult cases — but it is… surprise… difficult!*

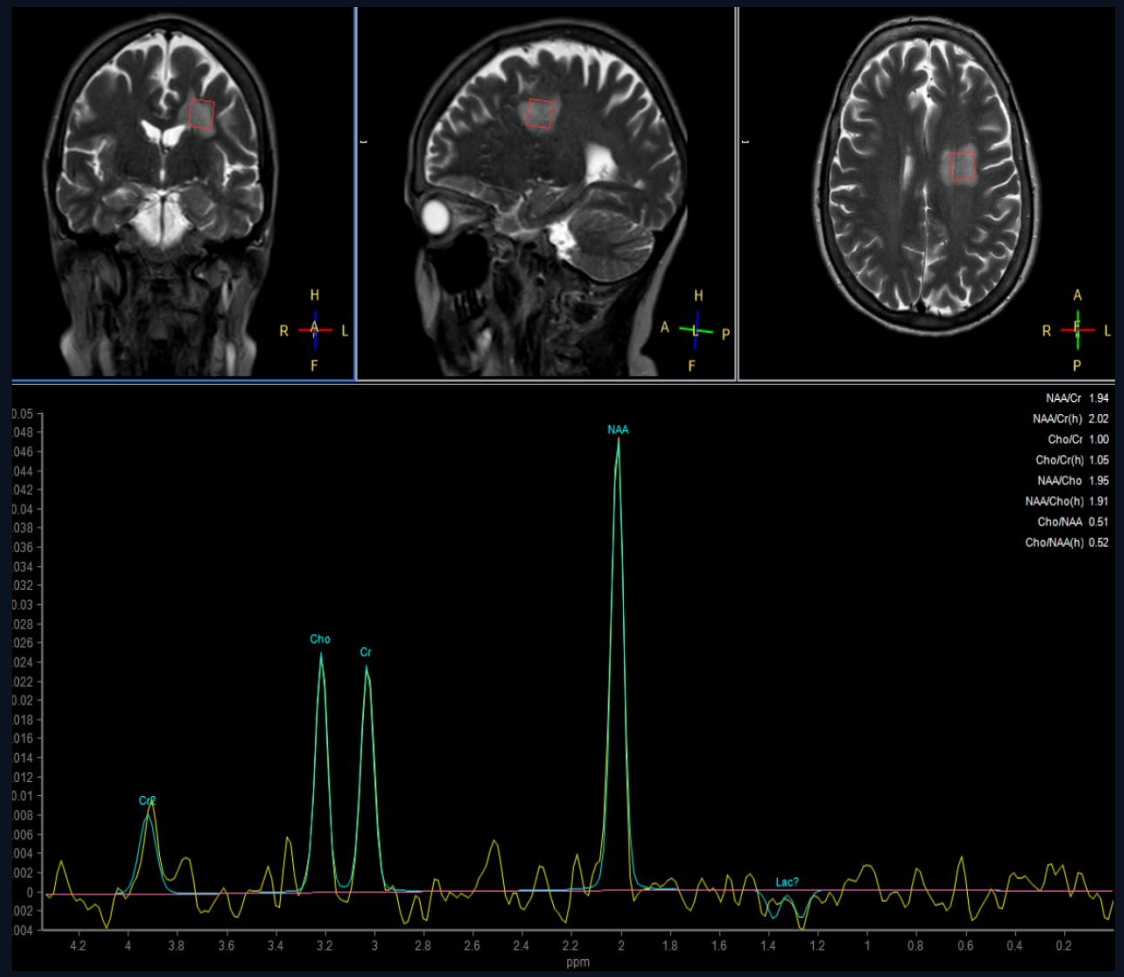


Wan et al. Medicine 2017.

Perfusion



- rCBV is higher in true tumour than in pure treatment effect
- Pooled accuracy ~88–93% — useful, but cut-offs vary widely between centres
    - Specificity ~78% - so it doesn’t change the pseudoprogression problem
- Big caveat: reactive changes and especially vessels also have high rCBV — false positives are real
- *Signal, yes — but no single threshold you can trust blindly*



Spectroscopy & amino-acid PET

- Spectroscopy: high choline, NAA is correlated with tumour grade
- Needs > 1–2 cm voxels in 3 planes
- Need to be planned by a radiologist
- Central necrosis routinely defeats it — most recurrences are small enhancing rims around a necrotic core
- Amino-acid-PET: strong tumour-to-background — but not immune to false positives

Bridge: PET in CNS tumours gets a dedicated talk — Prof. Ian Law, Day 3.

What advanced imaging actually delivers

- Must be feasible in your setting
- Must change the pathway — help when conventional MRI is not conclusive
- Interpretation must be robust — yet cut-offs/references vary widely
- *The Catch-22: we want it most for the doubtful cases — but those are exactly where it is least reliable*
- *The same trap AI is about to walk into*

Henssen et al., BJR 2023.

PART 5

The AI paradox

Powerful tools — aimed, too often, at the wrong question

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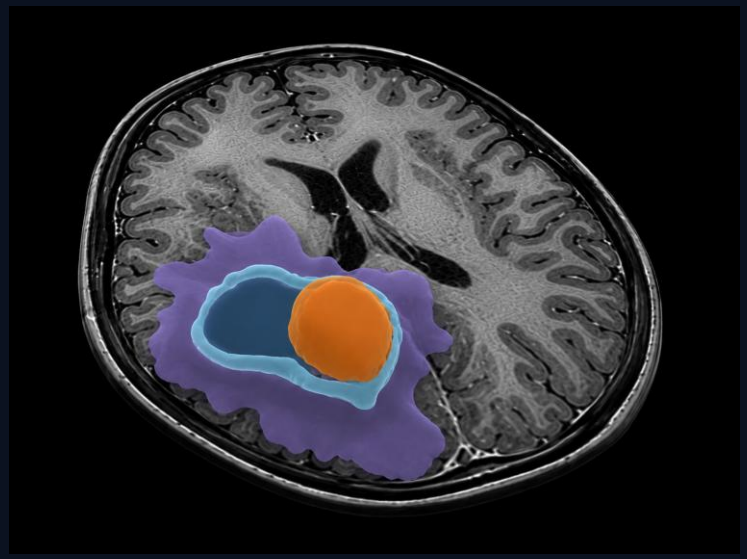
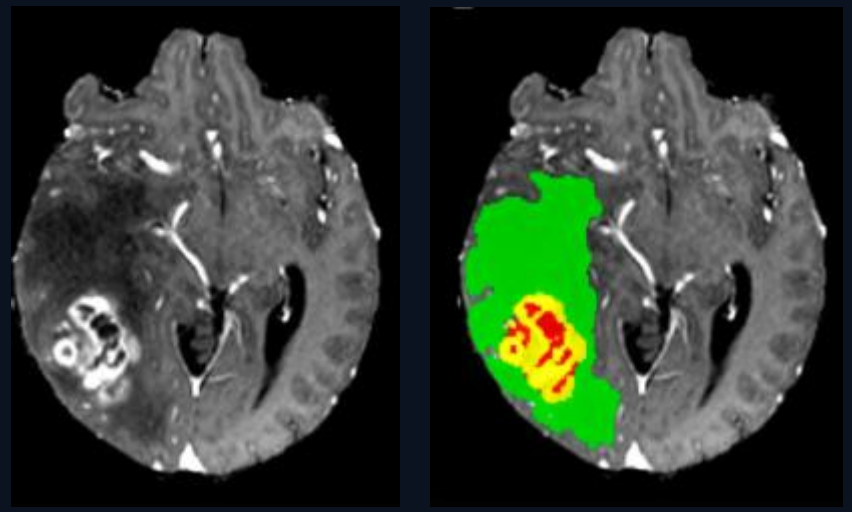
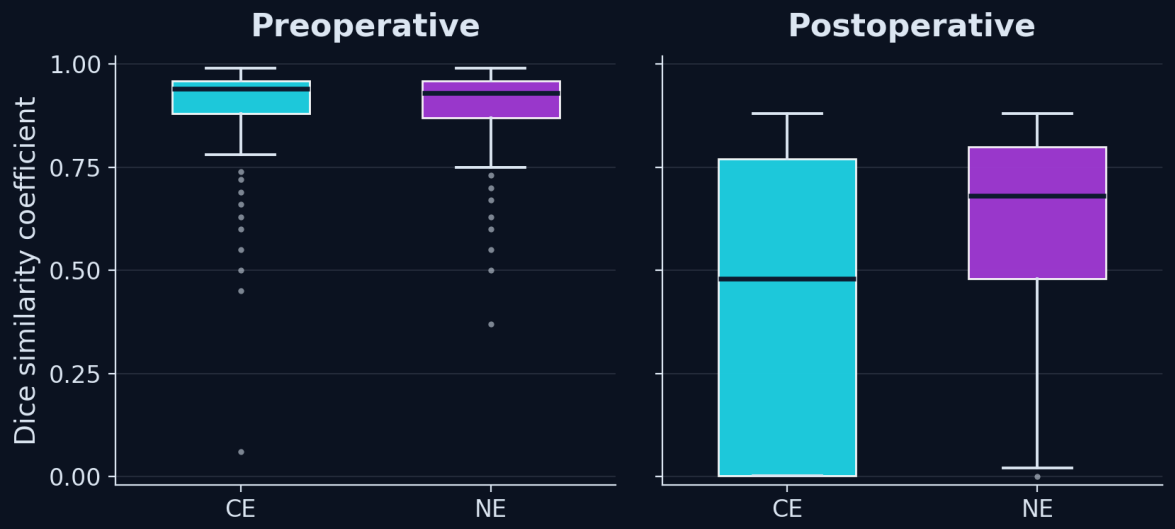


The BraTS challenge has driven the field since 2012.

AI in GBM: a long history

- Segmentation is technically “solved” — models reach >90% agreement with experts
- BraTS has driven the field since 2012 (>4000 expert-annotated scans)
- AI also predicts genetics — IDH/TERT, AUC ~0.89–0.99 (Zhang JMRI 2023); useful when biopsy is out of reach, but most still get tissue anyway
  - Might be valuable for non-operated IDH-mutant patients scheduled for vorasidenib
- *And yet — almost none of it is in routine clinical use*

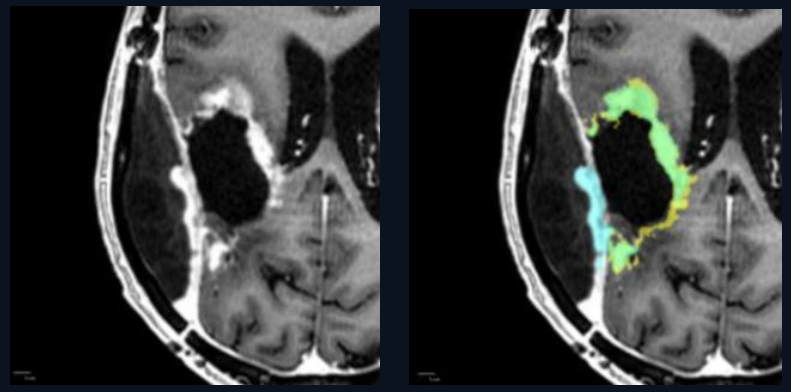


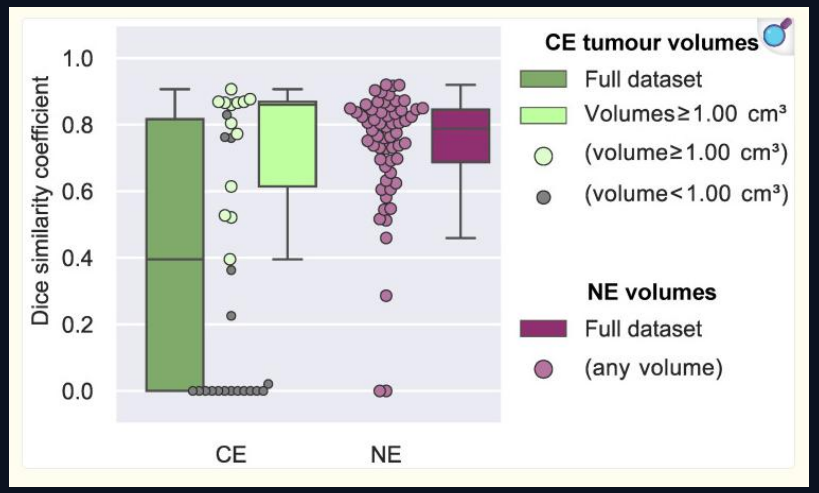


Sørensen et al., Diagnostics 2023 & Tomography 2024

Solving the wrong problem

- Pre-operatively, segmentation measures the size we can already see by eye
- It does not tell us how far the infiltration truly reaches
- *Impressive accuracy on a question that wasn't the hard one*





Sørensen et al., Diagnostics 2023 & Tomography 2024

Where AI could help — but doesn't yet

- The useful question is postoperative — but these models were almost trained on pre-op data until recently
- On the operated brain they slip — labelling reactive enhancements as tumour
- And miss small lesions!
- Retraining them on post-surgery scans helps — but small recurrences are still missed

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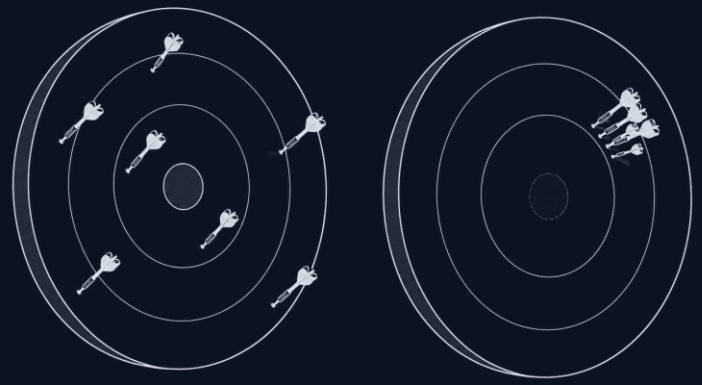
Does 3D even beat 2D?

- AI volumetry rests on 3D beating 2D — far from settled
- RANO 2.0 (2023): no conclusive benefit over 2D — rare exceptions in LGG
- Strongest pro-3D study (Vollmuth 2019): small edge only — HR 2.59 vs 2.07, overlapping CI_{95}. Others find none; Shah 2006 argues against
- Deeper problem — ground truth: large reader-to-reader variance, worst postop; no clean truth to train or validate against
- *AI's clear win: reader agreement — a more consistent number, not a bigger one (Vollmuth multi-reader, Neuro-Oncol 2023)*



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Take-home messages

- Our job is broad differentiation and tempo — not grading
- With tissue, the genetics — not the image — define the tumour
- After treatment is the hard part — don't be fooled by reactive enhancement / pseudoprogression and now the timing of your scan
- Advanced imaging and AI are powerful only when aimed at the right question
- *The limiting factor is rarely the tool — it is the question we point it at*

Thank you

Jonathan Frederik Carlsen · Department of Radiology, Rigshospitalet

KEY REFERENCES

Rykkje, Carlsen et al. Diagnostics 2021 & 2023 — surgically induced enhancement & timing (n=311).

Rykkje, Carlsen et al. Sci Rep 2024 — prognostic value of post-operative MRI (n=187).

Sørensen, Carlsen et al. Tomography 2024 — repurposing BraTS for post-operative segmentation.

Louis et al. Neuro-Oncology 2021 (WHO 2021) · Wen et al. JCO 2023 (RANO 2.0) · Stupp et al. NEJM 2005.

Vollmuth et al. Korean J Radiol 2025 · Henssen et al. BJR 2023.