2025 DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center
Where Science Becomes Hope

JULY 24 - 27, 2025 • SEA ISLAND, GEORGIA

This activity is jointly provided by Partners for Advancing Clinical Education and Bio Ascend

Disclosures

Advisory board member for Servier Pharmaceuticals

CONGRATULATIONS!

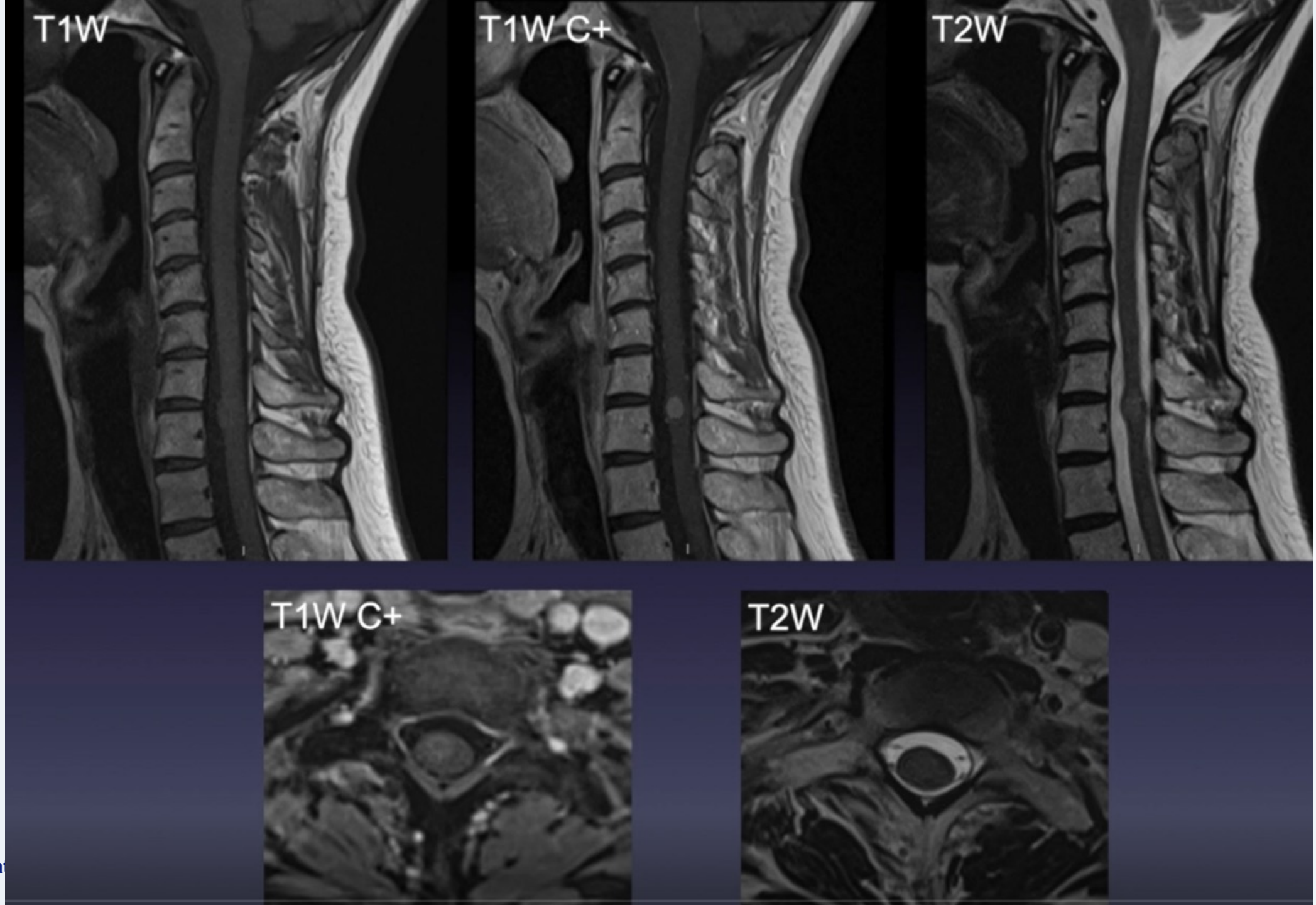
Congratulations to Suresh Ramalingam and Sagar Lonial on 25 years!

Why Methylation Profiling at Emory?

CNS tumors are among the most challenging tumors to diagnose accurately. Emory has invested in methylation profiling to improve diagnostic precision and align with modern standards in neuro-oncology.

Challenges in Diagnosing CNS Tumors

- CNS tumors are heterogeneous and may appear similar histologically
- Diagnosis often requires distinguishing among entities with overlapping features
- Accurate classification is critical for prognosis and therapy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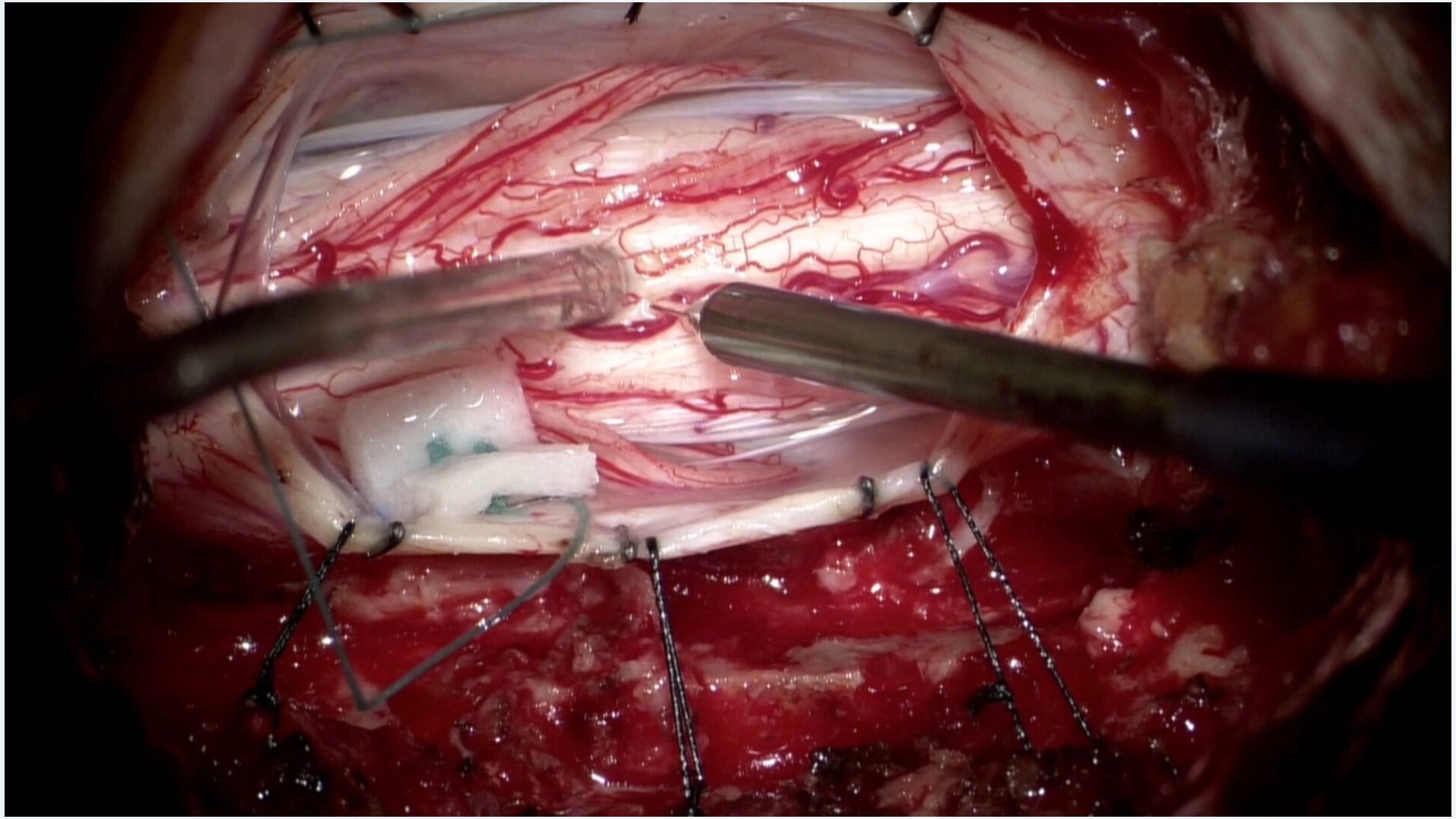

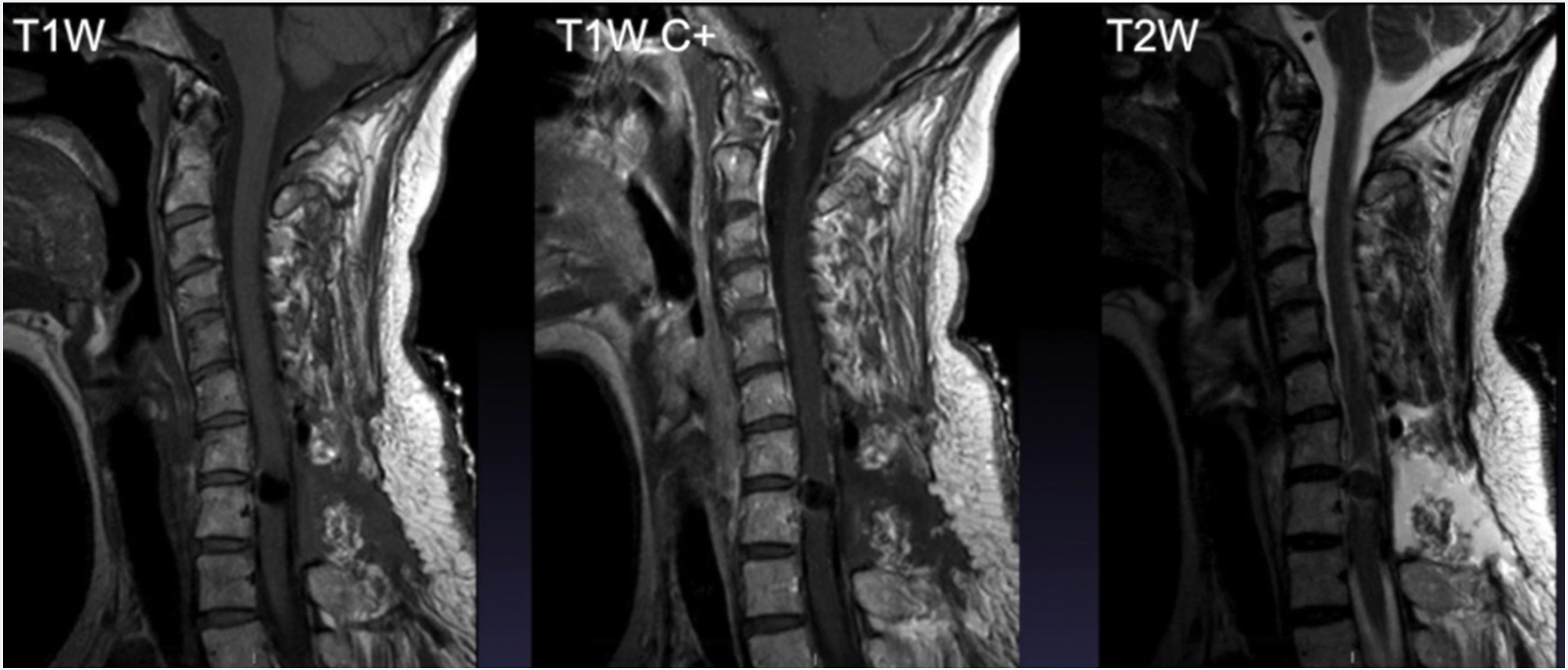
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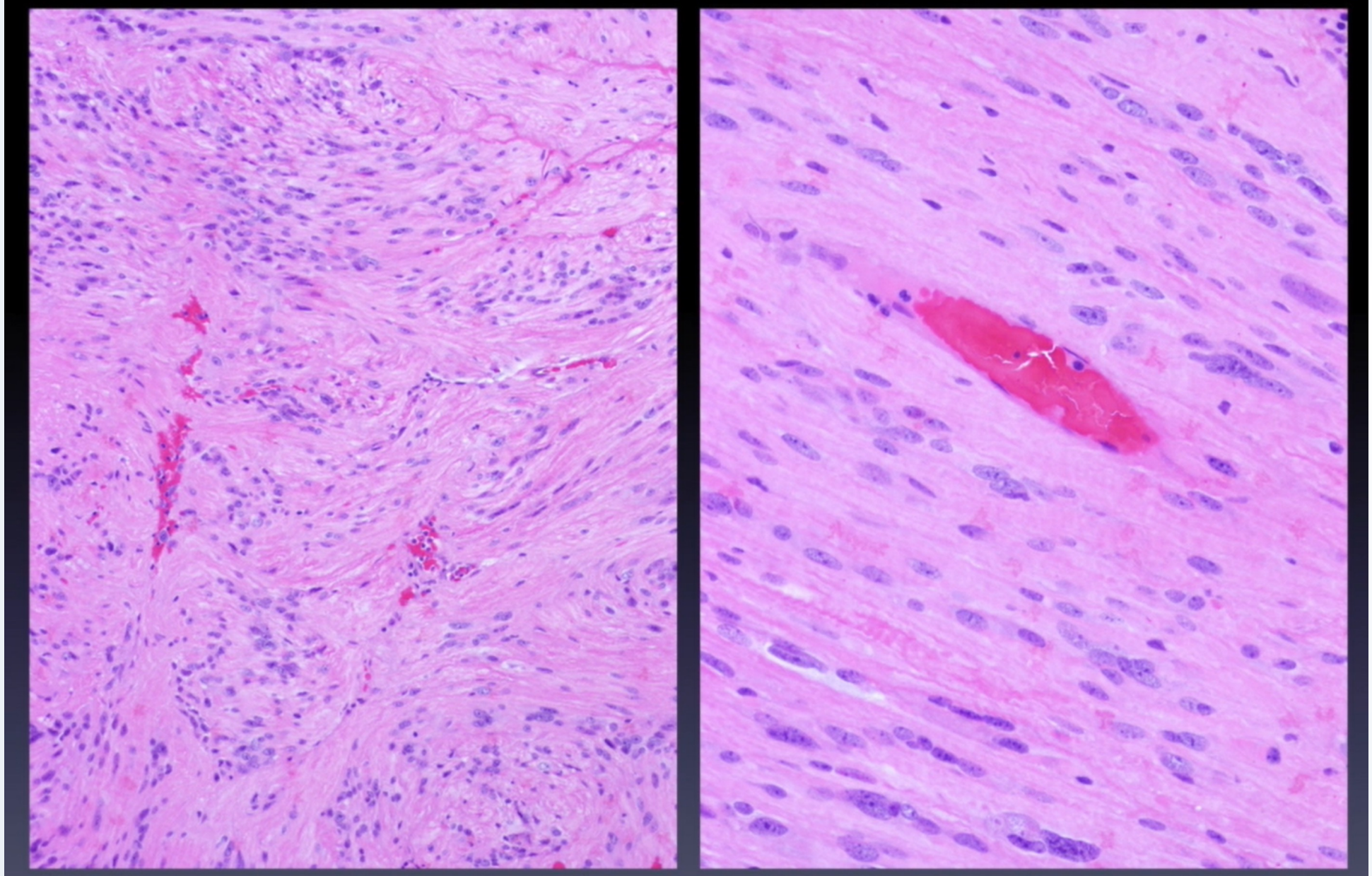
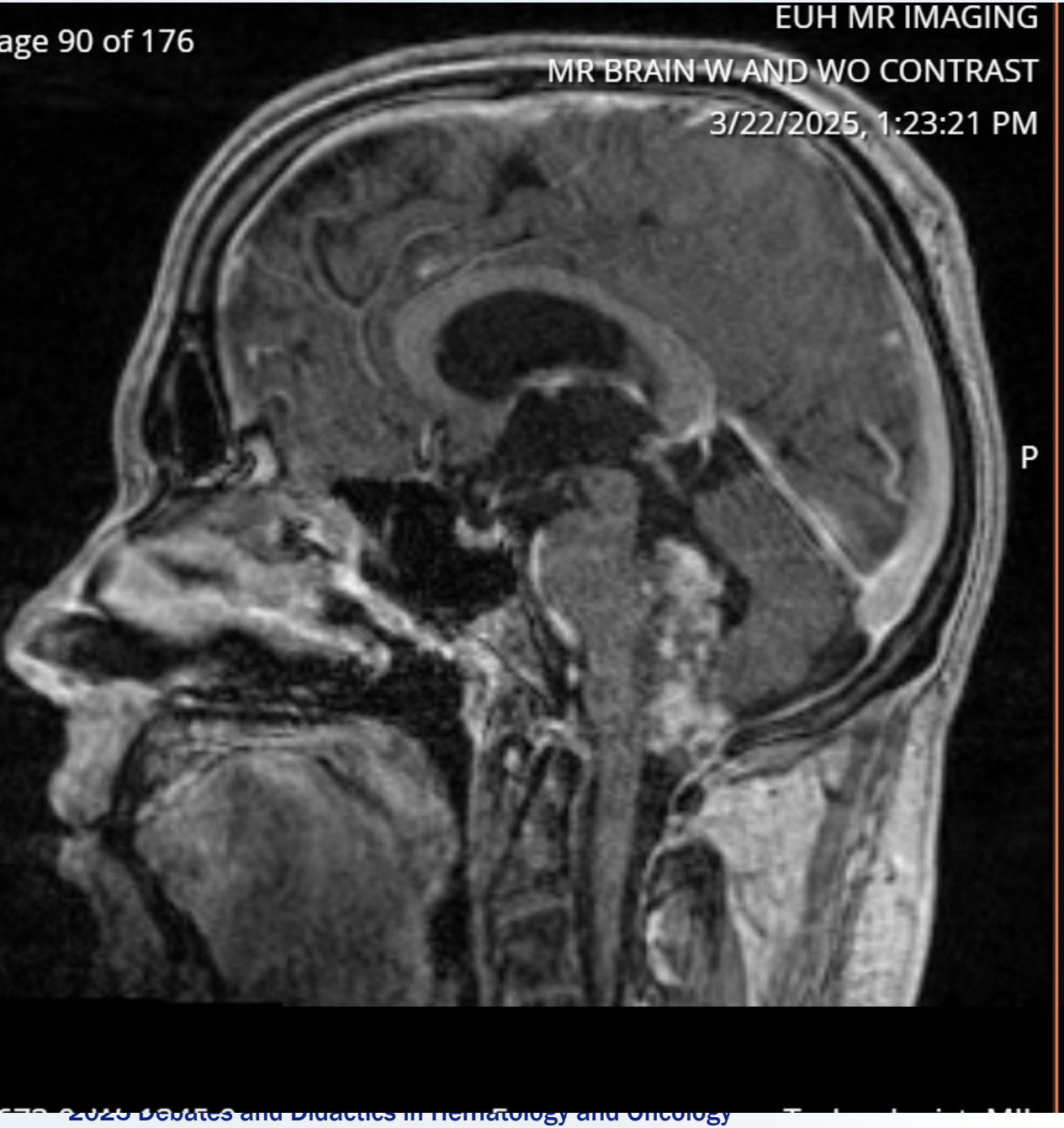


Proliferation of glial spindle cells with round/oval nuclei in a fibrillar background with vaguely delineated pseudorosettes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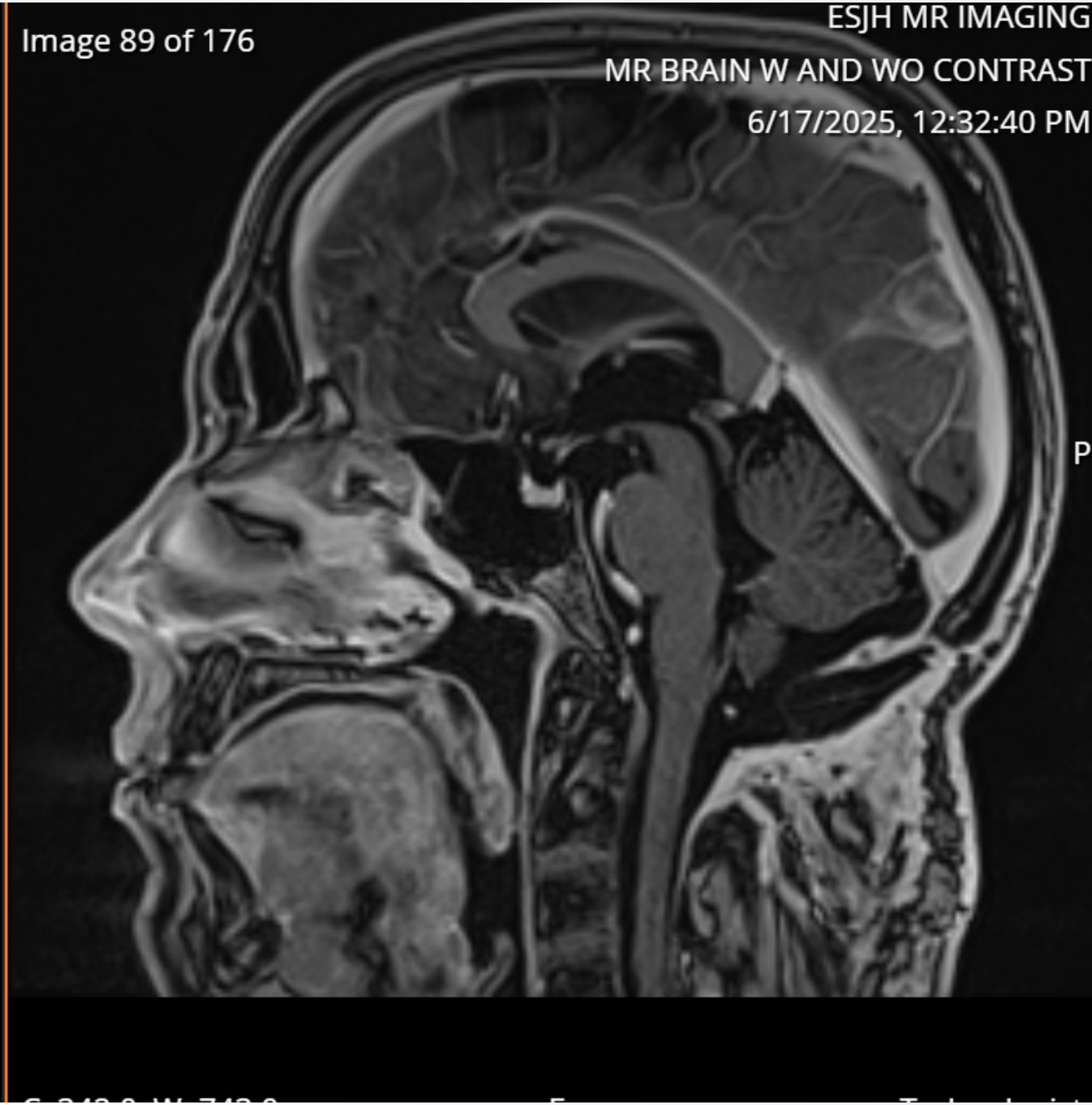
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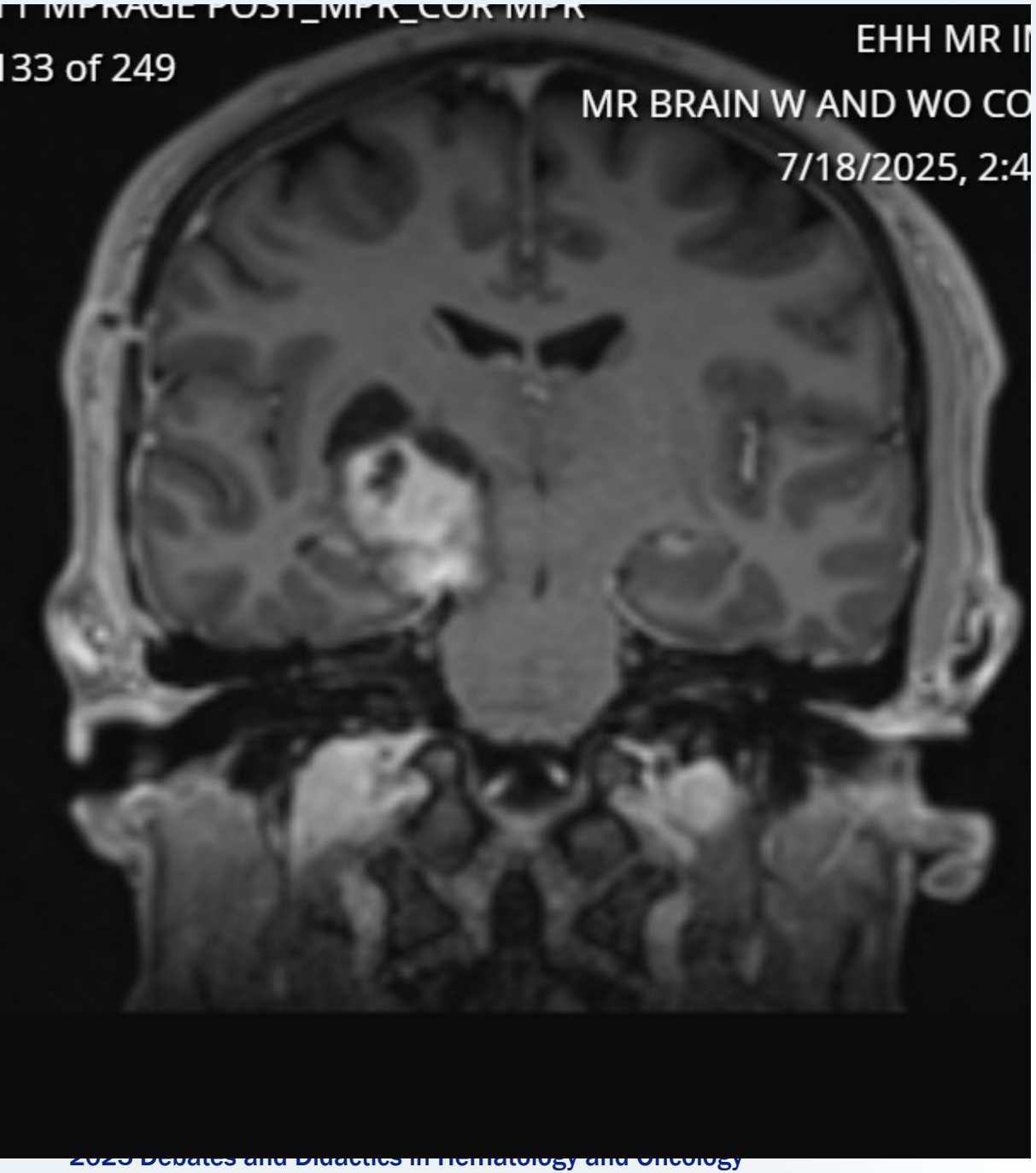
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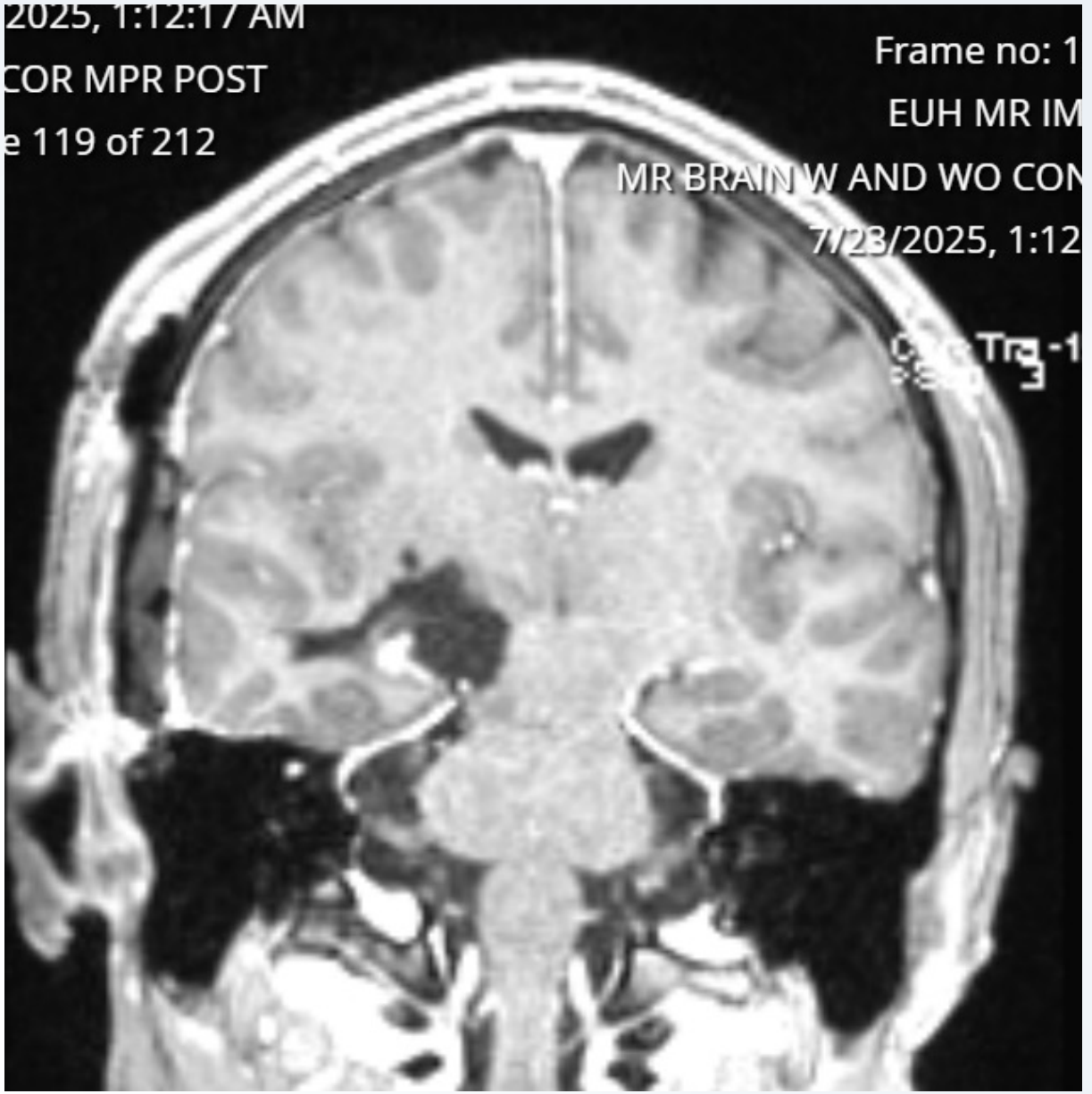
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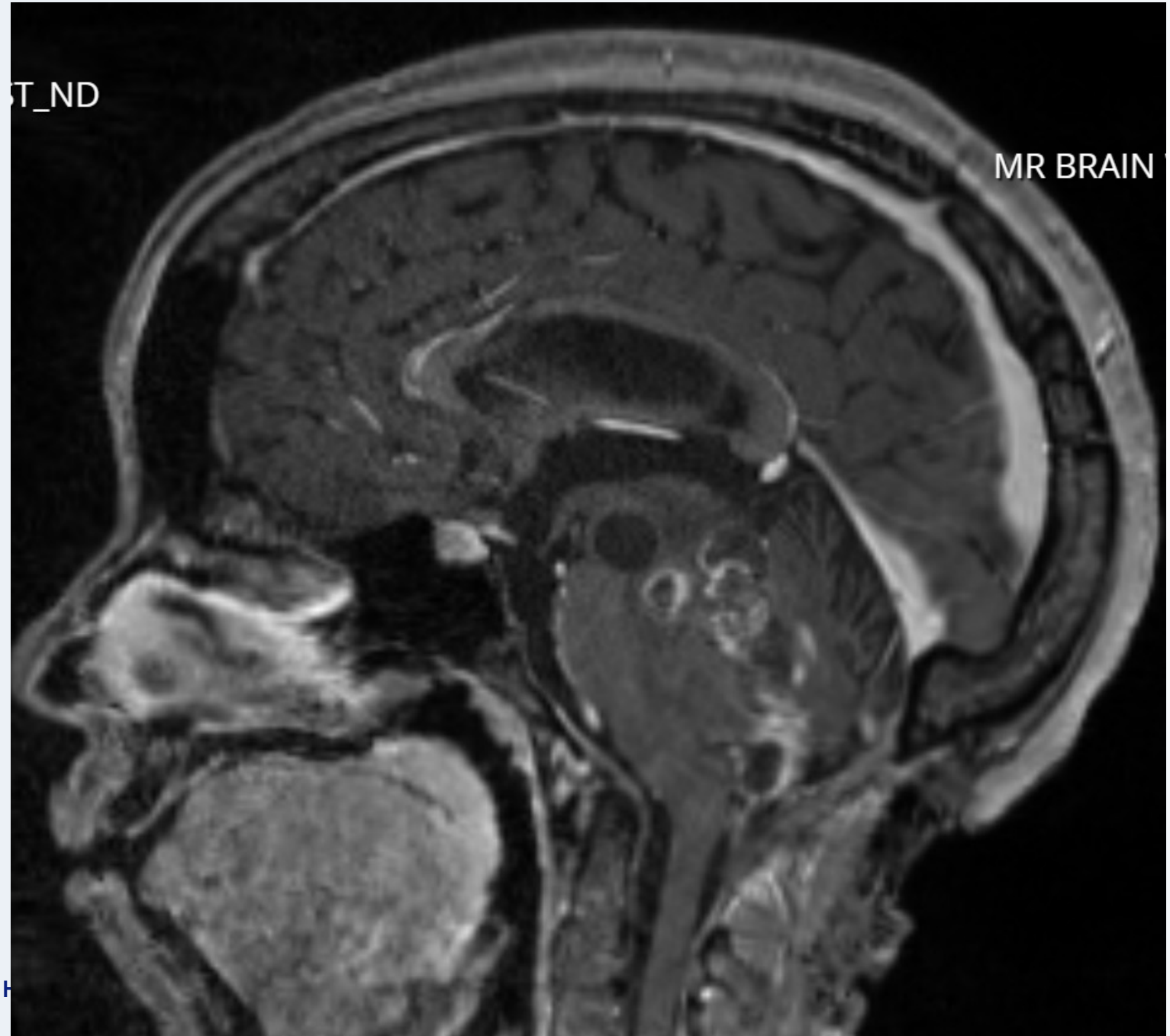
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Traditional Diagnosis: H&E Staining

Historically, pathologists relied on H&E slides to classify CNS tumors. While useful, this method often led to misclassification of rare or ambiguous tumors.

Anaplastic Astrocytoma

Key Features

Histology:

- Increased astrocytic cellularity
- Cellular atypia and mitosis, no necrosis

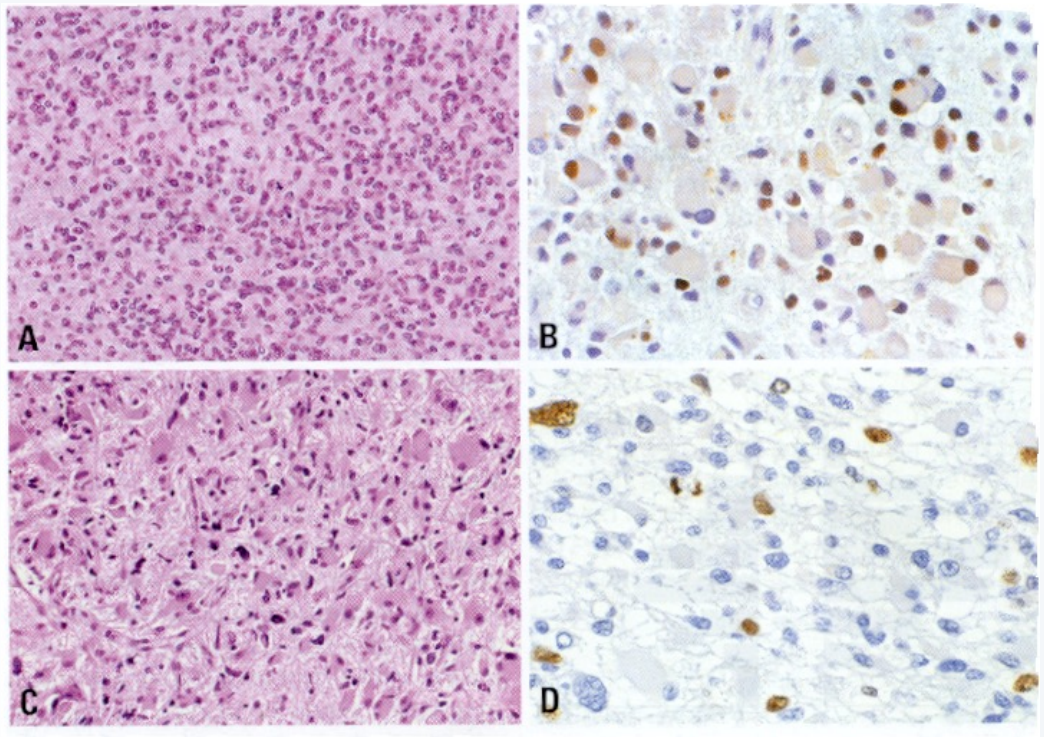
Median Survival:

- 2 - 3 years

Notes:

- Tissue sampling a major issue
- Progression to glioblastoma in some

High Cellularity



Nuclear Atypia

Ki 67

High Proliferation Index

Oligodendroglioma

Histology reveals characteristic “fried egg” appearance

Often microscopic and macroscopic calcification

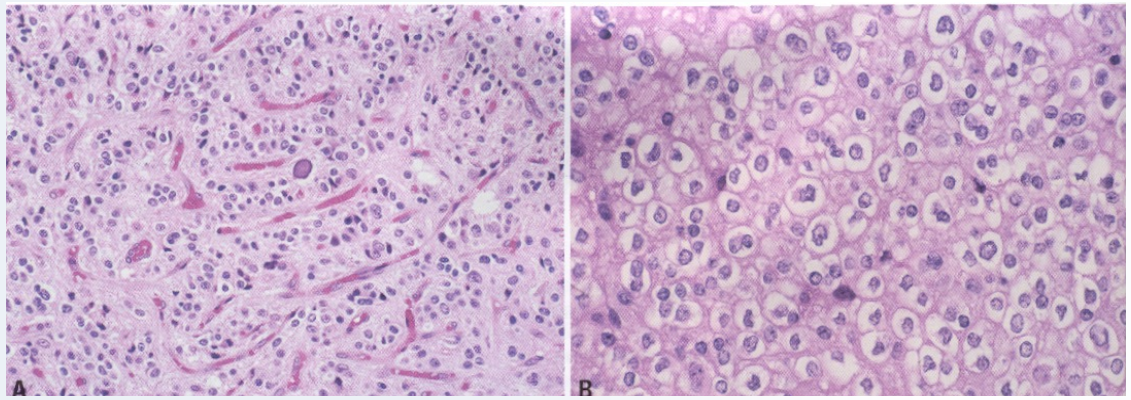
Classified as low-grade or anaplastic

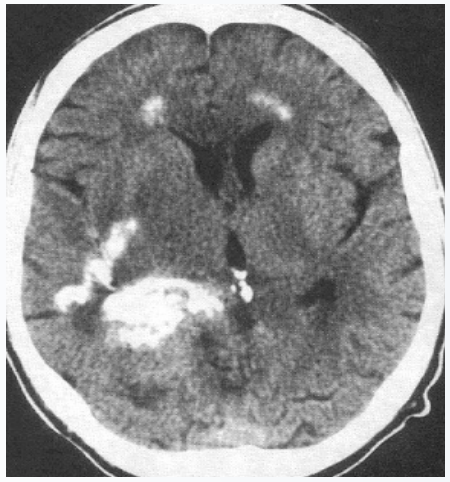
Very responsive to treatment: chemotherapy and radiation

Prognosis and response to treatment strongly correlated with 1p & 19q LOH

•Non-contrast CT shows macroscopic calcification

•MRI not very good at evaluating calcification





Anaplastic Oligodendroglioma

Oligodendrogliomas account for ~ 20% of adult brain tumors

AO classified as WHO Grade 3

Distinct histologic appearance

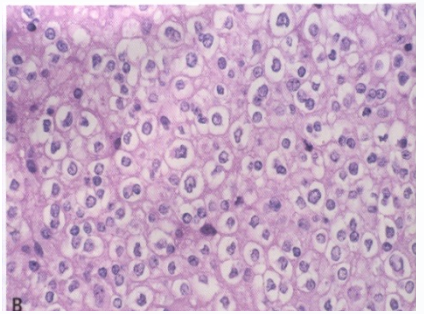
"Fried egg" cell morphology

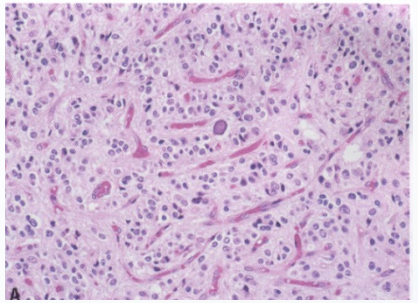
Capillary network –"chicken wire"

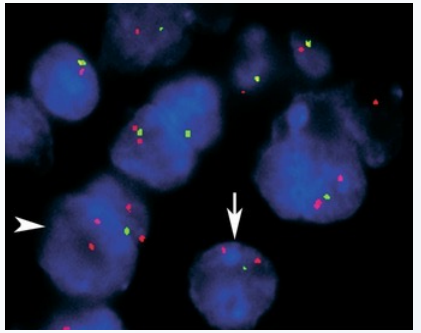
Combined allelic loss of 1p 19q uncovered by Cairncross et al (JNCI 1998) is found in 60-70%

Often results from unbalanced translocation of chr. 1 and19 → loss of short arm (q) of 1, long arm (p) of 19 (Jenkins et al Cancer Res 2006)

Mutations in CIC and FUBP1 genes found in some cases of AO with 1p 19q loss (Bettegowda et al Science 2011)







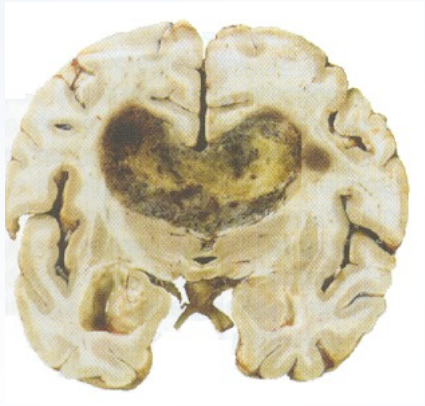
Glioblastoma Key Features

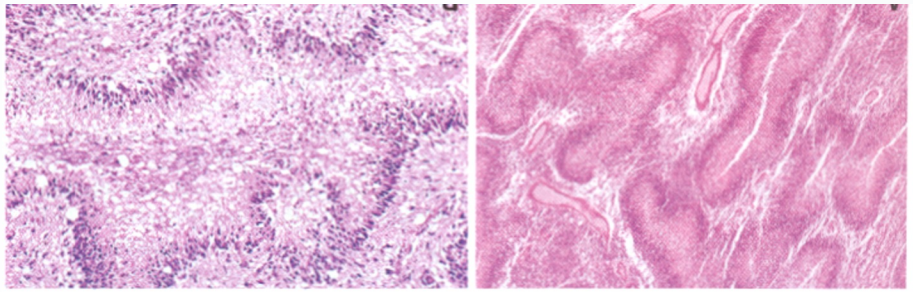
Histology

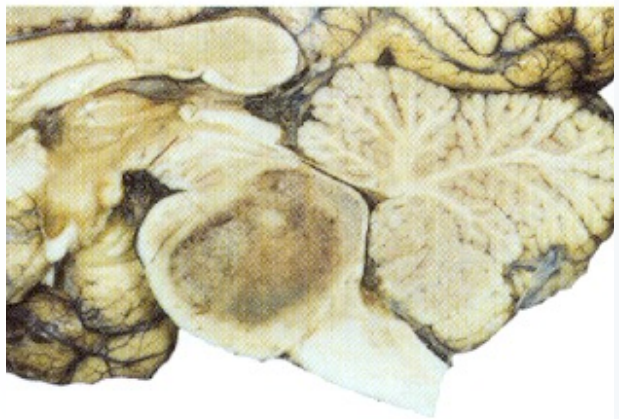
- Necrosis, mitosis, neovascularization and pseudopallisading
- 1993 WHO guidelines: hypercellular, mitosis, pleomorphism, & neovascularization or necrosis

Median Survival

- 9 - 12 months







Clinical and radiographic characteristics of diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma: a single institution review

Dayton Grogan [1], David P Bray [2], Megan Cosgrove [2], Andrew Boucher [2], Andrew Erwood [2], Daniel F Linder [3], Pia Mendoza [4], Bryan Morales [4], Gustavo Pradilla [2], Edjah K Nduom [2], Stewart Neill [4], Jeffrey J Olson [2], Kimberly B Hoang [2]

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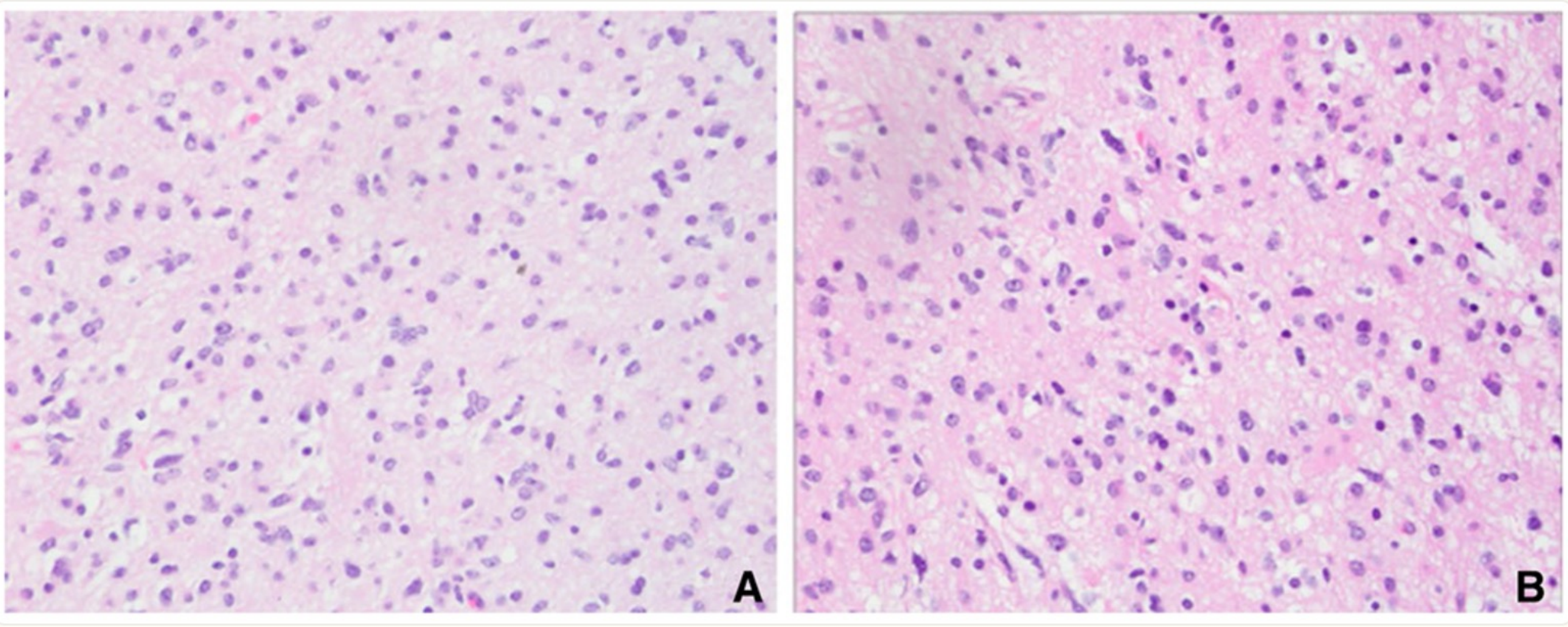
PMCID: PMC9703358 NIHMSID: NIHMS1849416 PMID: 35212929

Fig. 2.



Understanding the Epigenome

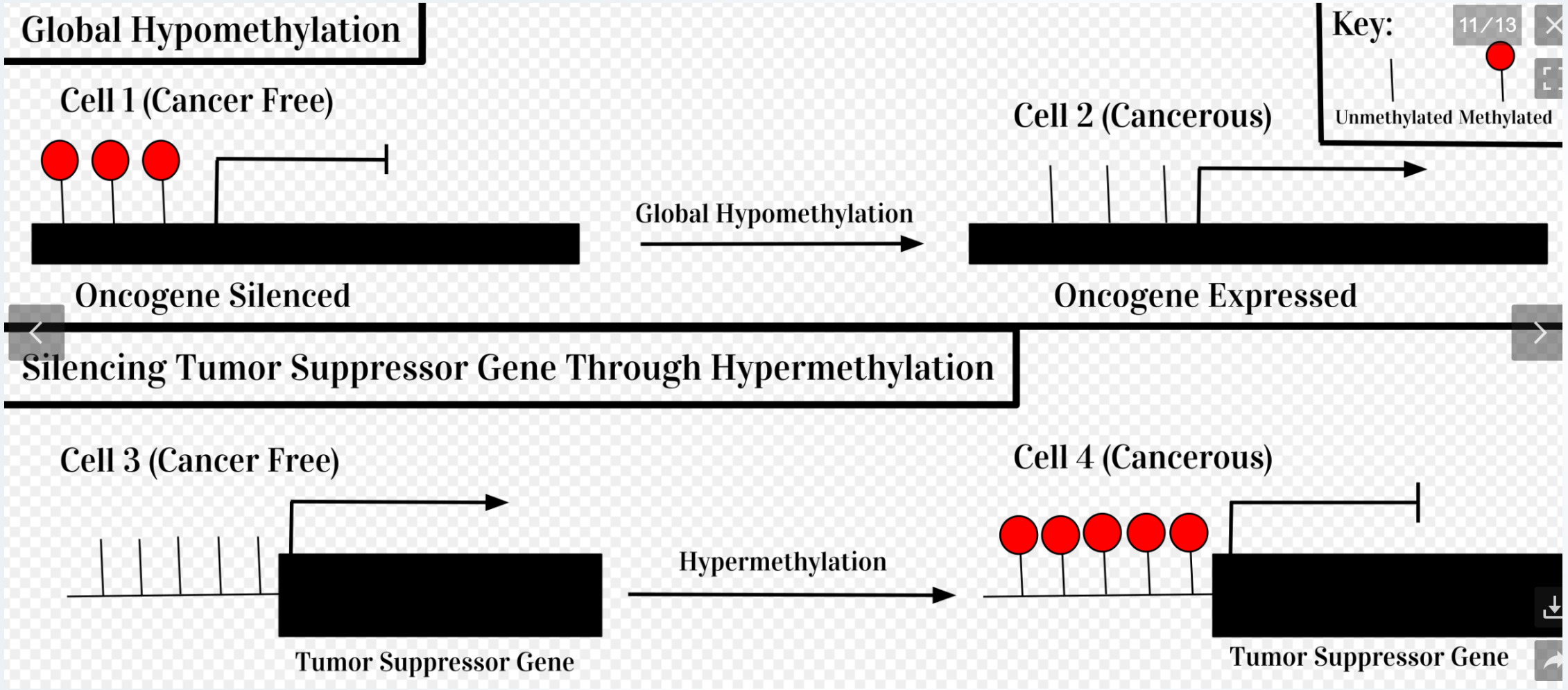
Cancer cells acquire the capacity for uncontrolled growth through genetic and epigenetic alterations.

DNA methylation of cytosines in CpG sites throughout the genome is an ancient evolutionary epigenetic modification contributing to chromatin structure, gene silencing, and genetic stability.

One striking feature in most cancer genomes is the overall reduction of DNA methylation compared with the level of DNA methylation in their normal tissue counterparts.

In contrast to global hypomethylation, promoter regions of tumor suppressor genes constantly are hypermethylated in cancer genomes (e.g., *CDKN2A/B*, *Rb, hMLH1*, *BRCA1*, and *MGMT*), and many others.

One thoroughly studied example is methylation mediated silencing of the DNA repair gene *MGMT*


Global Hypomethylation
Cell 1 (Cancer Free)
Key:
Unmethylated Methylated
Cell 2 (Cancerous)
Global Hypomethylation
Oncogene Silenced
Oncogene Expressed
Silencing Tumor Suppressor Gene Through Hypermethylation
Cell 3 (Cancer Free)
Cell 4 (Cancerous)
Hypermethylation
Tumor Suppressor Gene
Tumor Suppressor Gene

Using a machine learning algorithm to better classify tumors

Methylome profiling—using microarrays to determine DNA methylation patterns across the genome in a tumor sample—holds promise to increase the precision of CNS tumor classification, and thus enable more accurate diagnoses and more targeted treatment approaches.

These profiles are highly robust and reproducible in clinical pathology settings and have been widely used to subclassify CNS tumours.

A brain tumor methylation classifier has been developed at the German Cancer Research Center (DKFZ) and Heidelberg University in Heidelberg, Germany (henceforth in short “Classifier”), to identify distinct DNA methylation classes of CNS tumours. Currently, the Classifier comprises 82 CNS tumor methylation classes and nine control tissue methylation classes.

Biomathematical evaluation of the data obtained from the array can be standardized and automated. Packages for multiple tasks are freely available.

Misdiagnosis and Its Impact

- Misclassification leads to inappropriate treatment
- Prognostic errors can influence patient counseling
- A need for more objective, reproducible methods emerged

WHO 2016 and 2021 CNS Tumor Guidelines

- 2016 WHO introduced integrated diagnosis (histology + molecular)
- 2021 WHO further emphasized molecular profiling as essential for CNS tumor classification
- Methylation profiling is now a cornerstone of this diagnostic framework

The Role of DNA Methylation Profiling

- DNA methylation arrays allow for genome-wide tumor profiling
- Tumor classification is based on similarity to reference methylation classes
- Enables highly accurate, reproducible diagnoses

Neuro-Oncology Advances

5(1), 1–10, 2023 | https://doi.org/10.1093/noajnl/vdad076 | Advance Access date 26 June 2023

Clinical utility of whole-genome DNA methylation profiling as a primary molecular diagnostic assay for central nervous system tumors—A prospective study and guidelines for clinical testing

Kristyn Galbraith, Varshini Vasudevaraja, Jonathan Serrano, Guomiao Shen, Ivy Tran, Nancy Abdallat, Mandisa Wen, Seema Patel, Misha Movahed-Ezazi, Arline Faustin, Marissa Spino-Keeton, Leah Geiser Roberts, Ekrem Maloku, Steven A. Drexler, Benjamin L. Liechty, David Pisapia, Olga Krasnozhen-Ratush, Marc Rosenblum, Seema Shroff, Daniel R. Boué, Christian Davidson, Qinwen Mao, Mariko Suchi, Paula North, Amanda Hopp, Annette Segura, Jason A. Jarzembowski, Lauren Parsons, Mahlon D. Johnson, Bret Mobley, Wesley Samore, Declan McGuone, Pallavi P. Gopal, Peter D. Canoll, Craig Horbinski, Joseph M. Fullmer, Midhat S. Farooqi, Murat Gokden, Nitin R. Wadhwani, Timothy E. Richardson, Melissa Umphlett, Nadejda M. Tsankova, John C. DeWitt, Chandra Sen, Dimitris G. Placantonakis, Donato Pacione, Jeffrey H. Wisoff, Eveline Teresa Hidalgo, David Harter, Christopher M. William, Christine Cordova, Sylvia C. Kurz, Marissa Barbaro, Daniel A. Orringer, Matthias A. Karajannis, Erik P. Sulman, Sharon L. Gardner, David Zagzag, Aristotelis Tsirigos, Jeffrey C. Allen, John G. Golfinos, and Matija Snuderl

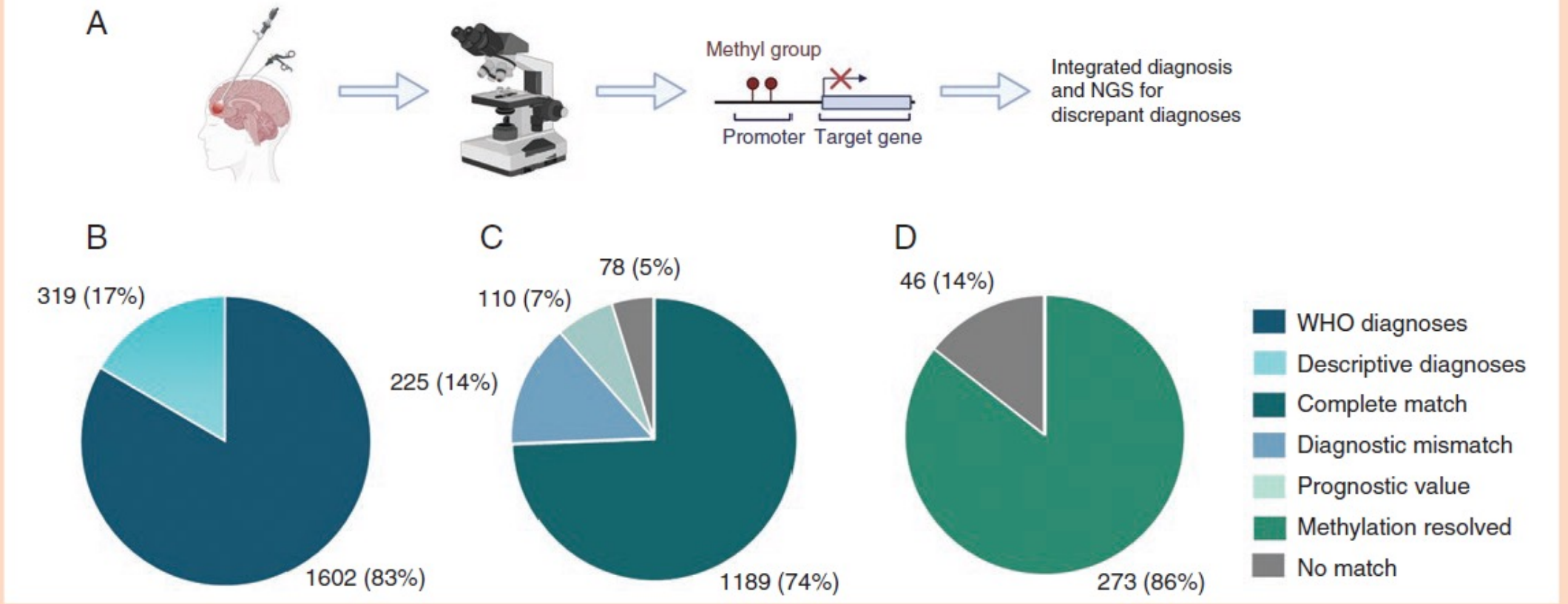
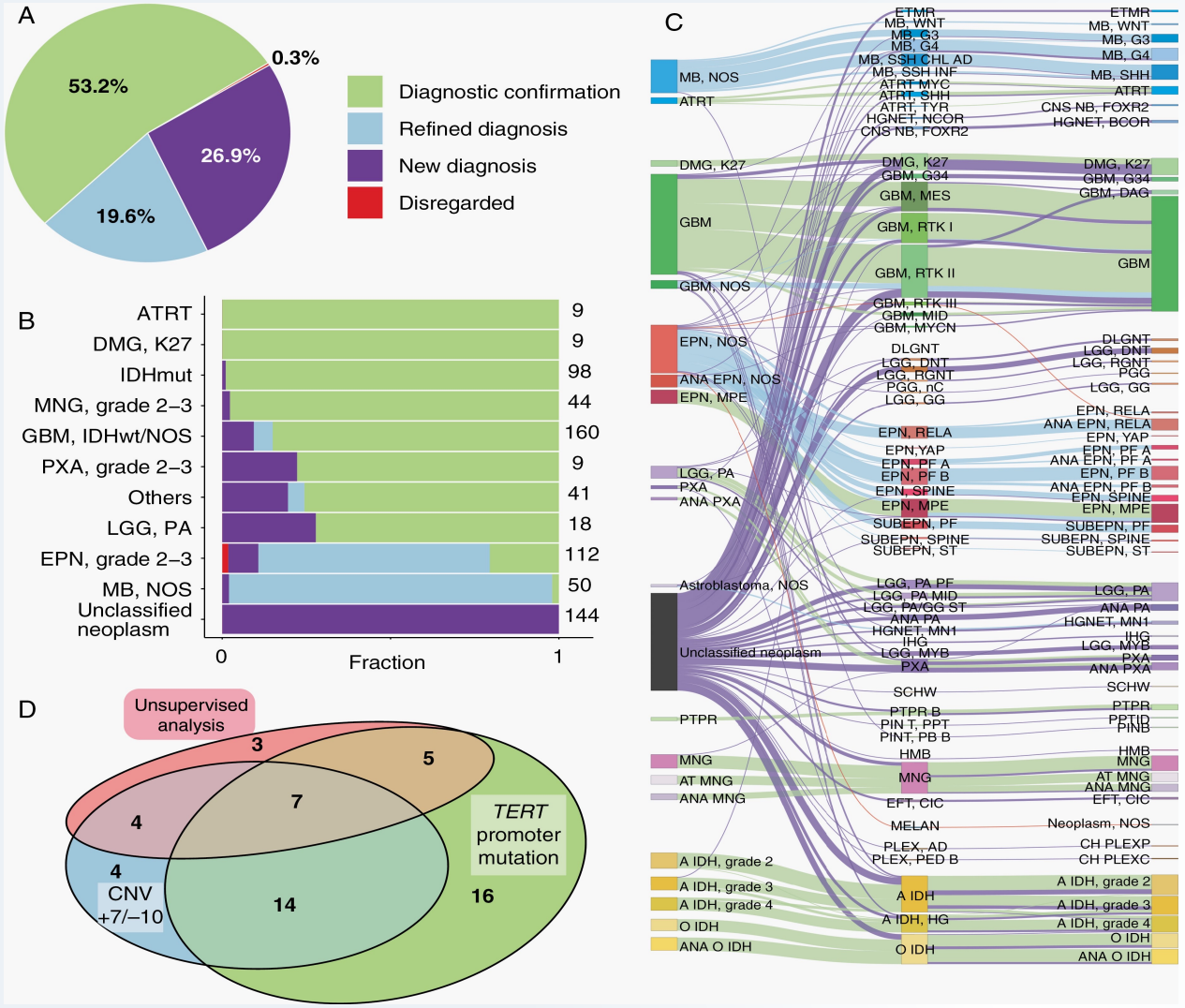


Figure 1. **(A)** This prospective study started with surgical resection of the brain tumor and tissue processing for a pathologist. All tumors received the standard of care pathology diagnosis as judged appropriate at the time of initial review, and simultaneous whole genome DNA methylation profiling. The histologic diagnosis and the DNA methylation diagnosis were compared and additional molecular studies including DNA and RNA NGS studies were performed as required to resolve discrepant cases. **(B)** Our cohort included 1921 primary central nervous system tumors, of which 1602 (83%) had World Health Organization (WHO) recognized diagnoses and 319 (17%) had descriptive diagnoses. **(C)** Of the 1602 WHO diagnoses, 1189 (74%) tumors showed concordance between histopathology and DNA methylation and were considered a complete diagnostic match, 225 (14%) tumors were a diagnostic mismatch with discrepant tumor type and/or grade, 110 (7%) tumors DNA methylation was able to add additional prognostic information, and 78 (5%) tumors did not classify by DNA methylation (referred to as "no match"). **(D)** Of the 319 tumors carrying descriptive diagnoses, DNA methylation provided a conclusive diagnosis in 273 (86%), 46 (14%) tumors did not classify and were therefore considered "no match."

Impact of methylation classifier on CNS tumor diagnosis

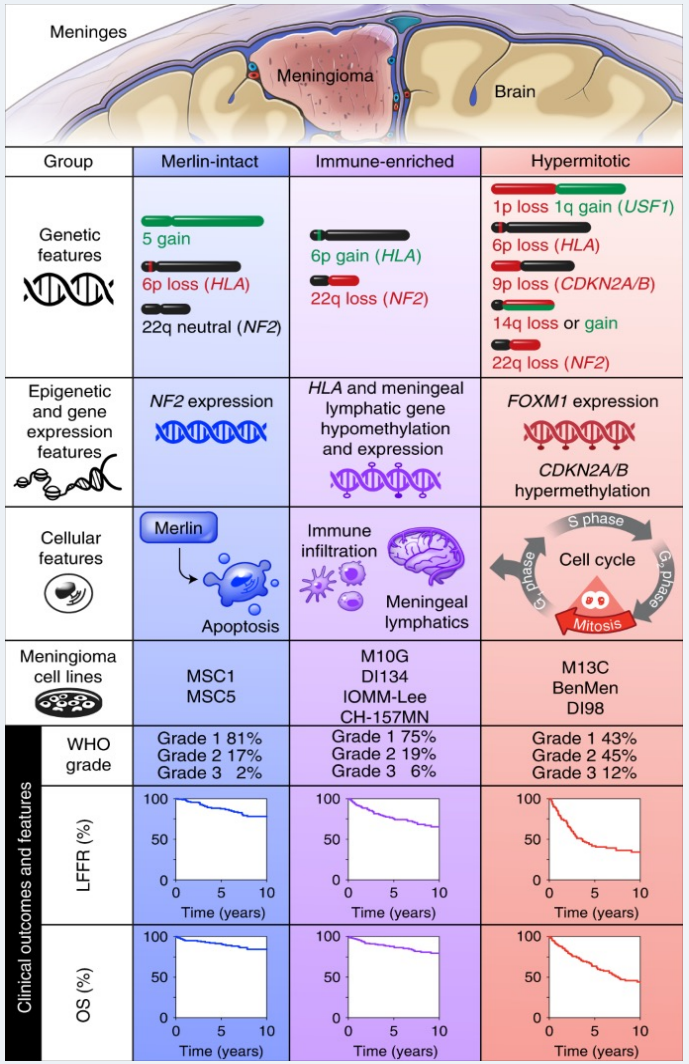


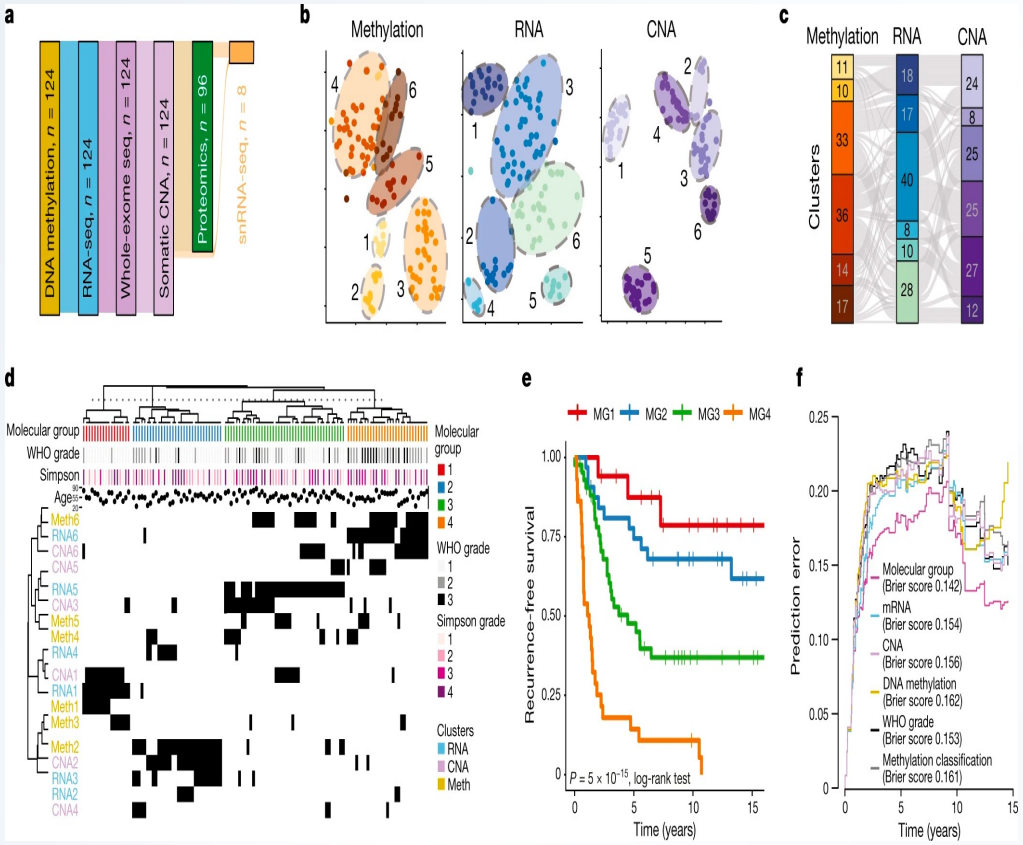
Integrated Diagnosis for CNS Tumor in a Consultative Practice (NCI experience)

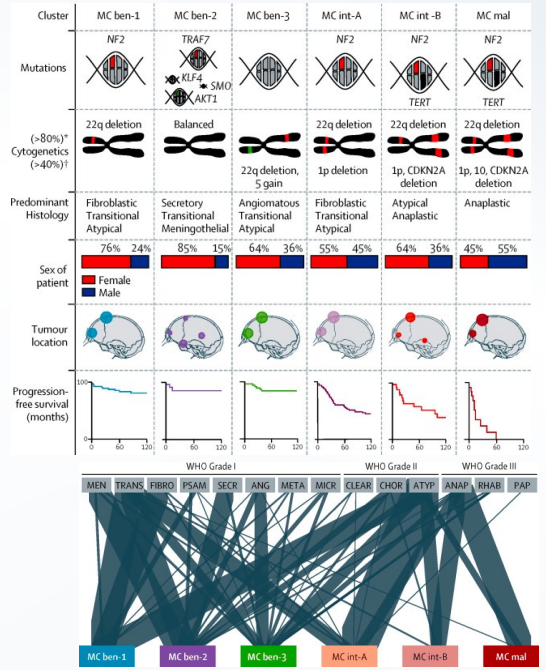
"We evaluated a consecutive series of 1258 surgical neuropathology cases in a predominantly consultative practice in the period between 2018 and 2020, of which 1045 were received from outside institutions for consultation."

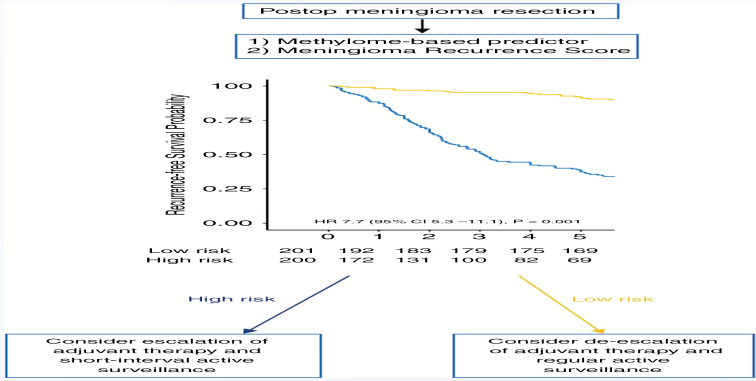
Neuro Oncol, Volume 24, Issue 4, April 2022, Pages 571–581, https://doi.org/10.1093/neuonc/noab227

DNA methylation profiling to predict recurrence risk in meningioma









DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol. 2017 May;18(5):682-694. doi: 10.1016/S1470-2045(17)30155-9. Epub 2017 Mar 15. PMID: 28314689.

Nassiri, F., Liu, J., Patil, V. *et al.* A clinically applicable integrative molecular classification of meningiomas. *Nature* **597**, 119–125 (2021). https://doi-org.proxy.library.emory.edu/10.1038/s41586-021-03850-3

Choudhury, A., Magill, S.T., Eaton, C.D. *et al.* Meningioma DNA methylation groups identify biological drivers and therapeutic vulnerabilities. *Nat Genet* **54**, 649–659 (2022). https://doi.org/10.1038/s41588-022-01061-8

Neuro Oncol, Volume 21, Issue 7, July 2019, Pages 901–910, https://doi.org/10.1093/neuonc/noz061

Standing Up the Program at Emory

- We established an internal methylation profiling pipeline
- Reduces turnaround time and improves patient care
- Positions Emory as a leader in precision neuro-oncology diagnostics

PROFILING DNA METHYLATION USING THE ILLUMINA INFINIUM PLATFORM

The Illumina Infinium platform with its high-density DNA methylation arrays, more specifically the **HumanMethylation450** with 485 577 CpGs (released in 2011) and its successor, the **Methylation EPIC** with 853 307 CpGs (released in 2015-2016) has been experienced as simple to use and generating reproducible data.

Several tissue sources, fresh, frozen, or FFPE embedded samples, are suitable for analysis.

Input of 250 ng DNA allows processing of small specimens such as from stereotactic biopsies or obtaining DNA from a few unstained slides with thickness, diameter, and cellularity of the sample, determining the number of sections required.

DNA methylation array is a 4 day process

Conclusion: A Transformative Investment

With methylation profiling, Emory is transforming the way CNS tumors are diagnosed, ensuring patients receive precise diagnoses and tailored treatments aligned with the latest WHO standards.

Acknowledgements – Winship Brain Tumor Program

Neuropathology:

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Radiation Oncology:

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Bree Eaton

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Natia Eshiashvili

Neuro Oncology:

Byram Ozer –WELCOME!

Laura Donovan – NEW!

Neurosurgery:

Jeff Olson

Kimberly Hoang

Chris Deibert

Neuroradiology:

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Research Team

Renee Read

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