Classification of Diffuse Gliomas: Progress, Pearls and Pitfalls

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Objectives

- Explain why the designation ‘high grade glioma’ is preferable to ‘GBM’ for intraoperative diagnosis.
- State the diagnostic pathologic requirements for the diagnosis of oligodendroglioma.
- Recognize that retained ATRX immunostaining suggests 1p/19q codeletion in IDH-mut glioma.

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Illustrative Case 1

- 34 yo woman
- Severe headaches
- Left frontal mass resected
- Received chemotherapy (PCV)
- Recurred 13 years later
- Re-resection specimen sent to Moffitt for review

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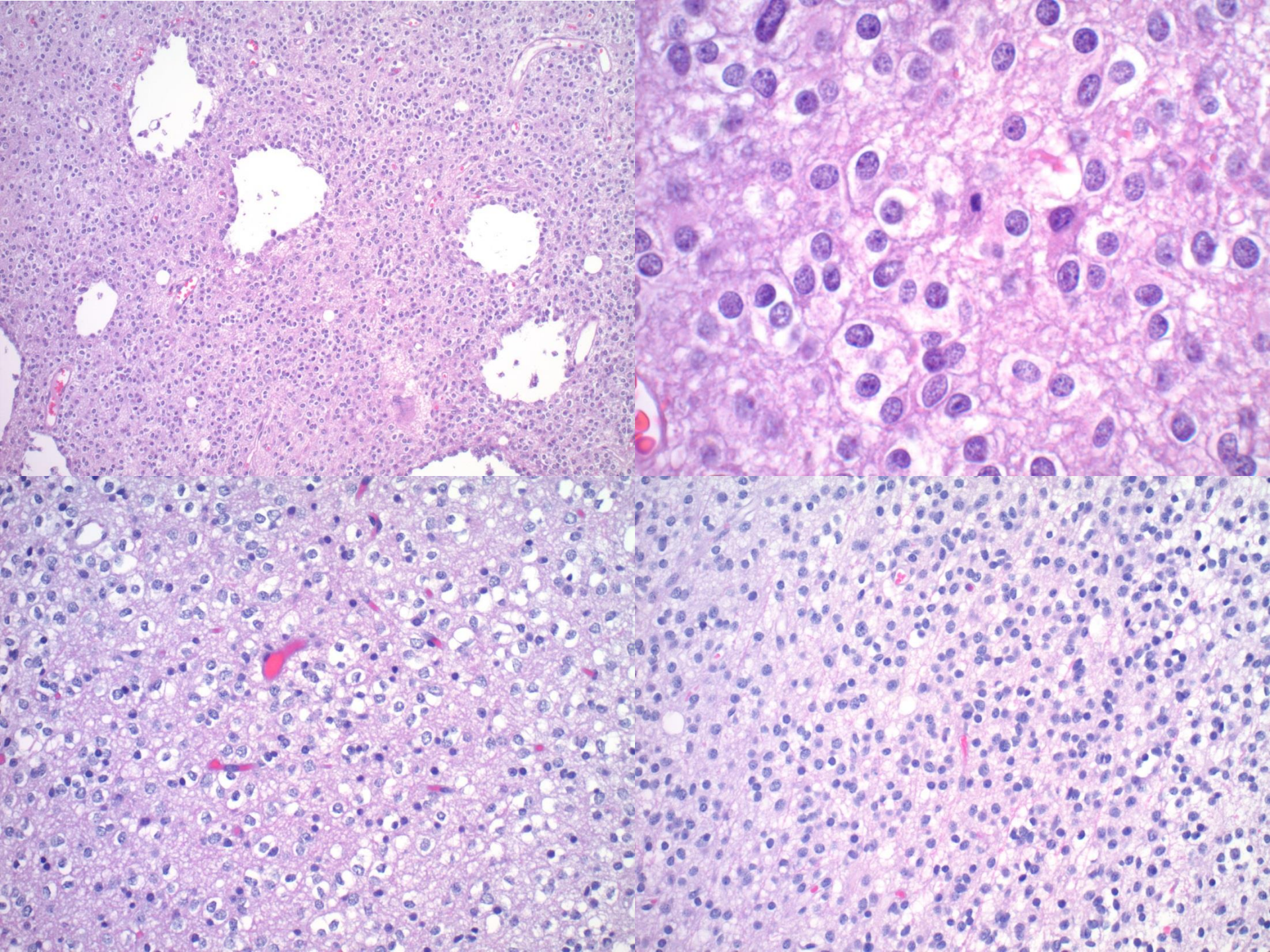

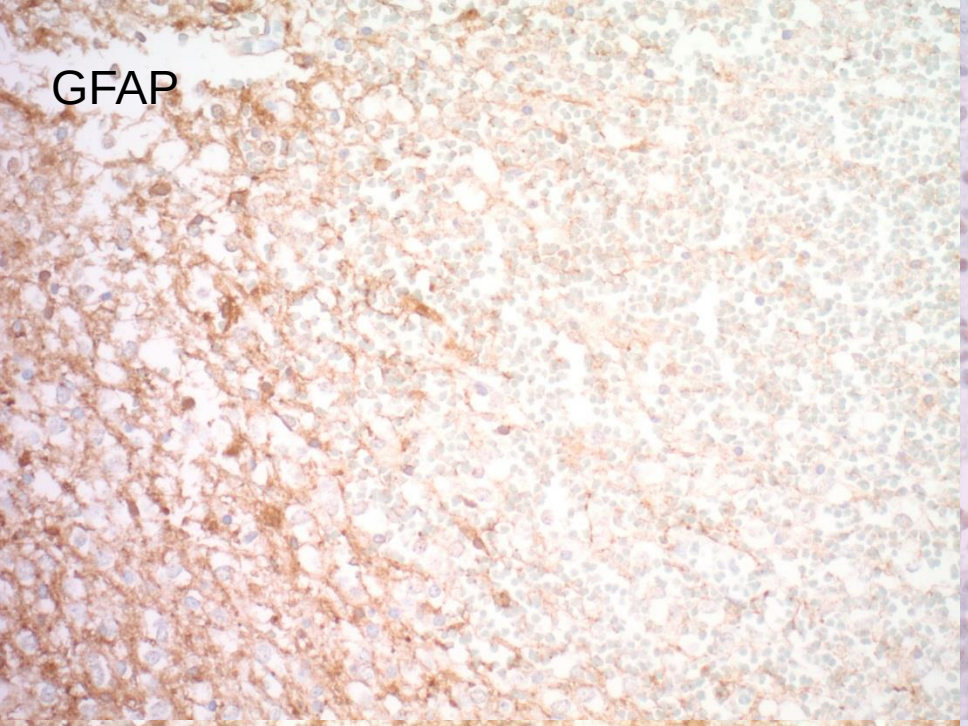
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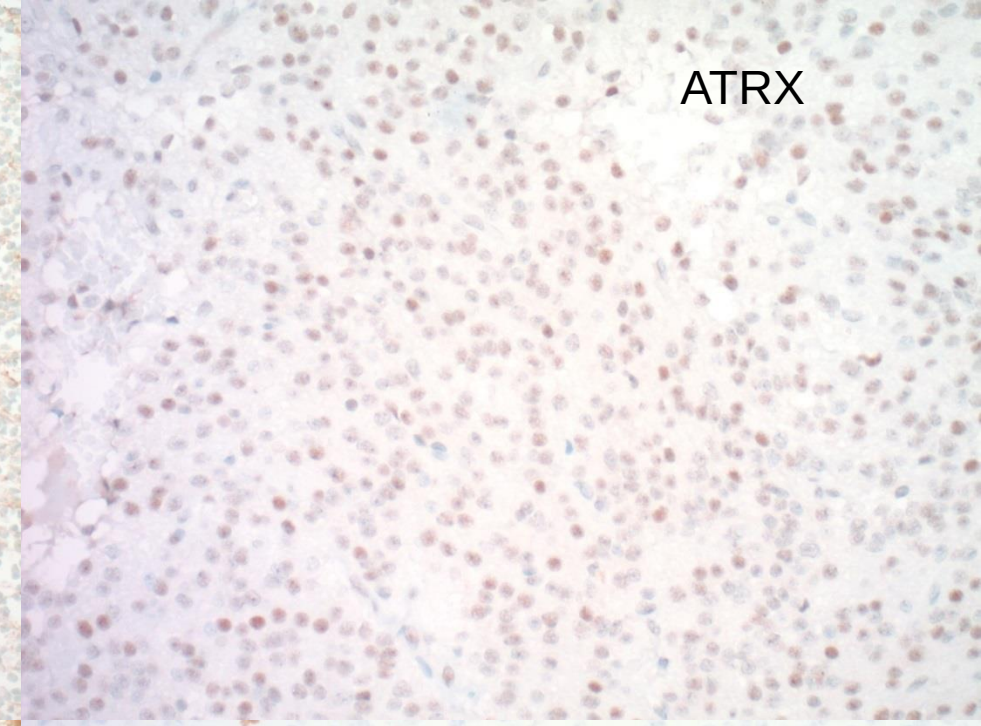
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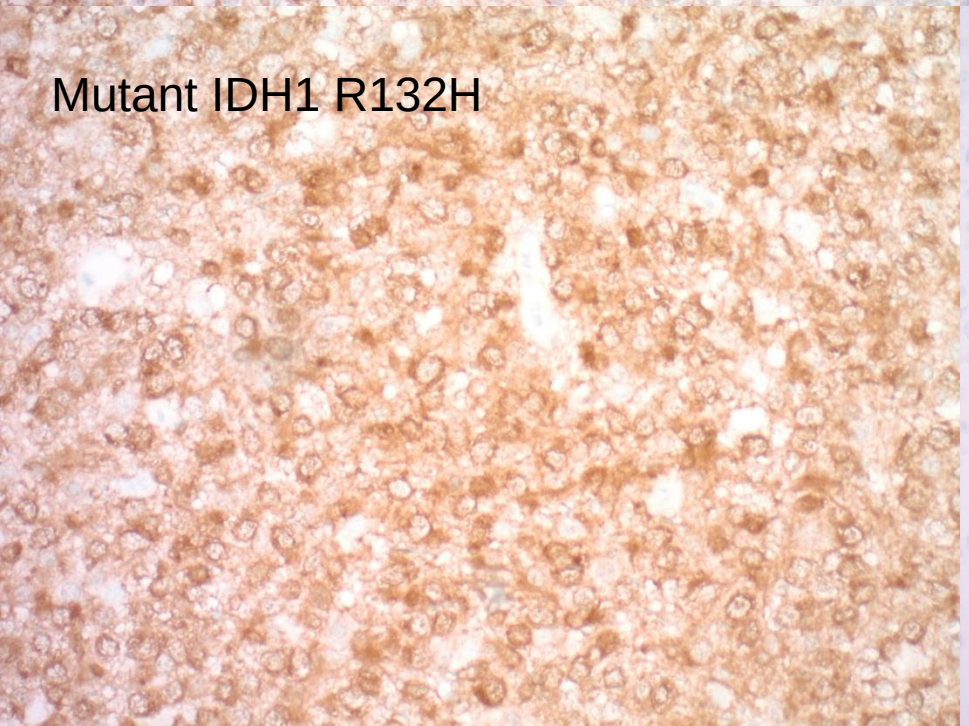
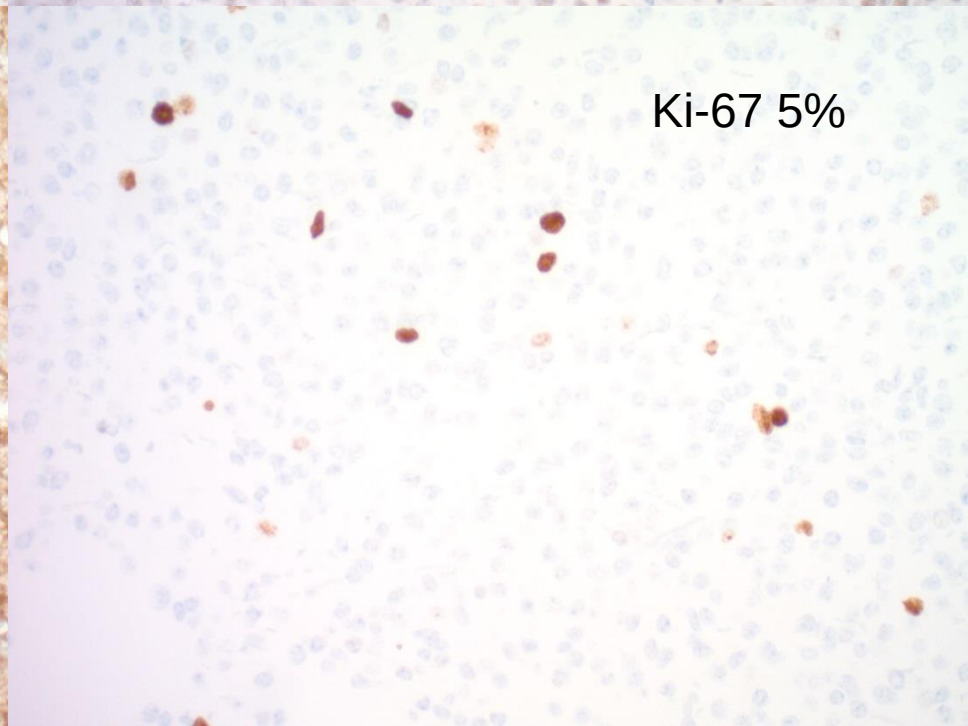

Mutant IDH1 R132H


Ki-67 5%

Diagnosis

- POSITIVE for 1p/19q codeletion
- Oligodendroglioma WHO grade 2
  - IDH mutated
  - ATRX retained
  - Does not meet criteria for anaplastic oligo

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Glial neoplasms

- Resemble astrocytes, oligodendrocytes or ependyma
  - Precursor cells unknown in most cases
- Diffuse vs circumscribed
- Incidence depends on age, location
  - Childhood
    - Cerebrum – diffuse or pilocytic astrocytoma
    - Brainstem - diffuse or exophytic astrocytoma, ependymoma
    - Cerebellum – pilocytic astrocytoma, ependymoma
    - Spinal cord – diffuse or pilocytic astrocytoma, ependymoma
  - Adults
    - Cerebrum – astrocytoma, oligodendroglioma, ependymoma
    - Others similar to childhood but relatively less frequent
- WHO Grades 1-4, depends on histologic subtype

Diffuse Gliomas

- IDH-mutated
  - Astrocytoma (including grade 4 => glioblastoma-IDH-mut)
  - Oligodendroglioma (including grade 3 => anaplastic)

- IDH-wildtype
  - Glioblastoma (including ‘pre-GbM’ or undersampled)
  - Epithelioid GbM
  - Diffuse midline glioma, histone H3 K27M-mutant
  - Hemispheric GbM, histone H3F3A G34R/V mutation

- IDH-unknown
  - ‘NOS’ => incomplete work-up

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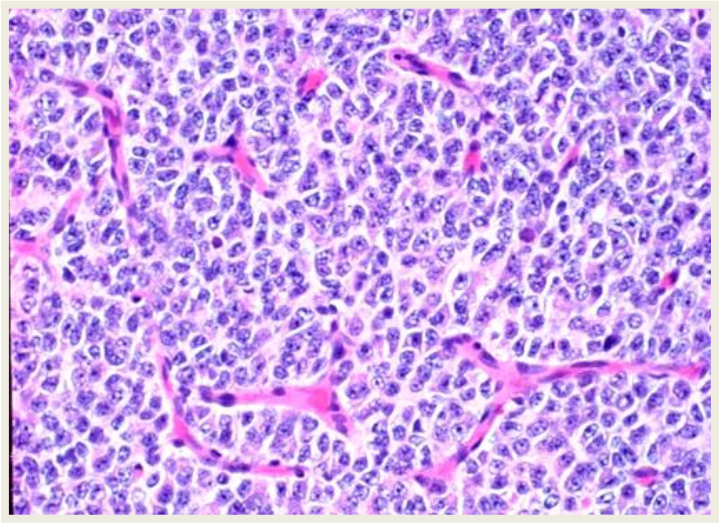
Oligodendroglioma

- Neoplastic cells resemble oligos: small, round
  - Morphology no longer a criterion for classification
- WHO grades 2 or 3, never grade 4
- Requires IDH-mutation **and** 1p/19q codeletion
  - TERT promoter mutation in > 90%
- Other characteristics
  - CIC (>50%)
  - FUBP1 (25%)
  - Notch1
  - PIK3CA



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Diagnosis of Diffuse Glioma

- STEP ONE:
  - Nuclear atypia required to label as ‘neoplasm’
  - Hypercellularity, satellitosis, aggregation helpful
- IDH Status is now STEP TWO
  - Most common IDH mutation is IDH1 R132H, but
    - About 10% of IDH-mut are not IDH1 R132H
  - IDH2 mutations rare, usually R172H
  - Fundamental to pathobiology, diagnosis, progression, treatment response, outcome
- IDH R132H immunopositivity is **diagnostic** even without nuclear atypia or hypercellularity (peripheral margin)

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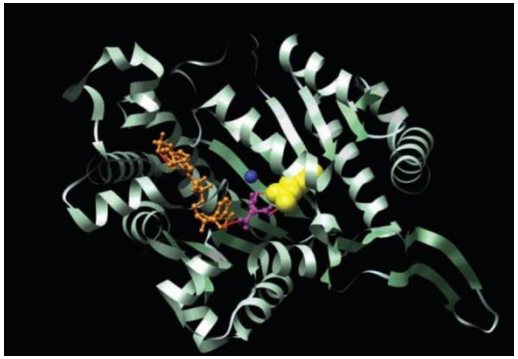
IDH-Mutation is Carcinogenic

- Mutant IDH generates 2-hydroxyglutarate (2-HG)
  - Disrupts chromatin structure
  - Global hypermethylation/ g-CIMP
- Likely early (?initiating) event
  - Not documented before mid-teens
  - Subsequent genetic and epigenetic events determine phenotype and grade



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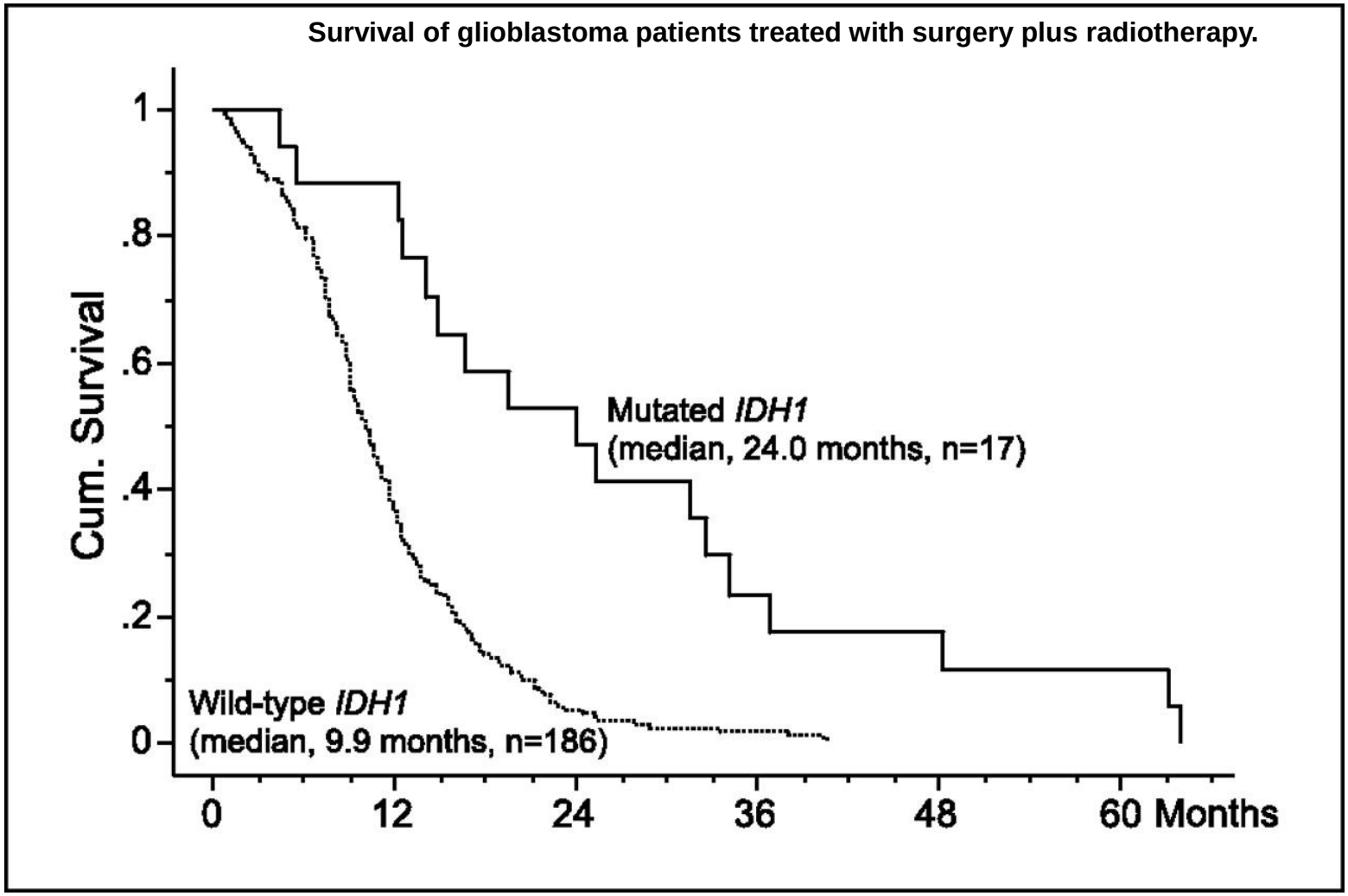
IDH-mutation status is clinically relevant



Sumihito Nobusawa et al. Clin Cancer Res 2009;15:6002-6007

Clinical Cancer Research
AACR American Association for Cancer Research
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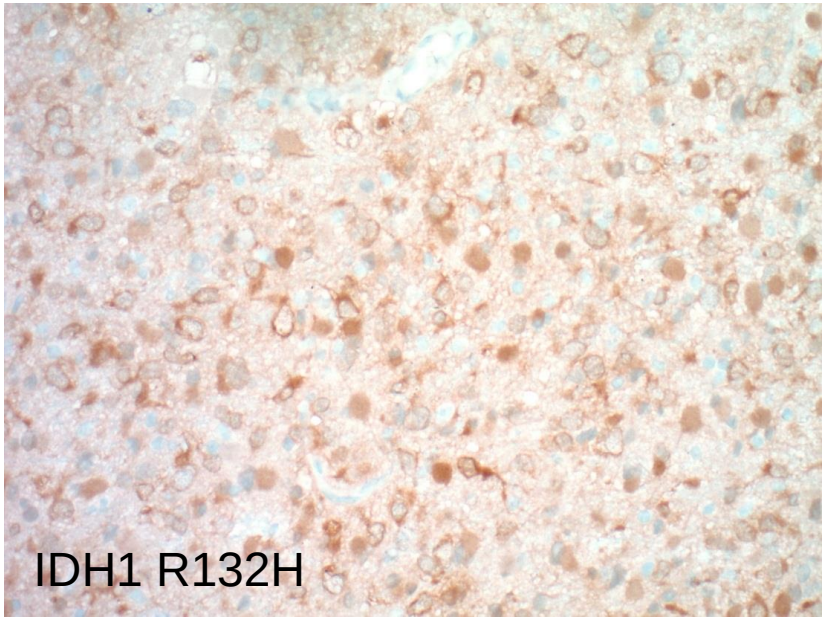

IDH1 (C2) or IDH2 (C15) mutations

- Astrocytoma WHO grade 2 or 3 (80%)
  - Negative for 1p/19q codeletion (by definition)
- Oligodendroglioma grade 2 or 3 (by definition)
  - Positive for 1p/19q codeletion (by definition)
- Glioblastoma: fewer than 10% have IDH-mutation

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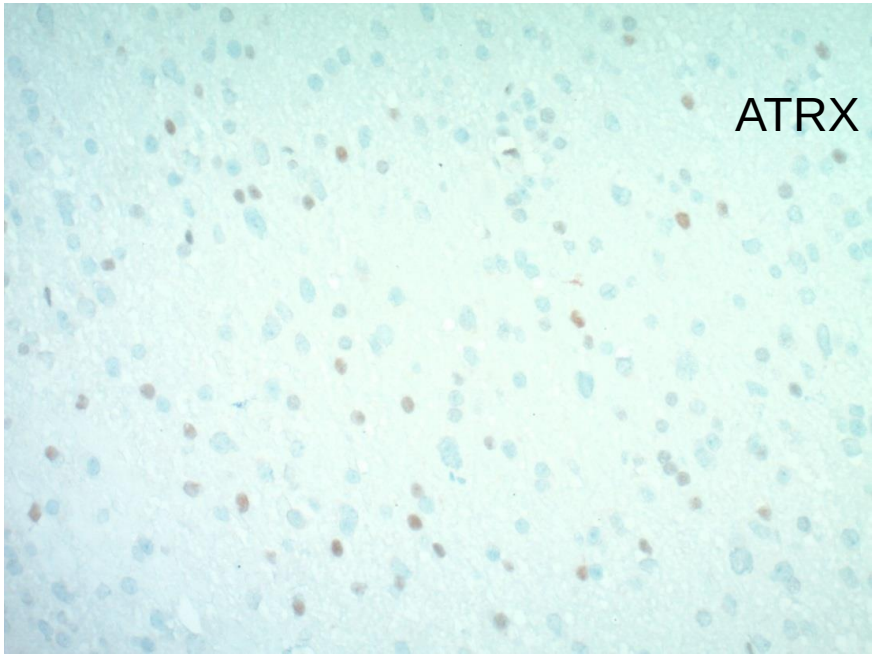
Telomeres in Diffuse Gliomas

- Telomerase – RNA/protein complex: hTERT subunit
  - TERT promoter mutations common in gliomas
- Alpha thalassemia/mental retardation syndrome X-linked (ATRX)
  - Linked to epigenetic stability/chromatin remodelling
  - ATRX(-) tumors exhibit alternate lengthening of telomeres
  - Mutated/lost in a variety of neoplasms including gliomas



ATRX loss of expression in tumor cells

If 1p/19q is codeleted: ATRX is retained
- hTERT promoter mutations in >90%
- No quick test for HTERT promoter mutation (yet)

If 1p/19q is not codeleted: ATRX is usually lost
- Some astrocytomas do not show ATRX loss (?significance)

Preliminary Classification of IDH-mutated Gliomas
- In practice, ATRX loss is highly predictive of astrocytoma
- Retained ATRX is highly suggestive of oligodendroglioma

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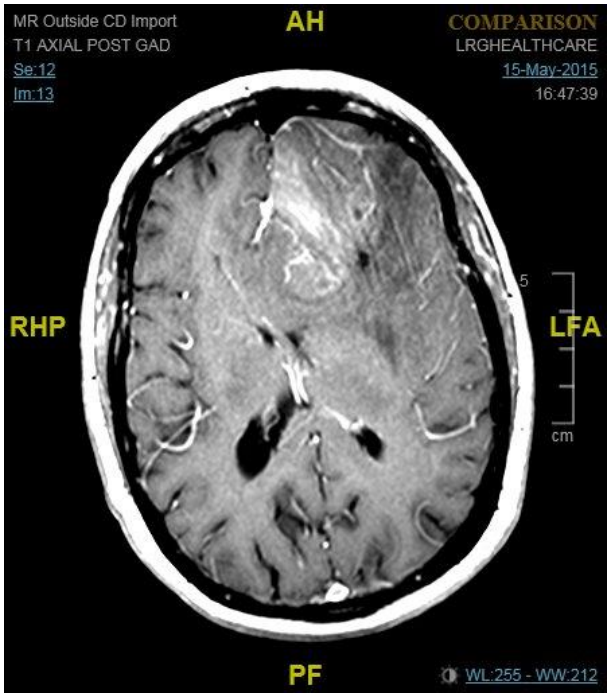
Illustrative Case 2

- 74 yo woman
- Gradually progressive personality change



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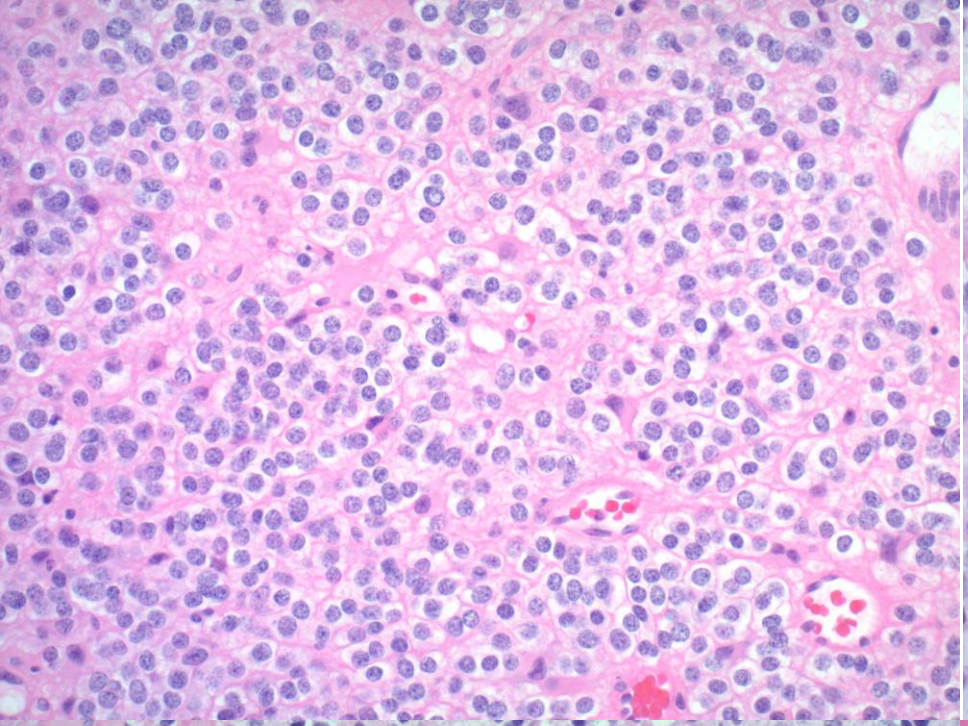
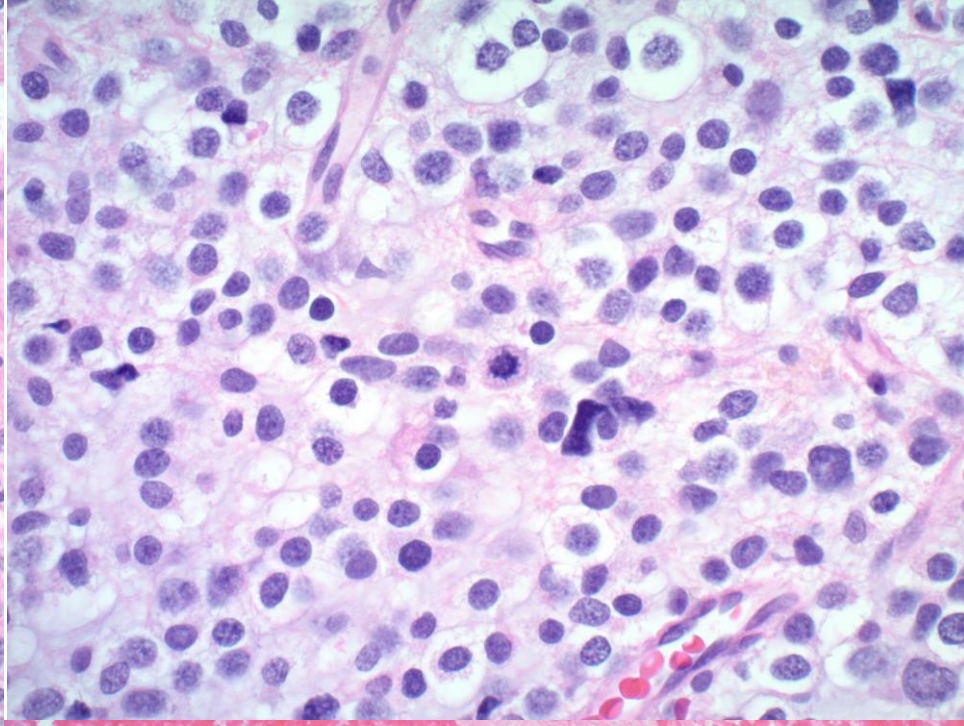
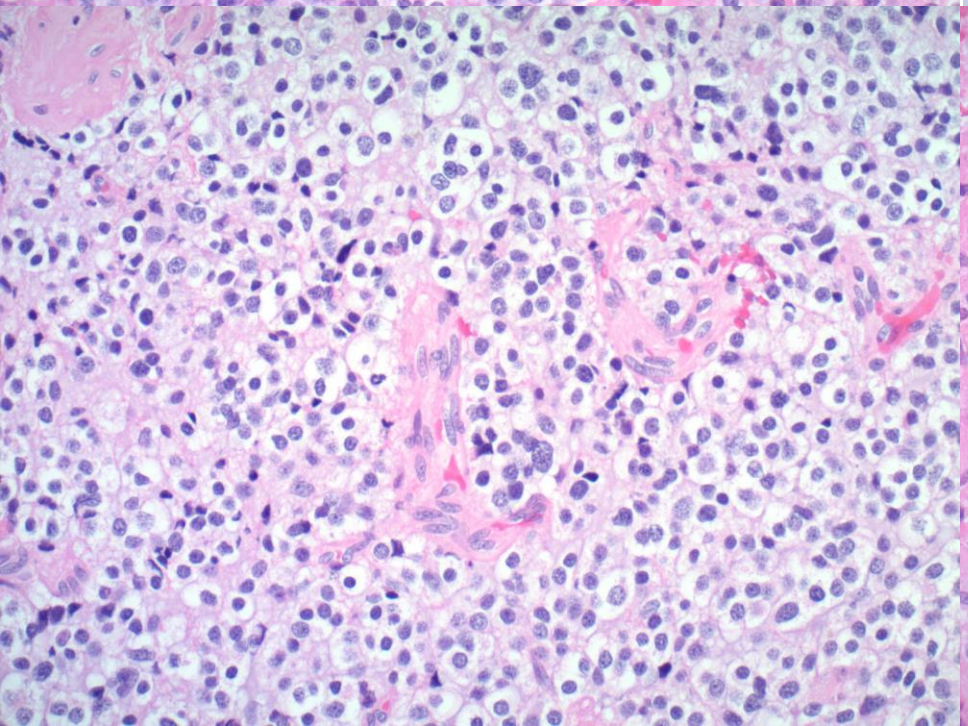
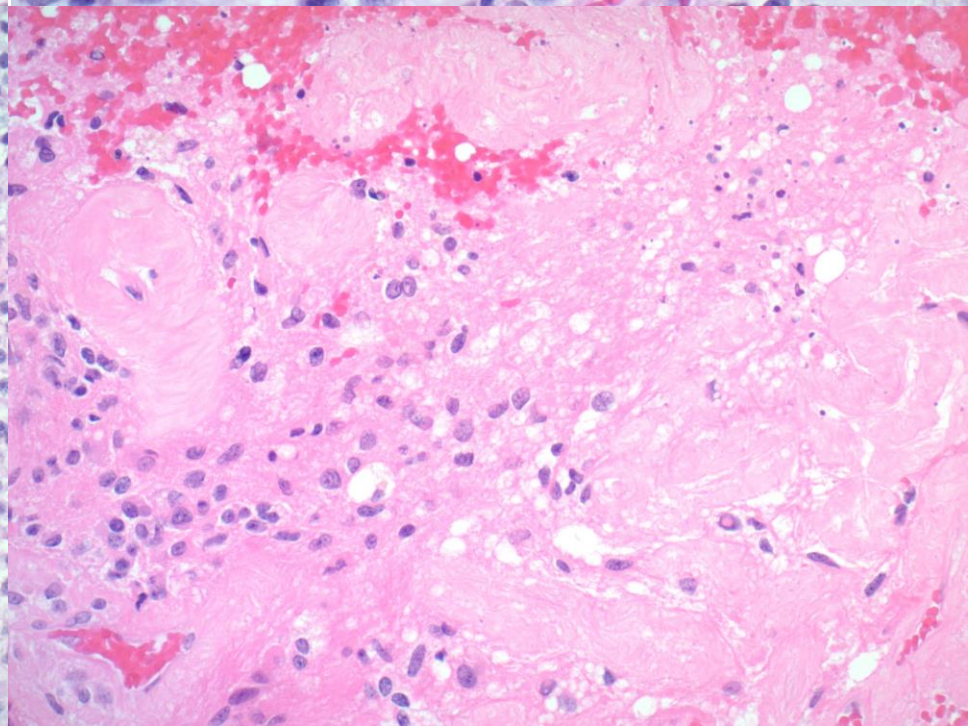

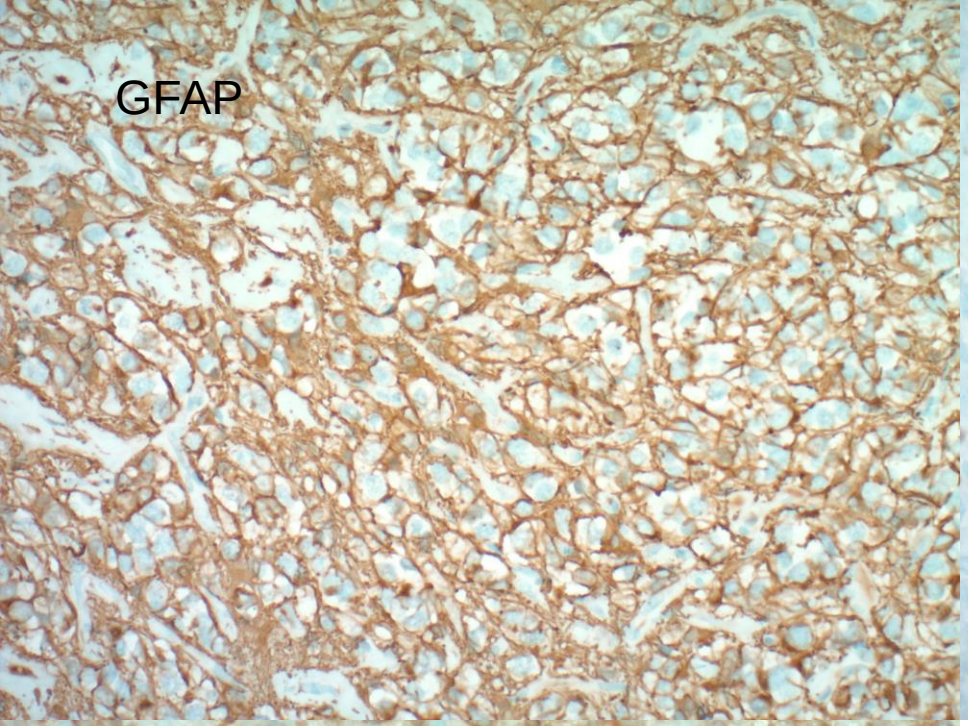

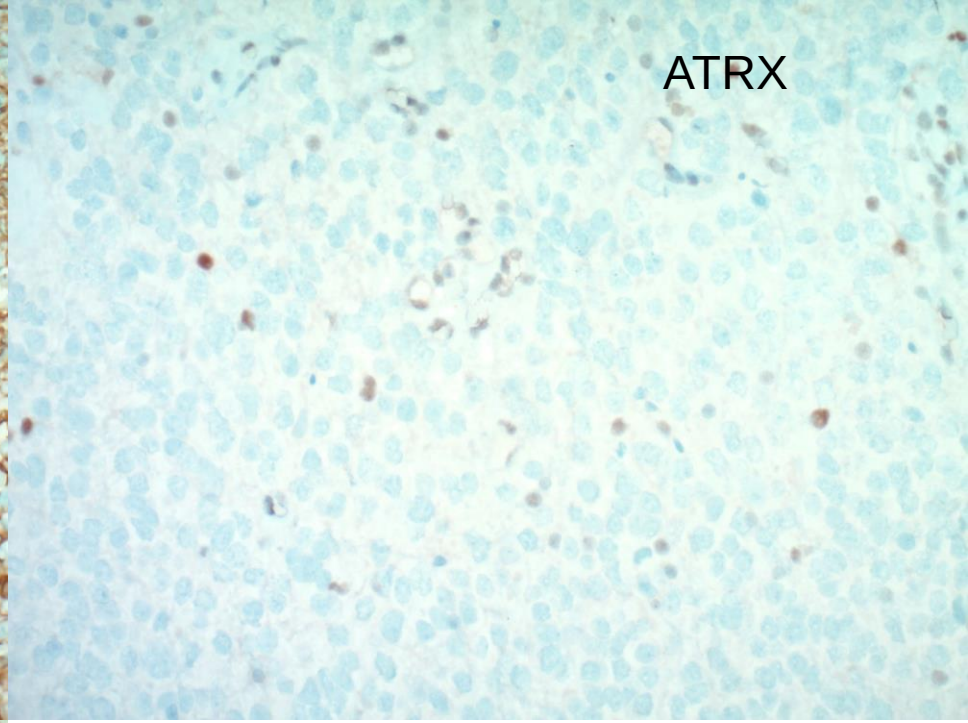

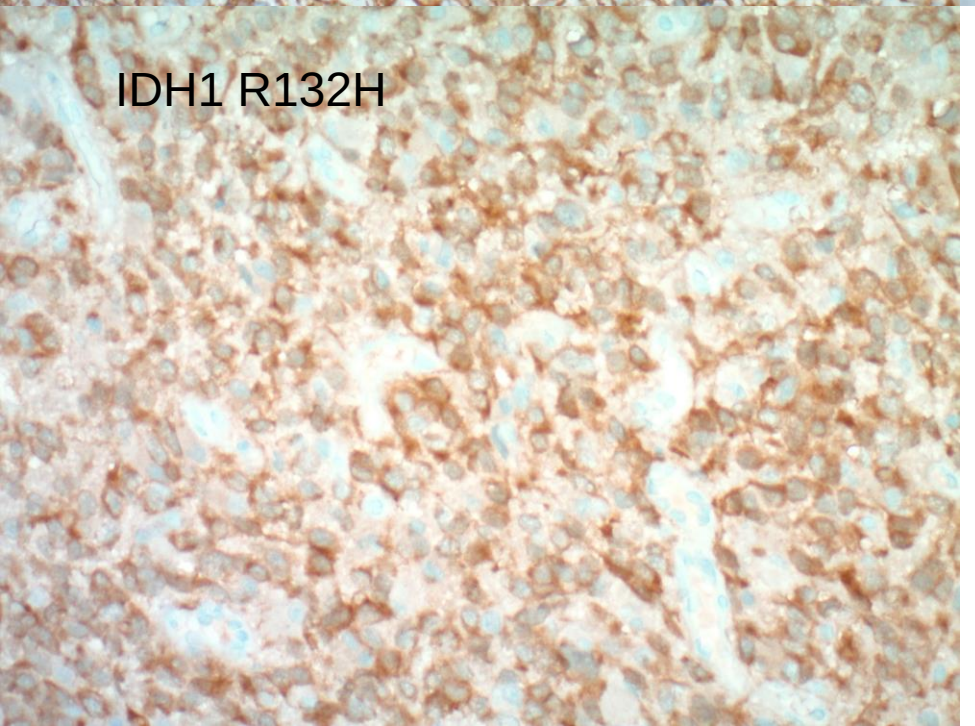

NEGATIVE for 1p/19q codeletion

Diagnosis:
Glioblastoma- IDH-mutated, WHO grade 4
ATRX lost, TP53 mutated

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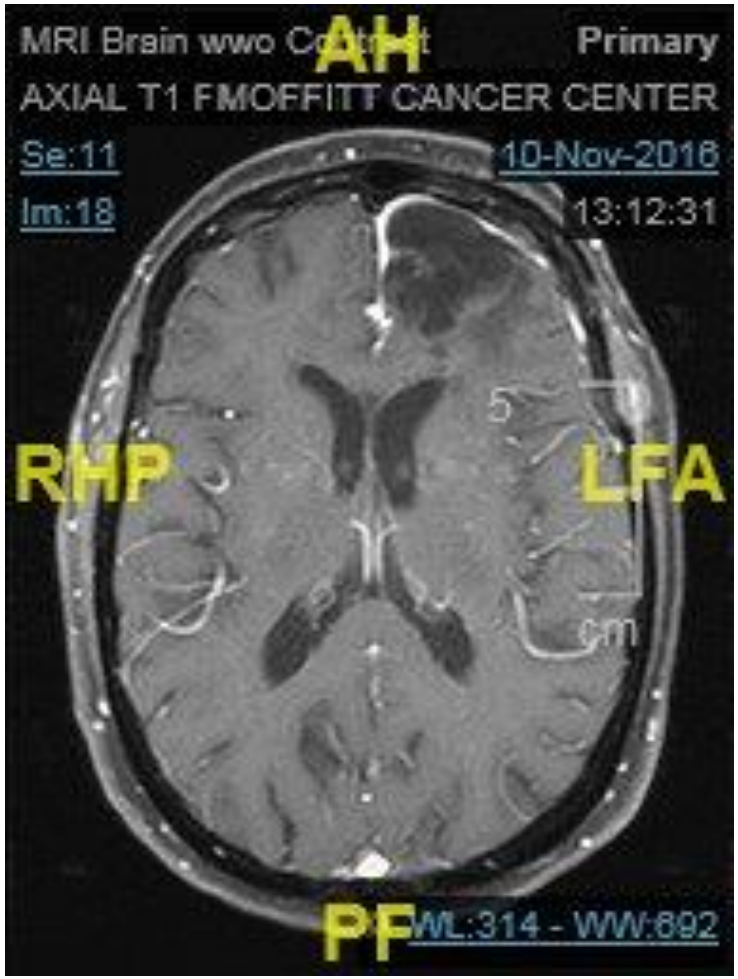
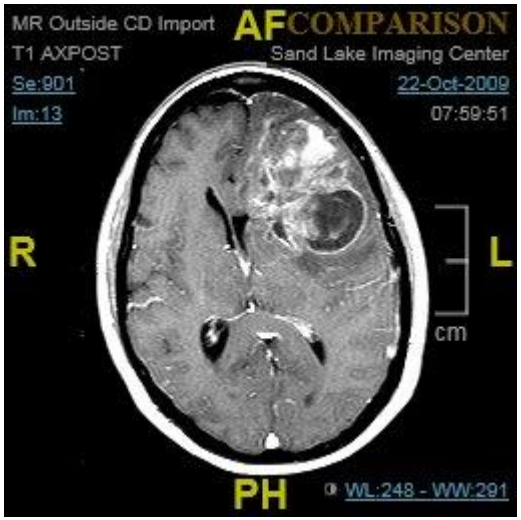
Clinical course

2 year follow-up imaging: no recurrence



Illustrative Case 3

- 54 yo woman
- Generalized seizure
- Left frontoparietal mass previously resected
- Aphasia prompted rescanning



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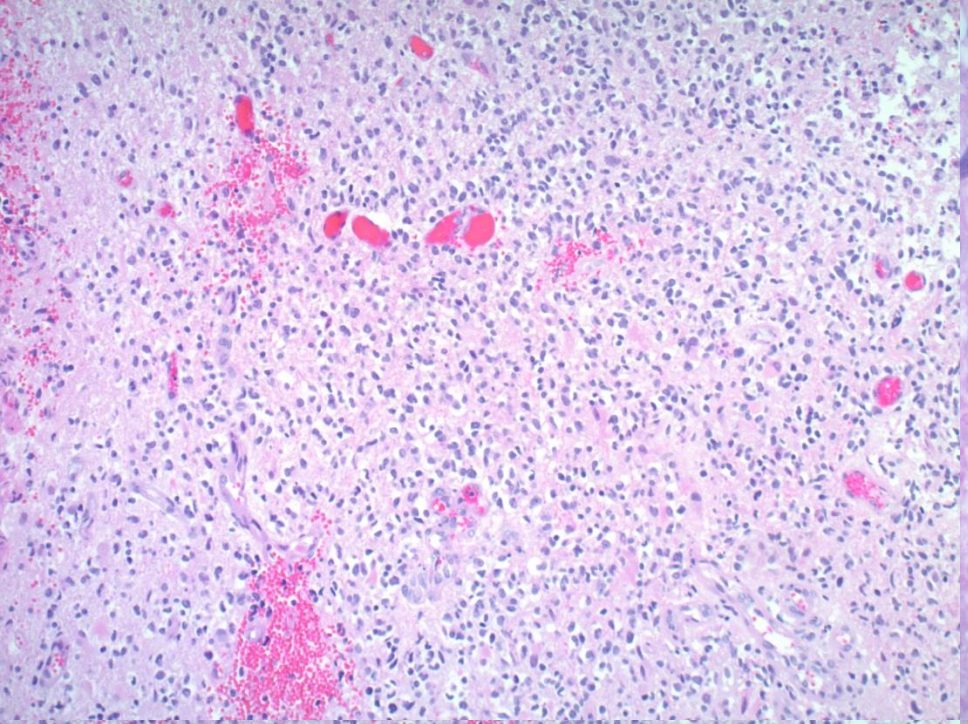
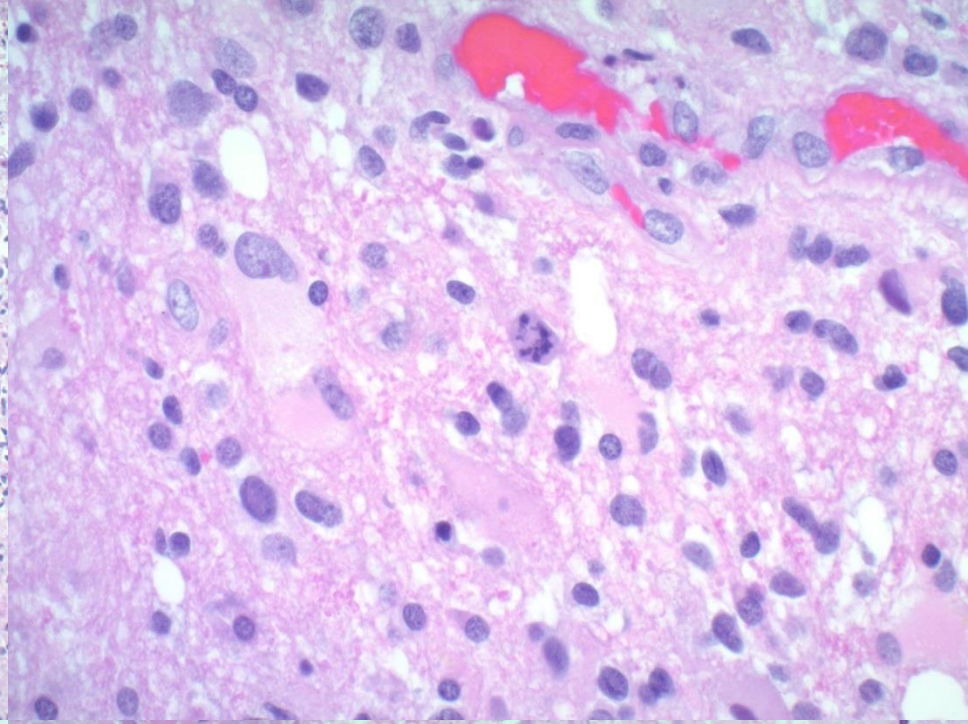
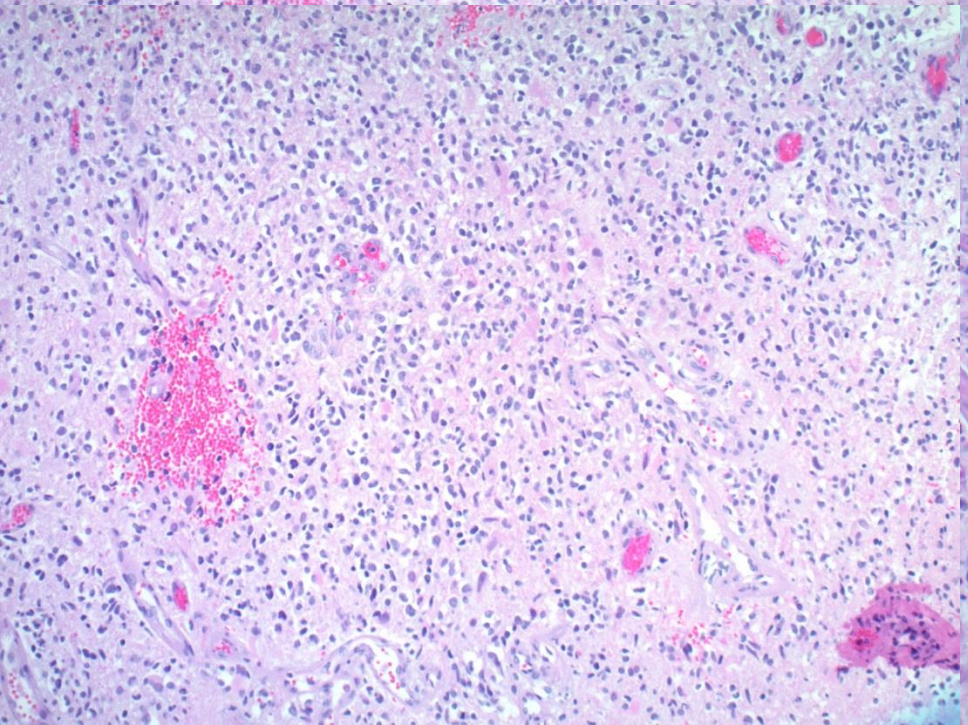
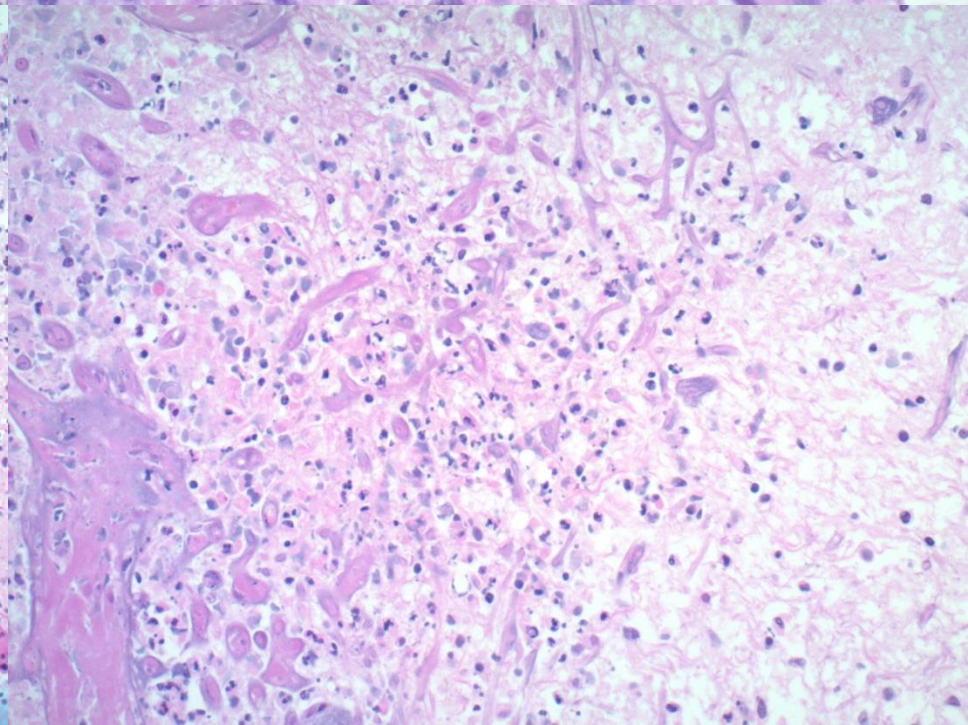
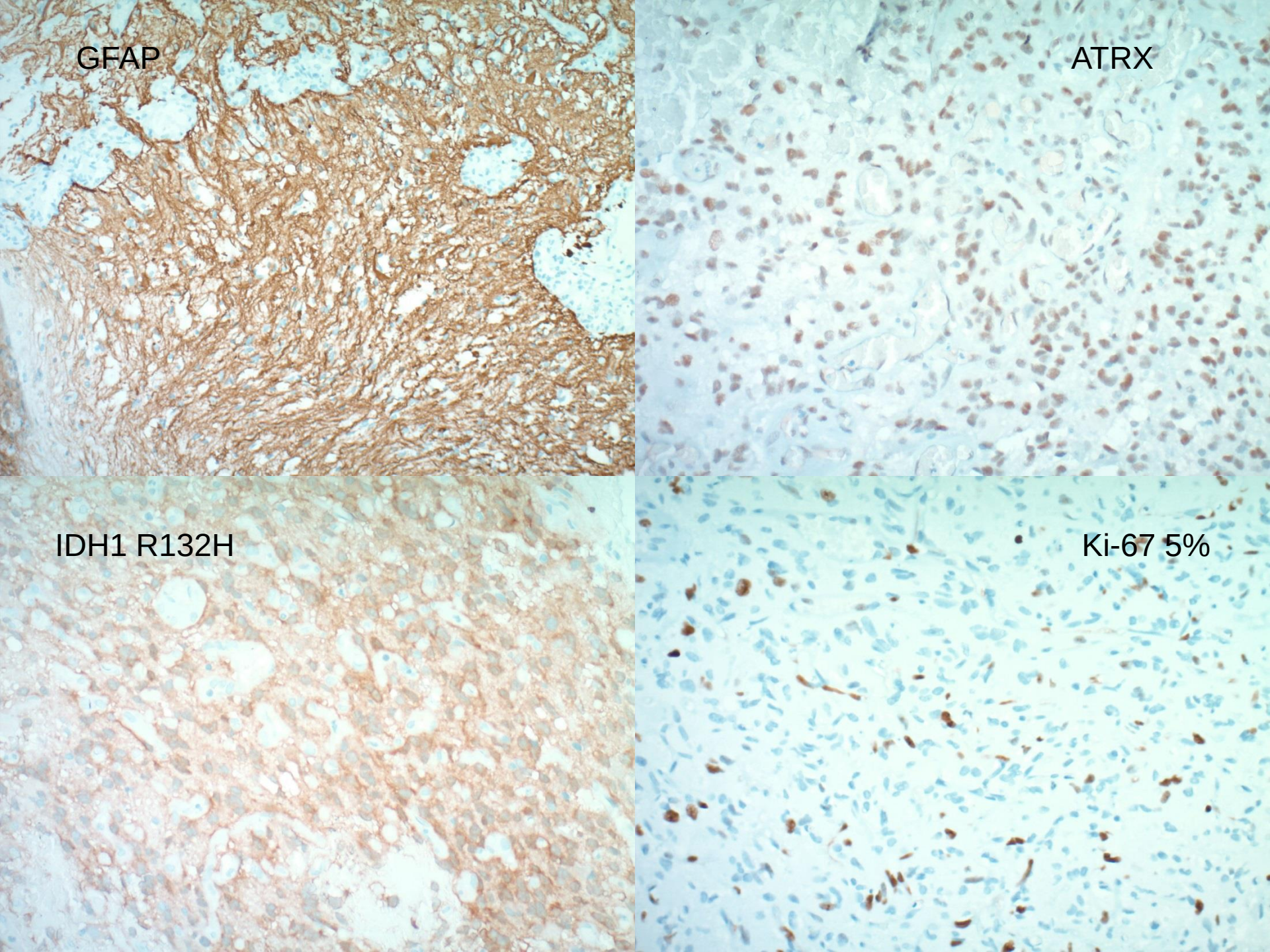
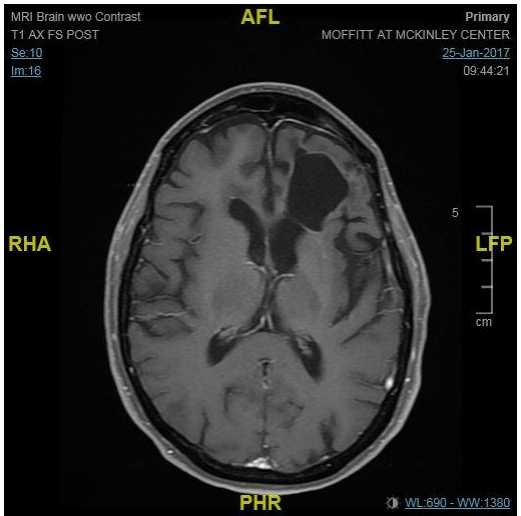






GFAP
ATRX
IDH1 R132H
Ki-67 5%

Diagnosis

- Anaplastic oligodendroglioma WHO grade 3
  - Positive for IDH R132H mutation
  - Retained ATRX
  - Positive for 1p/19q codeletion
  - Positive for KRAS, EGFR and PIK3CA mutations



Contrast enhanced,
2 years after recurrence
& Chemoradiotherapy

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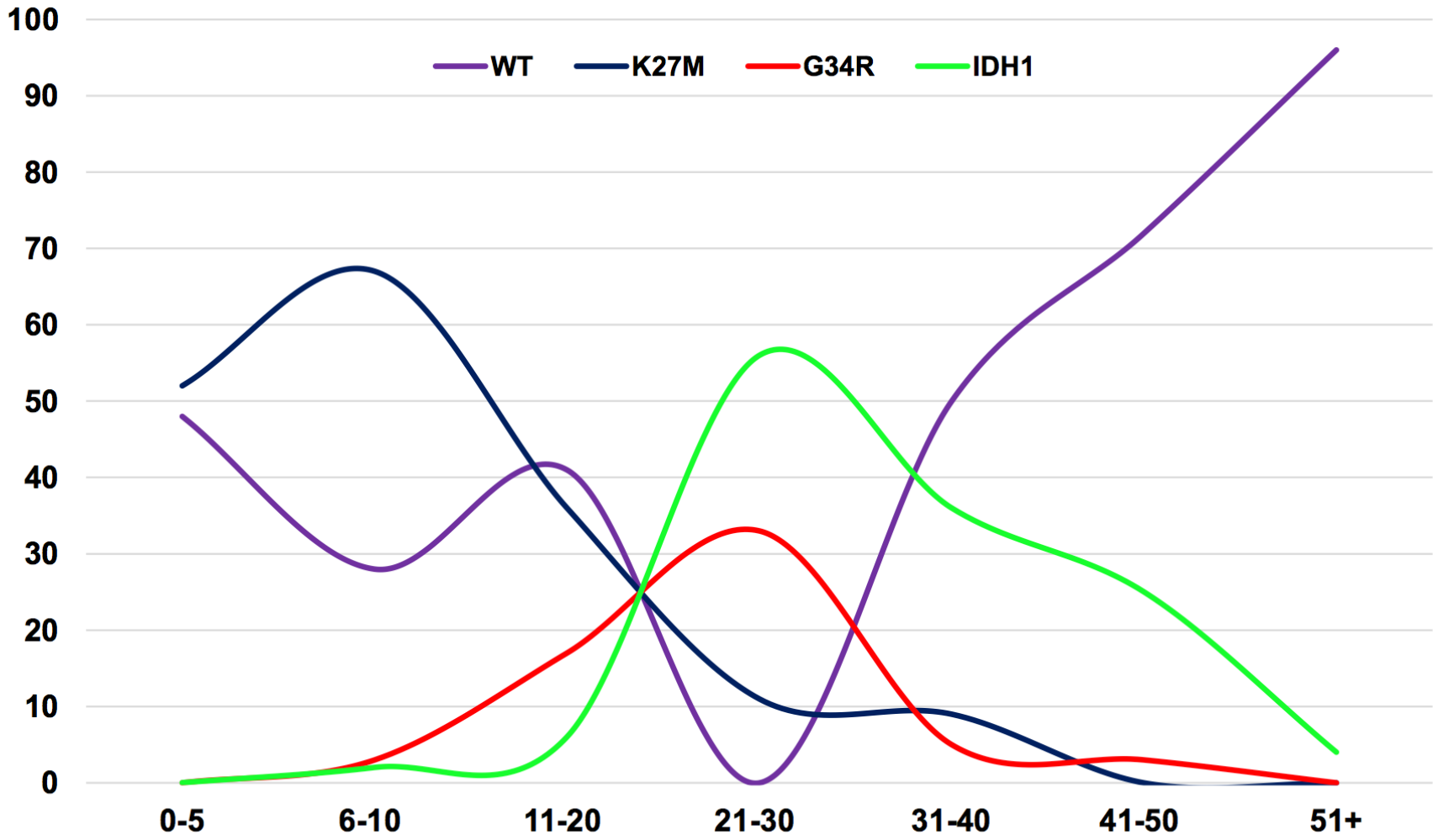
Grading of Diffuse Gliomas

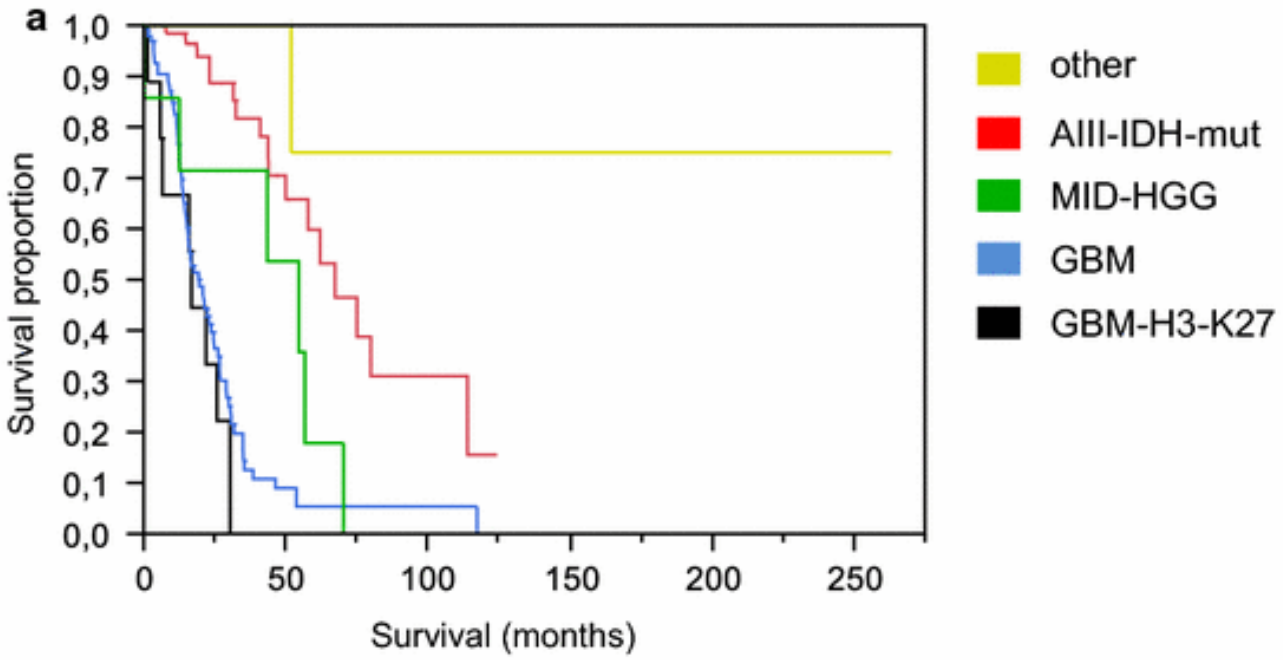
- Features predicting progression (i.e. grade)
  - Mitotic figures (any, in A, >5/10 hpf for OGD)
  - Vascular proliferation (glomeruloid)
  - Necrosis (with or without palisading)
  - None of these features is helpful for diagnosis, since they may occur in non-neoplastic conditions
- Astrocytoma can be grade 2, 3 or 4 (=GbM)
  - Add one grade per met criterion
- Oligo can be 2 or 3 (= anaplastic OGD)

Mutations vs Age in HGG



[courtesy Dr Cynthia Hawkins]

Survival data of molecular subtypes



Reuss DE et al, Acta Neuropathologica, September 2015 130(3): 407-17

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Conclusions

- IDH mutational status is essential for glioma diagnosis
  - IDH-mut gliomas are either:
    - astrocytoma (ATRX lost) WHO grades 2, 3 or 4(GbM); or
    - oligodendroglioma (1p/19q codel) WHO grades 2 or 3
- IDH-wildtype GBM is a mixed bag
  - Adult IDH-wt gliomas are underdiagnosed GBMs
- Intraoperative diagnosis of GBM is hazardous
  - If IDH-mut and 1p/19q codeleted, AO grade 3
  - More accurate to use ‘high grade glioma’

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Questions?

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