A National Cancer Institute Designated Cancer Center

FRED & PAMELA BUFFETT CANCER CENTER

Adult CNS Tumor Pathology – WHO 2021 Brief Update and Case Examples

Grey Matters Symposium

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Nebraska Medicine

BRAIN AND SPINE CANCER CENTER

I have NO financial relationships or conflicts of interests relating to the subject matter of this presentation.

ICD-O coding of central nervous system tumours

ICD-O-3.2 ICD-O label (subtypes are indicated in grey text, with the label indented);
Please note that the WHO classification of tumour types is more readily reflected in the table of contents

Gliomas, glioneuronal tumours, and neuronal tumours

Adult-type diffuse gliomas

	Astrocytoma, IDH-mutant
9400/3	Astrocytoma, IDH-mutant, grade 2
9401/3	Astrocytoma, IDH-mutant, grade 3
9445/3	Astrocytoma, IDH-mutant, grade 4
	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
9450/3	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 2
9451/3	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 3
9440/3	Glioblastoma, IDH-wildtype

Paediatric-type diffuse low-grade gliomas

9421/1	Diffuse astrocytoma, *MYB*- or *MYBL1*-altered†
9431/1	Angiocentric glioma
9413/0	Polymorphous low-grade neuroepithelial tumour of the young†
9421/1	Diffuse low-grade glioma, MAPK pathway–altered†

Paediatric-type diffuse high-grade gliomas

9385/3	Diffuse midline glioma, H3 K27–altered†
9385/3	Diffuse hemispheric glioma, H3 G34–mutant†
9385/3	Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype†
9385/3	Infant-type hemispheric glioma†

Circumscribed astrocytic gliomas

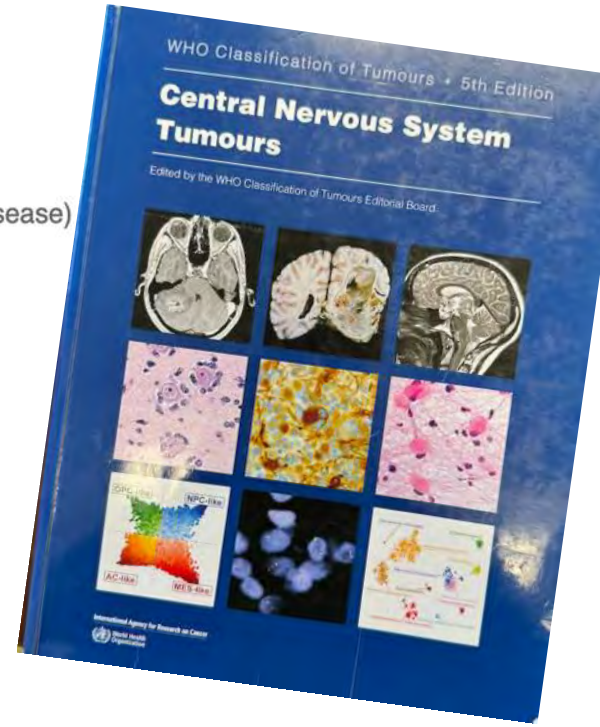
9421/1	Pilocytic astrocytoma
9421/3*	High-grade astrocytoma with piloid features
9424/3	Pleomorphic xanthoastrocytoma
9384/1	Subependymal giant cell astrocytoma
9444/1	Chordoid glioma
9430/3	Astroblastoma, *MN1*-altered†

Glioneuronal and neuronal tumours

9505/1	Ganglioglioma
9492/0	Gangliocytoma
9412/1	Desmoplastic infantile ganglioglioma
9412/1	Desmoplastic infantile astrocytoma
9413/0	Dysembryoplastic neuroepithelial tumour
n/a	Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters (provisional entity)
9509/1	Papillary glioneuronal tumour
9509/1	Rosette-forming glioneuronal tumour
9509/1	Myxoid glioneuronal tumour†
9509/3*	Diffuse leptomeningeal glioneuronal tumour
9509/0*	Multinodular and vacuolating neuronal tumour
9493/0	Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)
9506/1	Central neurocytoma
9506/1	Extraventricular neurocytoma
9506/1	Cerebellar liponeurocytoma

Ependymal tumours

9391/3	Supratentorial ependymoma, NOS†
9396/3	Supratentorial ependymoma, *ZFTA* fusion–positive†
9396/3	Supratentorial ependymoma, *YAP1* fusion–positive†
9391/3	Posterior fossa ependymoma, NOS†
9396/3	Posterior fossa group A (PFA) ependymoma†
9396/3	Posterior fossa group B (PFB) ependymoma†
9391/3	Spinal ependymoma, NOS†
9396/3	Spinal ependymoma, *MYCN*-amplified†
9394/1	Myxopapillary ependymoma
9383/1	Subependymoma



ICD-O coding of central nervous system tumours

ICD-O-3.2 ICD-O label (subtypes are indicated in grey text, with the label indented);
Please note that the WHO classification of tumour types is more readily reflected in the table of contents

Choroid plexus tumours

9390/0 Choroid plexus papilloma
9390/1 Atypical choroid plexus papilloma
9390/3 Choroid plexus carcinoma

Embryonal tumours

Medulloblastomas, molecularly defined

9475/3 Medulloblastoma, WNT-activated
9471/3 Medulloblastoma, SHH-activated and *TP53*-wildtype
9476/3 Medulloblastoma, SHH-activated and *TP53*-mutant
9477/3 Medulloblastoma, non-WNT/non-SHH

Medulloblastomas, histologically defined

9470/3 Medulloblastoma, histologically defined
9471/3 Desmoplastic nodular medulloblastoma
9471/3 Medulloblastoma with extensive nodularity
9474/3 Large cell medulloblastoma
9474/3 Anaplastic medulloblastoma

Other CNS embryonal tumours

9508/3 Atypical teratoid/rhabdoid tumour
n/a Cribriform neuroepithelial tumour (provisional entity)
9478/3 Embryonal tumour with multilayered rosettes
9500/3 CNS neuroblastoma, *FOXR2*-activated†
9500/3 CNS tumour with *BCOR* internal tandem duplication†
9473/3 CNS embryonal tumour, NEC/NOS

Pineal tumours

9361/1 Pineocytoma
9362/3 Pineal parenchymal tumour of intermediate differentiation
9362/3 Pineoblastoma
9395/3 Papillary tumour of the pineal region
n/a Desmoplastic myxoid tumour of the pineal region, *SMARCB1*-mutant (provisional entity)

Cranial and paraspinal nerve tumours

9560/0 Schwannoma
9540/0 Neurofibroma
9550/0 Plexiform neurofibroma
9571/0 Perineurioma
9563/0 Hybrid nerve sheath tumour
9540/3 Malignant melanotic nerve sheath tumour
9540/3 Malignant peripheral nerve sheath tumour
8693/3 Cauda equina neuroendocrine tumour (previously paraganglioma)

Meningioma

9530/0 Meningioma

Mesenchymal, non-meningothelial tumours involving the CNS

Fibroblastic and myofibroblastic tumours

8815/1 Solitary fibrous tumour

Vascular tumours

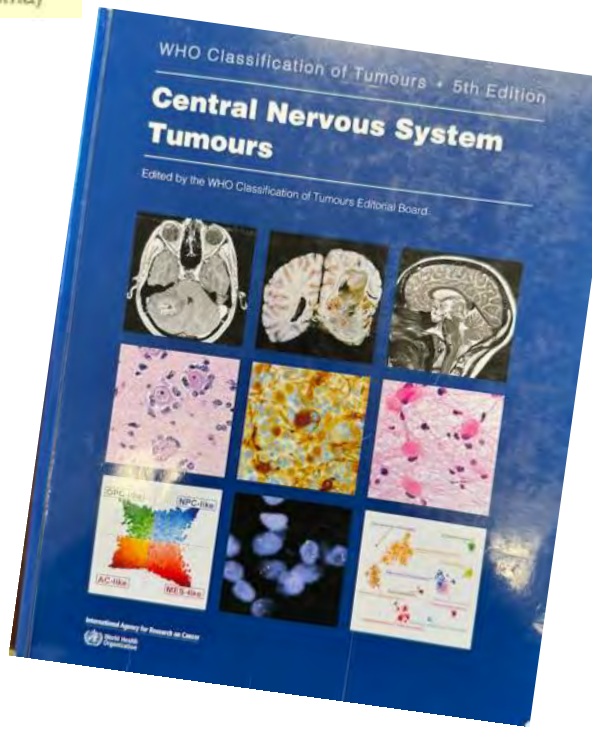
9121/0 Cavernous haemangioma
9131/0 Capillary haemangioma
9123/0 Arteriovenous malformation
9161/1 Haemangioblastoma

Skeletal muscle tumours

8910/3 Embryonal rhabdomyosarcoma
8920/3 Alveolar rhabdomyosarcoma
8901/3 Rhabdomyosarcoma, pleomorphic-type
8912/3 Spindle cell rhabdomyosarcoma

Tumours of uncertain differentiation

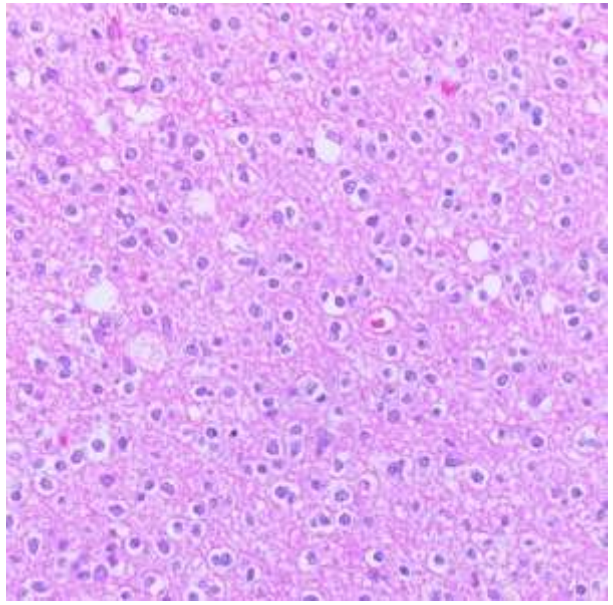
n/a Intracranial mesenchymal tumour, FET::CREB fusion–positive (provisional entity)
9367/3 *CIC*-rearranged sarcoma
9480/3 Primary intracranial sarcoma, *DICER1*-mutant†
9364/3 Ewing sarcoma

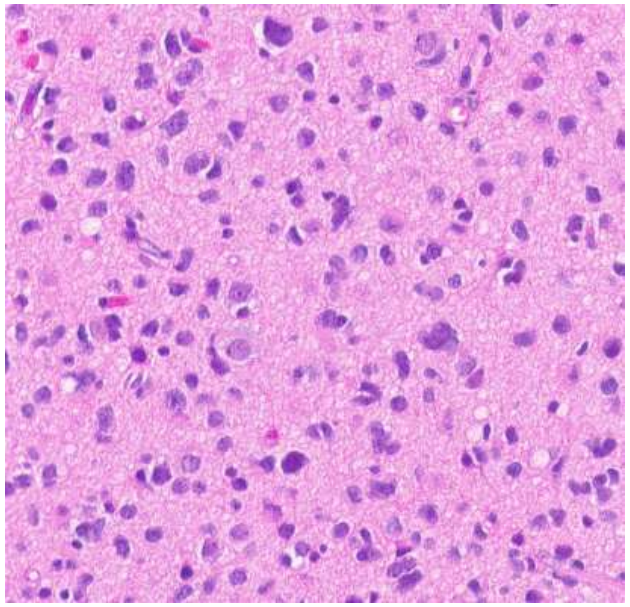


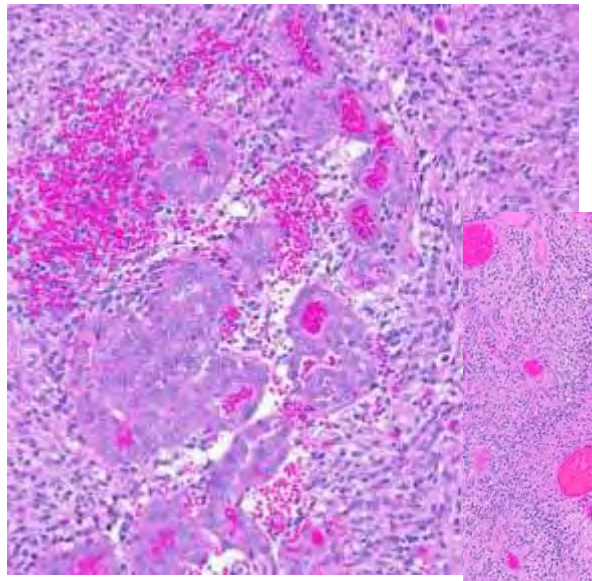
2007 CNS WHO (4th Edition)

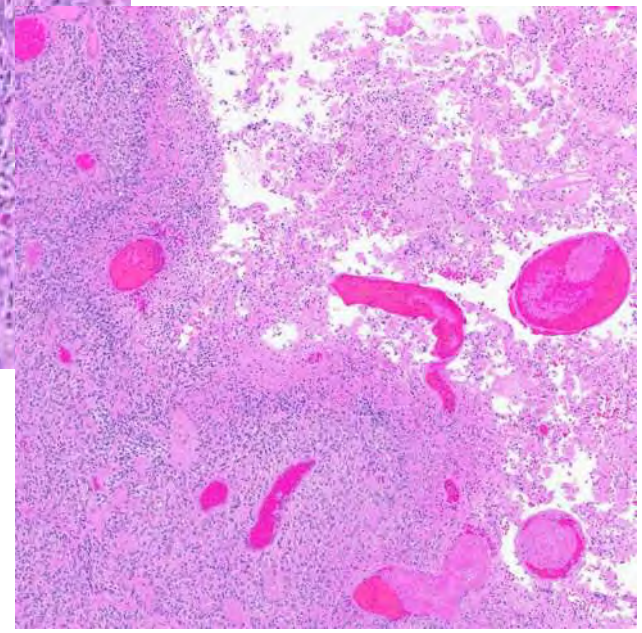
Adult Infiltrating Gliomas

- Oligodendroglioma
- Oligoastroctyoma
- Astrocytoma
- microvascular proliferation (or) necrosis → Glioblastoma









Adult Infiltrating Gliomas

2016 CNS WHO
(4th Edition Revised)

microvascular proliferation (or) necrosis

Oligodendroglioma

IDH1/2-mutant 1p/19q co-deleted

Oligodendroglioma, IDH-mutant, 1p/19q co-deleted
WHO grade 2

mitoses, necrosis, MVP

Anaplastic oligodendroglioma, IDH-mutant, 1p/19q co-deleted
WHO grade 3

Classic features:
*TERT*p mutation
*MGMT*p methylation

~~Oligoastroctyoma~~

ATRX loss & 1p/19q co-del mutually exclusive

Astrocytoma

Non-1p/19q co-deleted

Diffuse astrocytoma, IDH-mutant/wildtype
WHO grade 2

mitoses

Anaplastic astrocytoma, IDH-mutant/wildtype
WHO grade 3

rare cases of IDH-wildtype lower-grade astrocytomas

Classic features:
IDH1/2 mutation
ATRX loss
TP53 mutation
*MGMT*p methylation

Glioblastoma

IDH1/2-mutant

Glioblastoma, IDH-mutant
WHO grade 4
"secondary GBM"

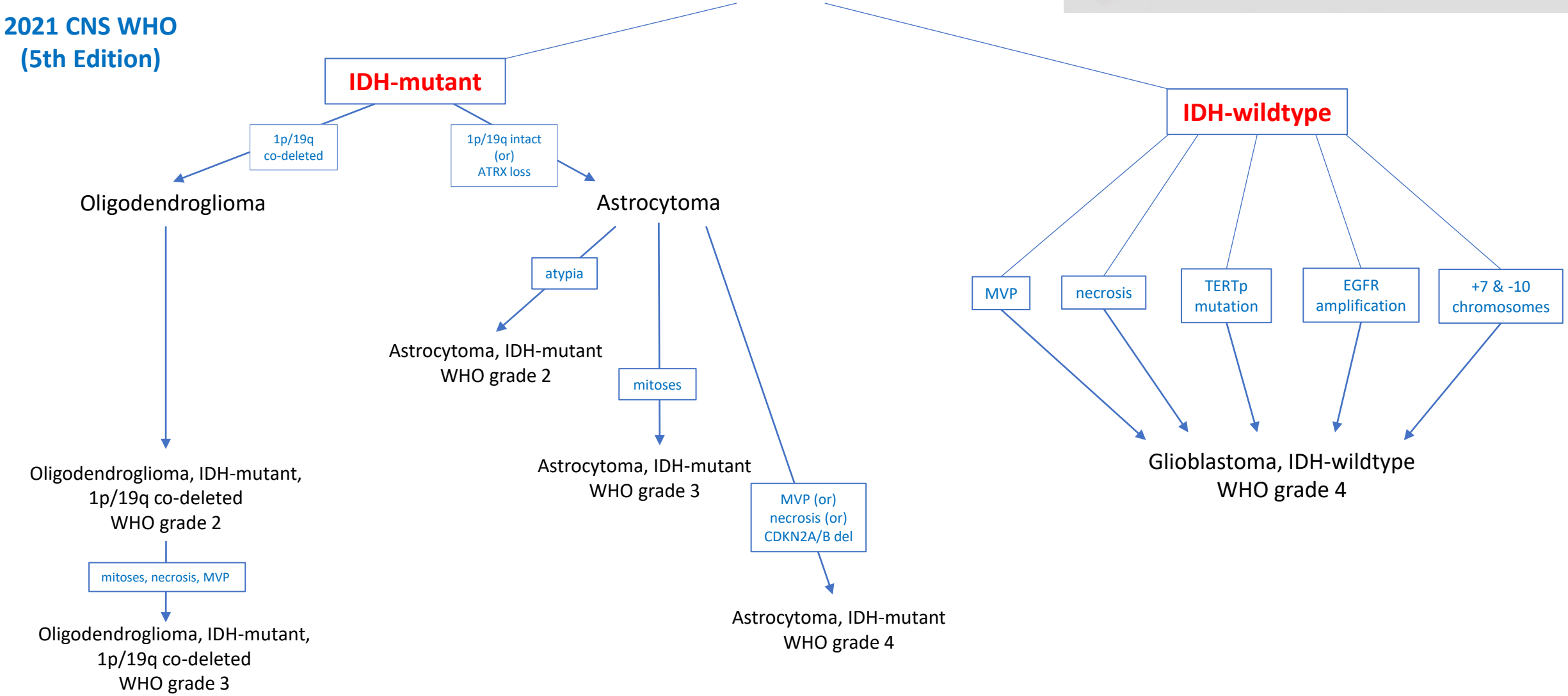
IDH1/2-wildtype

Glioblastoma, IDH-wildtype
WHO grade 4
"primary GBM"

Classic features:
*TERT*p mutation
EGFR amplification
PTEN mutation

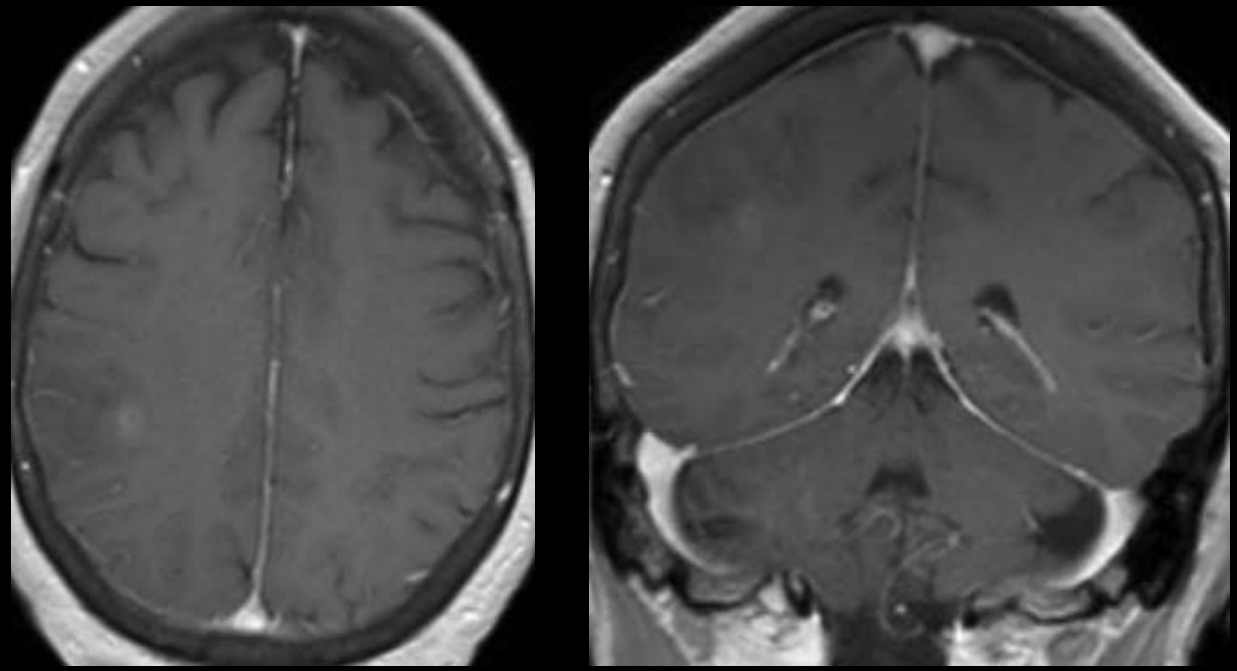
Adult Infiltrating Gliomas

2021 CNS WHO (5th Edition)

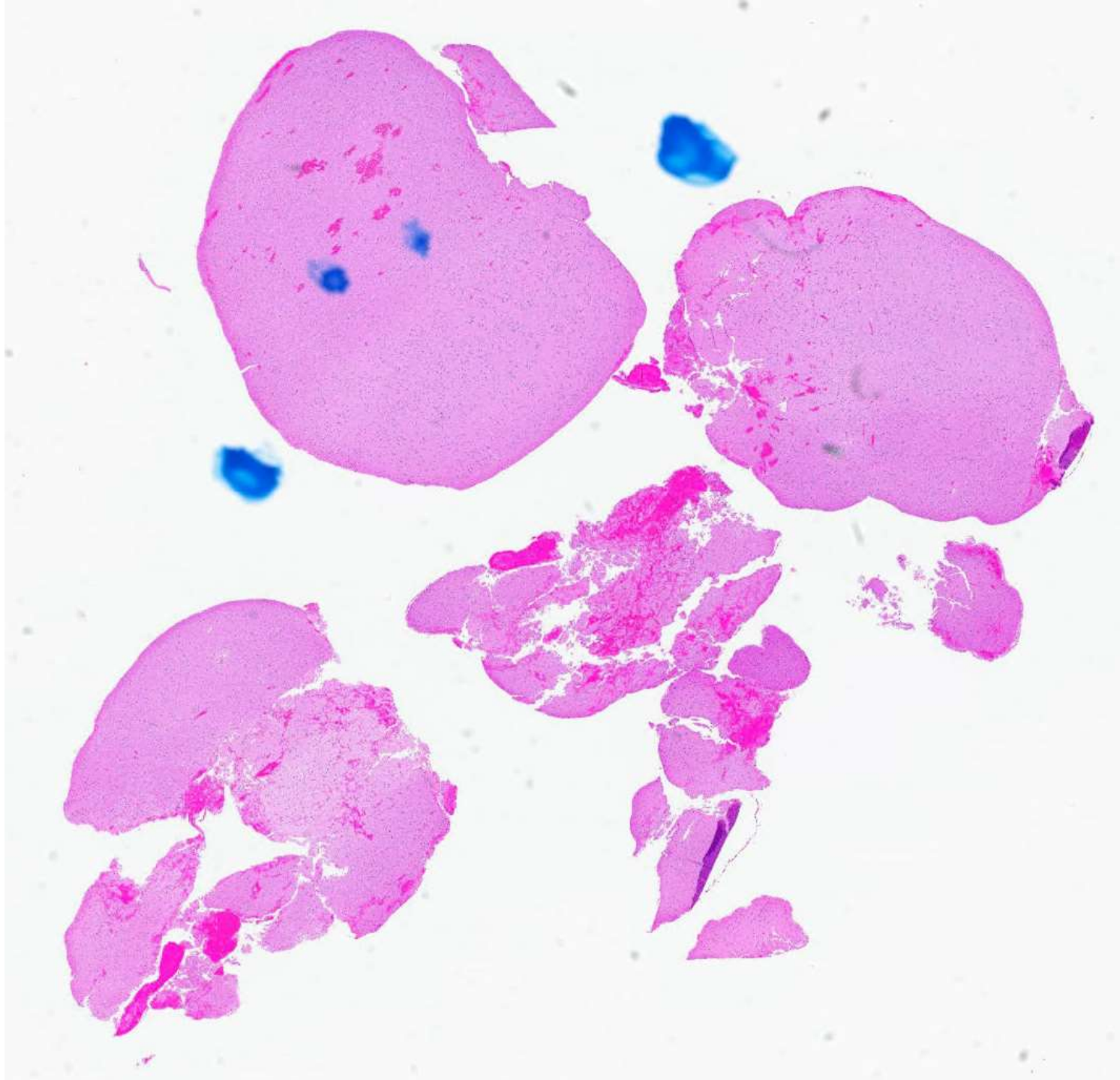


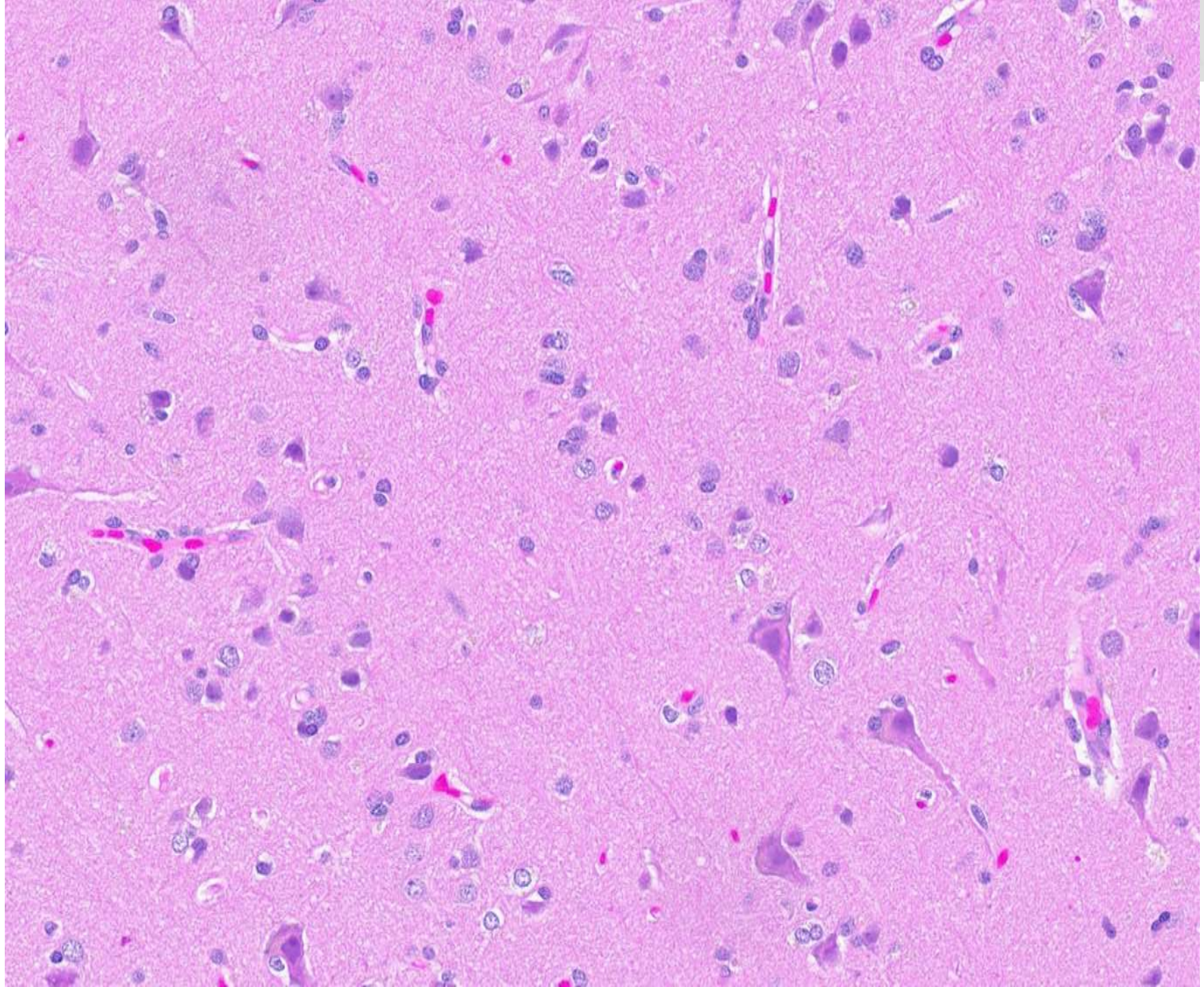
Classic features:
*TERT*p mutation
*MGMT*p methylation

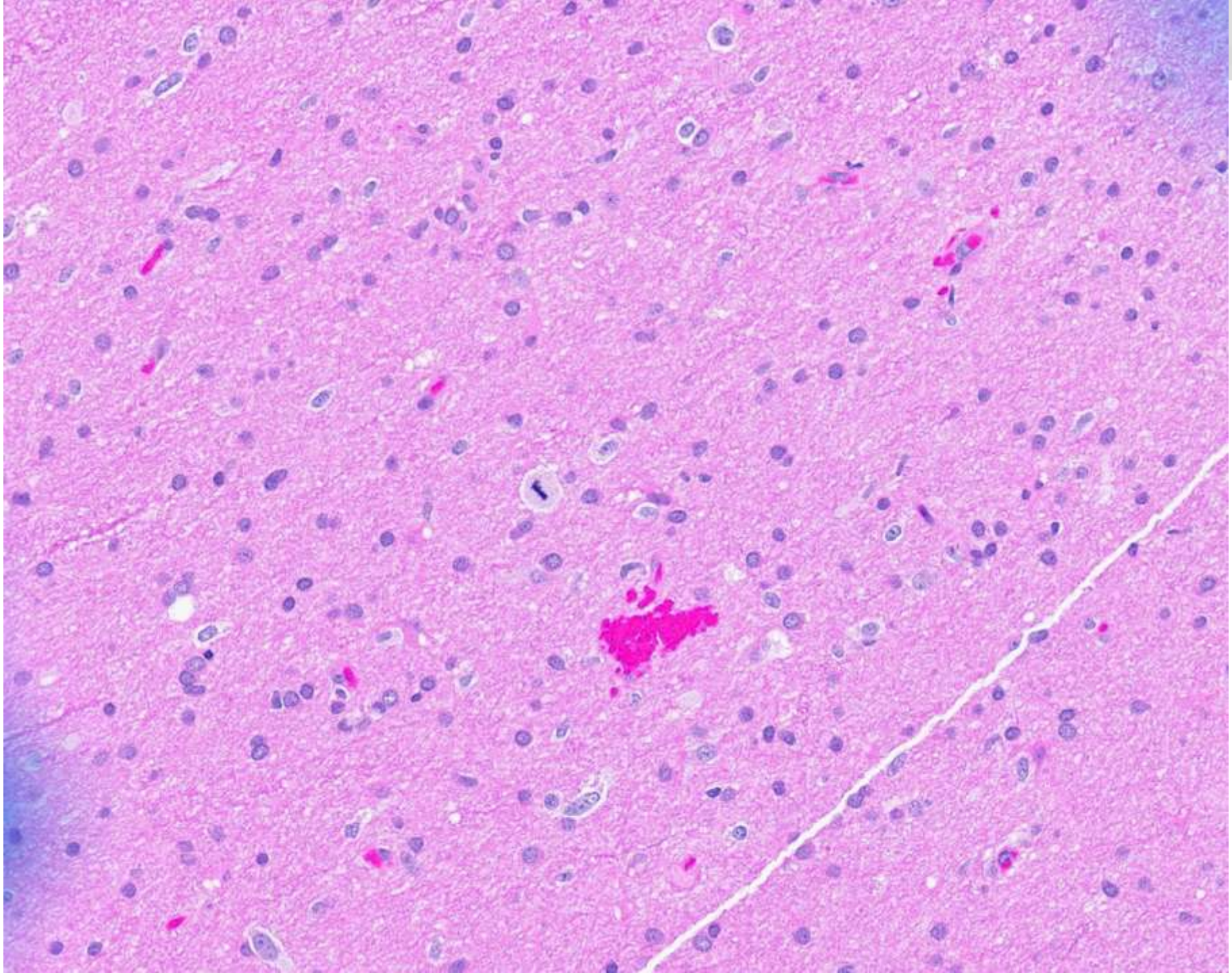
74F admitted to OSH with possible amphetamine overdose and was found to have a brain lesion



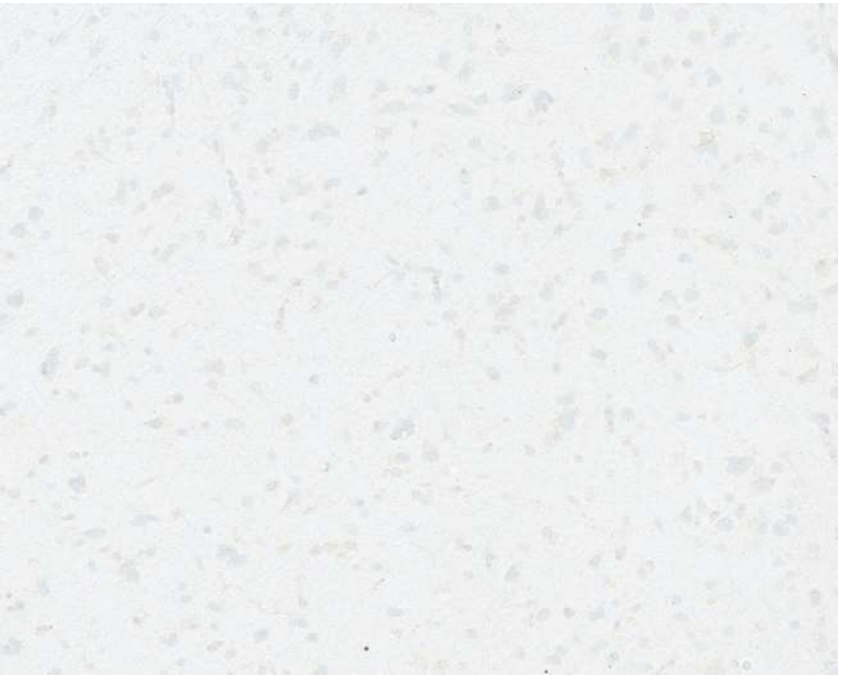
T1 +C



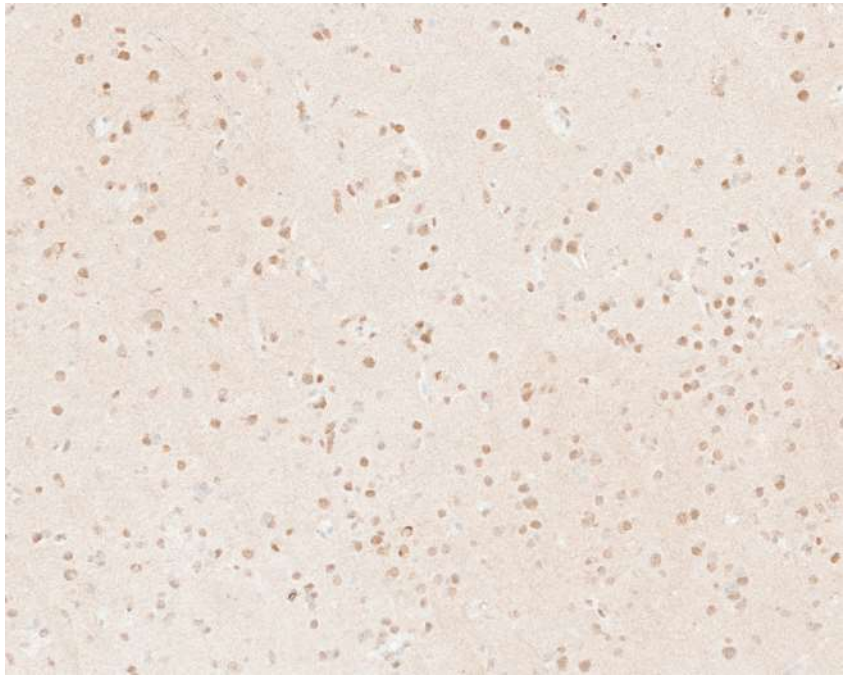




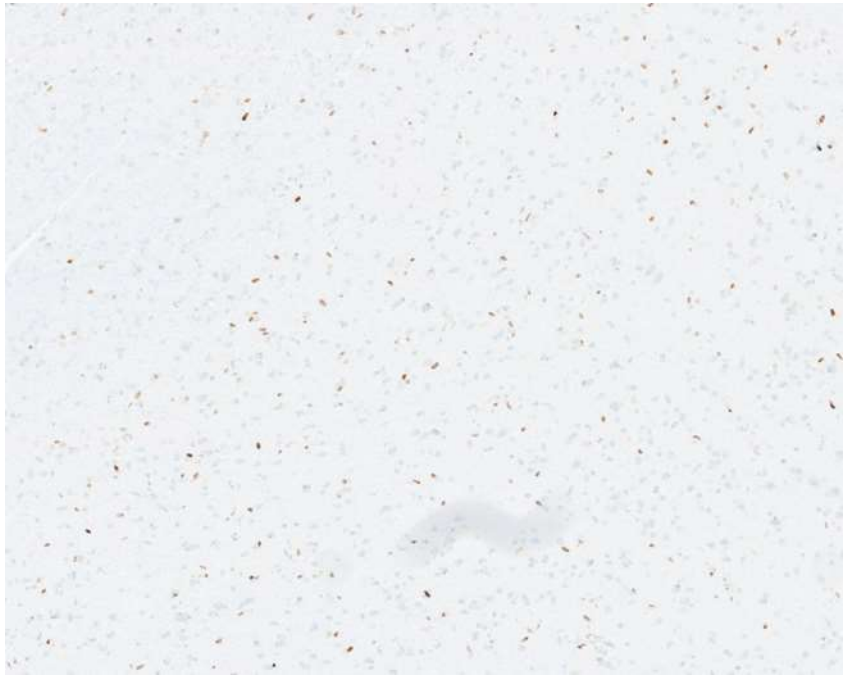
Ki67



IDH1 p.R132H

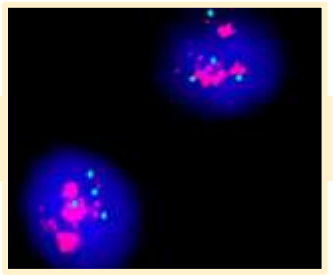


ATRX



p53

Fluorescent In Situ Hybridization (*EGFR*, *PTEN*):



EGFR (7p11.2) FISH Analysis Final Report

AMPLIFICATION of *EGFR* (7p11.2) with five copies of chromosome 7 centromere in 45% of cells.

PTEN (10q23.32) FISH Analysis Final Report

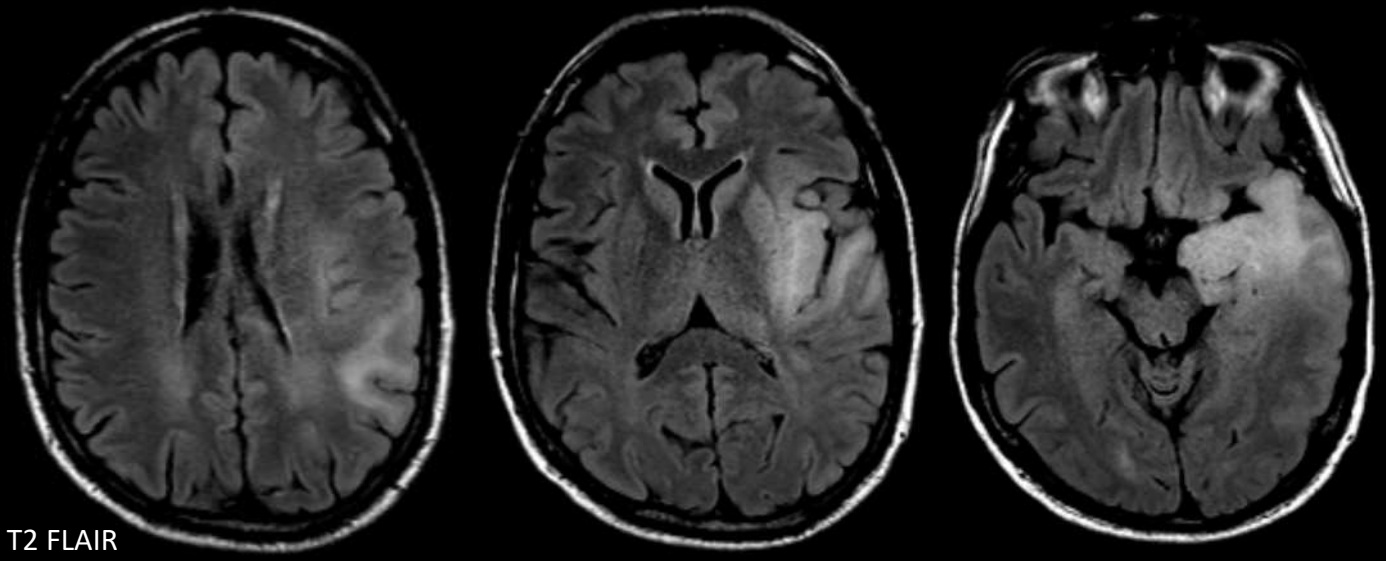
ABNORMAL and consistent with monosomy 10 in 54% of cells.

Brain, right parietal lesion, stereotactic biopsy:

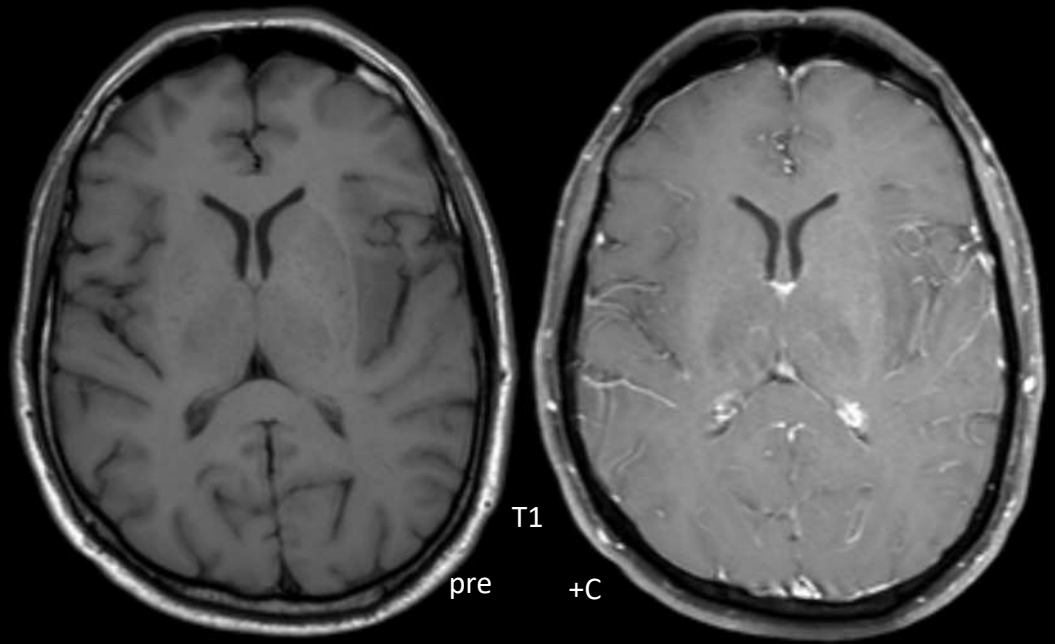
Glioblastoma, IDH-wildtype
CNS WHO grade 4

IDH1 (IHC): Negative for p.R132H mutant protein expression
EGFR/Ch7 (FISH): POSITIVE for *EGFR* amplification; POSITIVE for Ch7 gain (45%)
PTEN/Ch10 (FISH): Negative for *PTEN* deletion; POSITIVE for Ch10 monosomy (54%)
MGMT (methyl-PCR): POSITIVE for promoter hypermethylation

61M who presented with 3-month history of hot flashes, speech difficulties, and forgetfulness

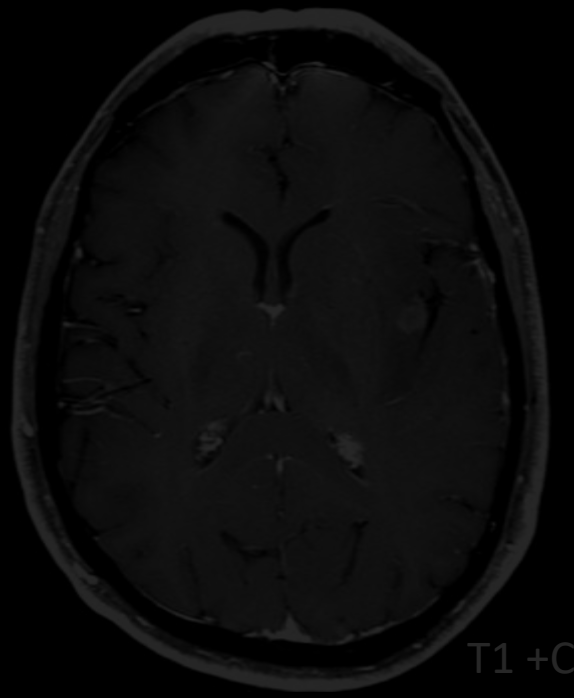


T2 FLAIR



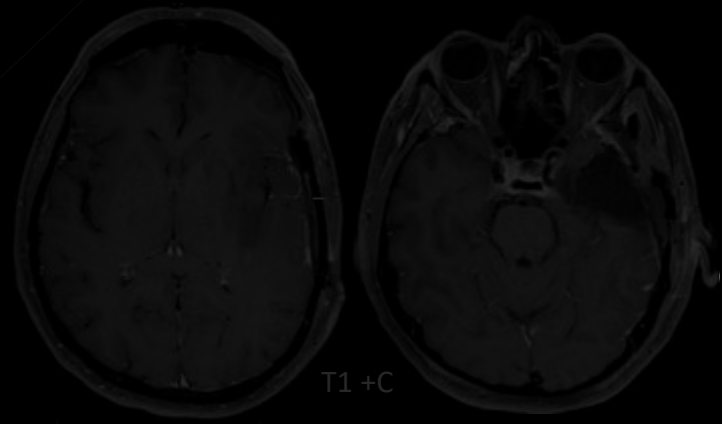
T1

pre +C



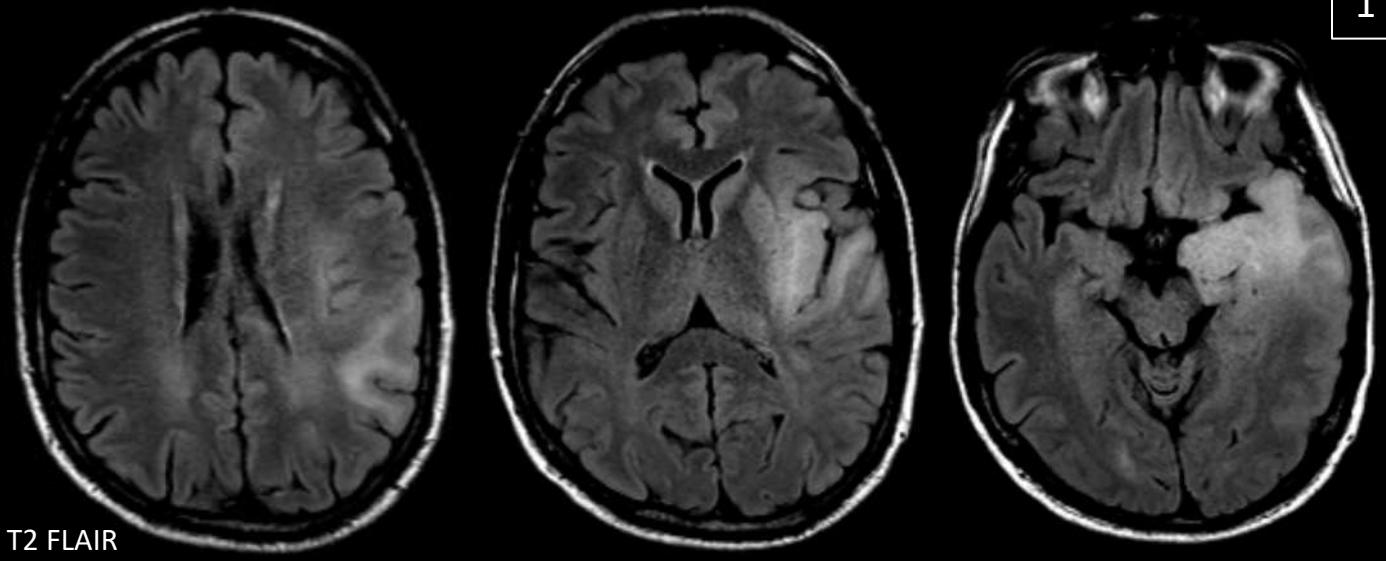
T1 +C

Post-operative MRI – contrast-enhancing area not sampled

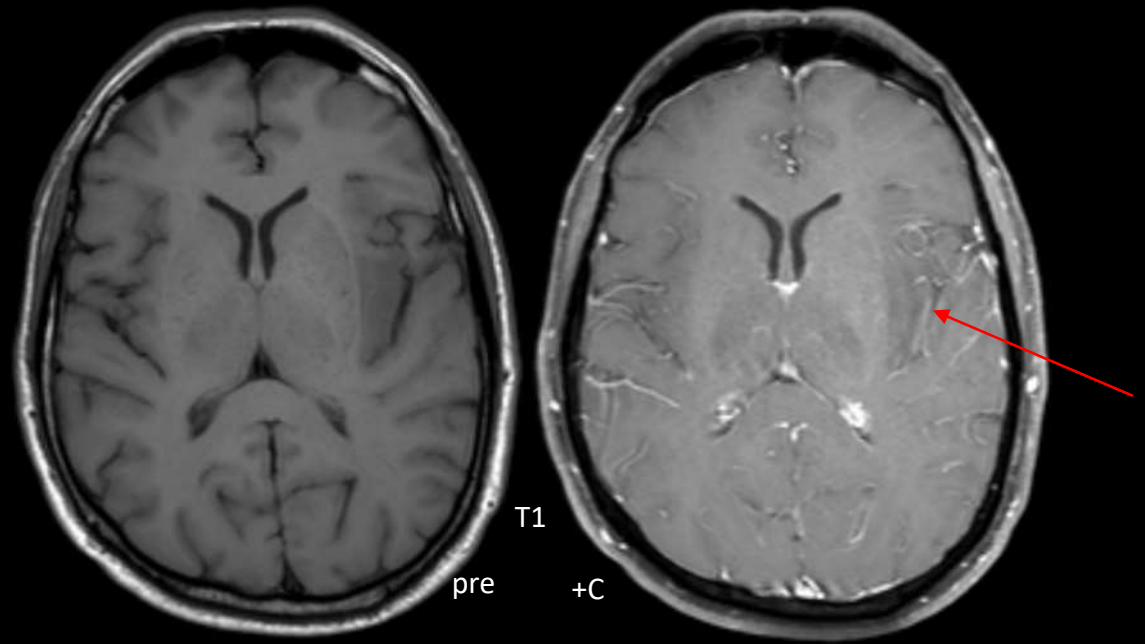


T1 +C

61M who presented with 3-month history of hot flashes, speech difficulties, and forgetfulness



T2 FLAIR

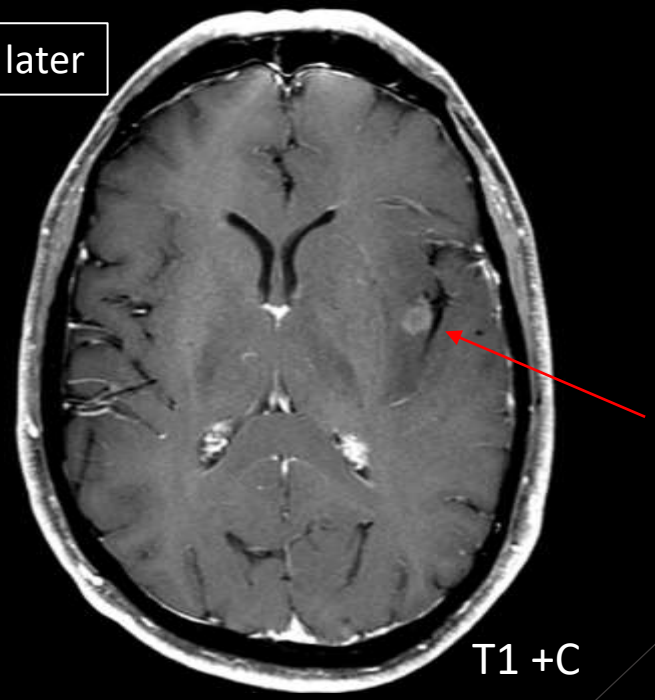


T1

pre

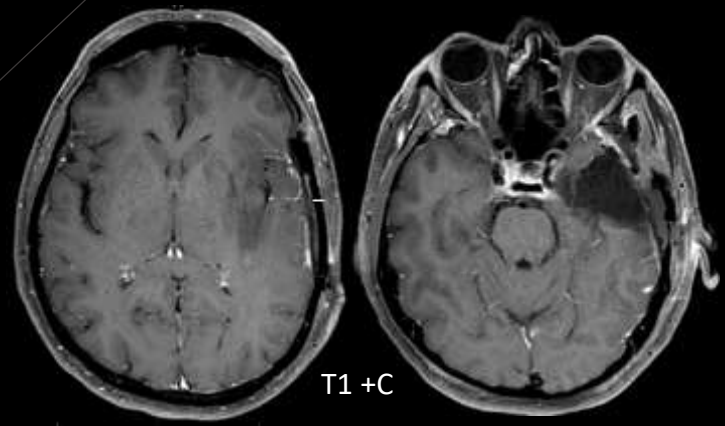
+C

1 month later

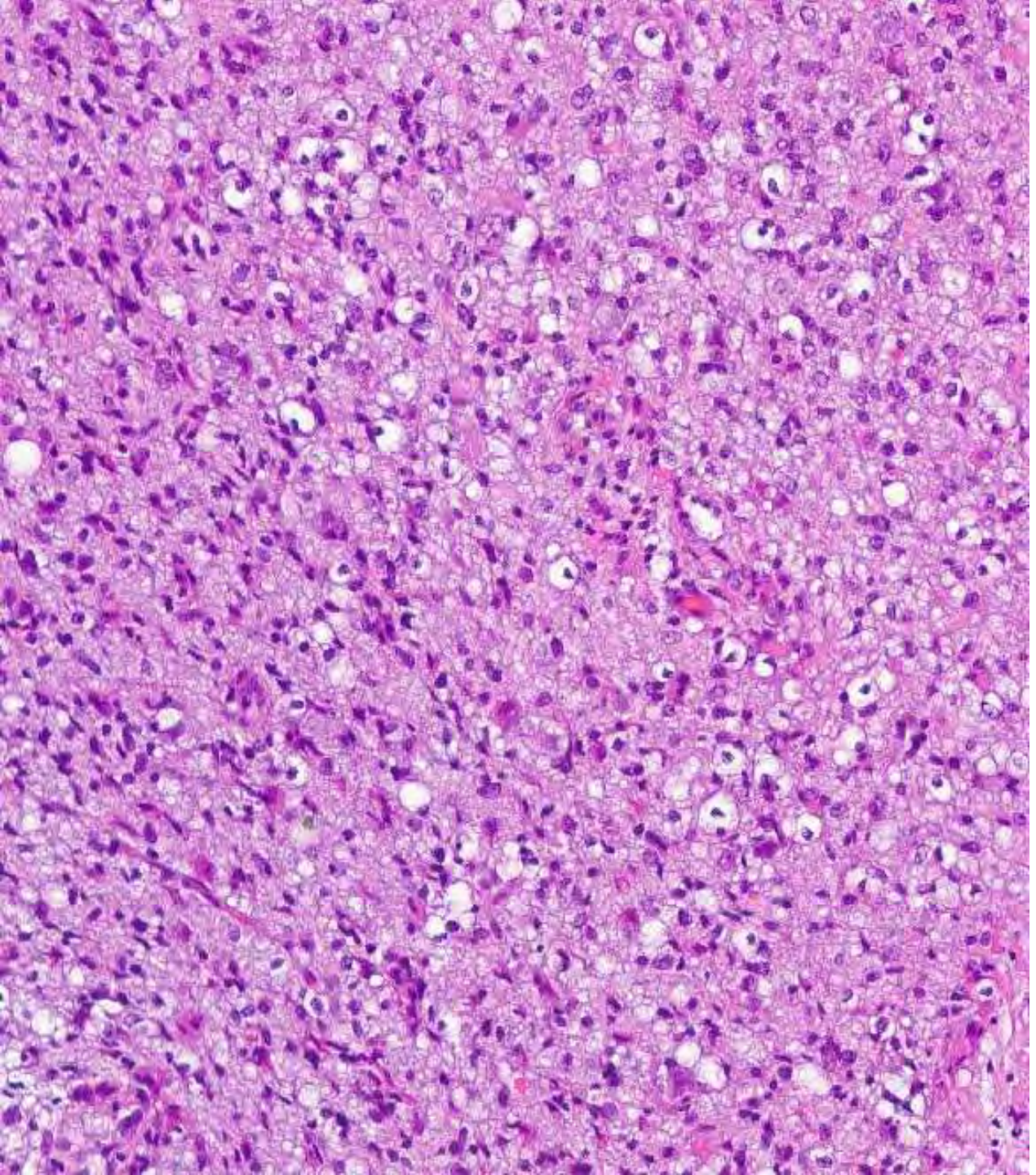


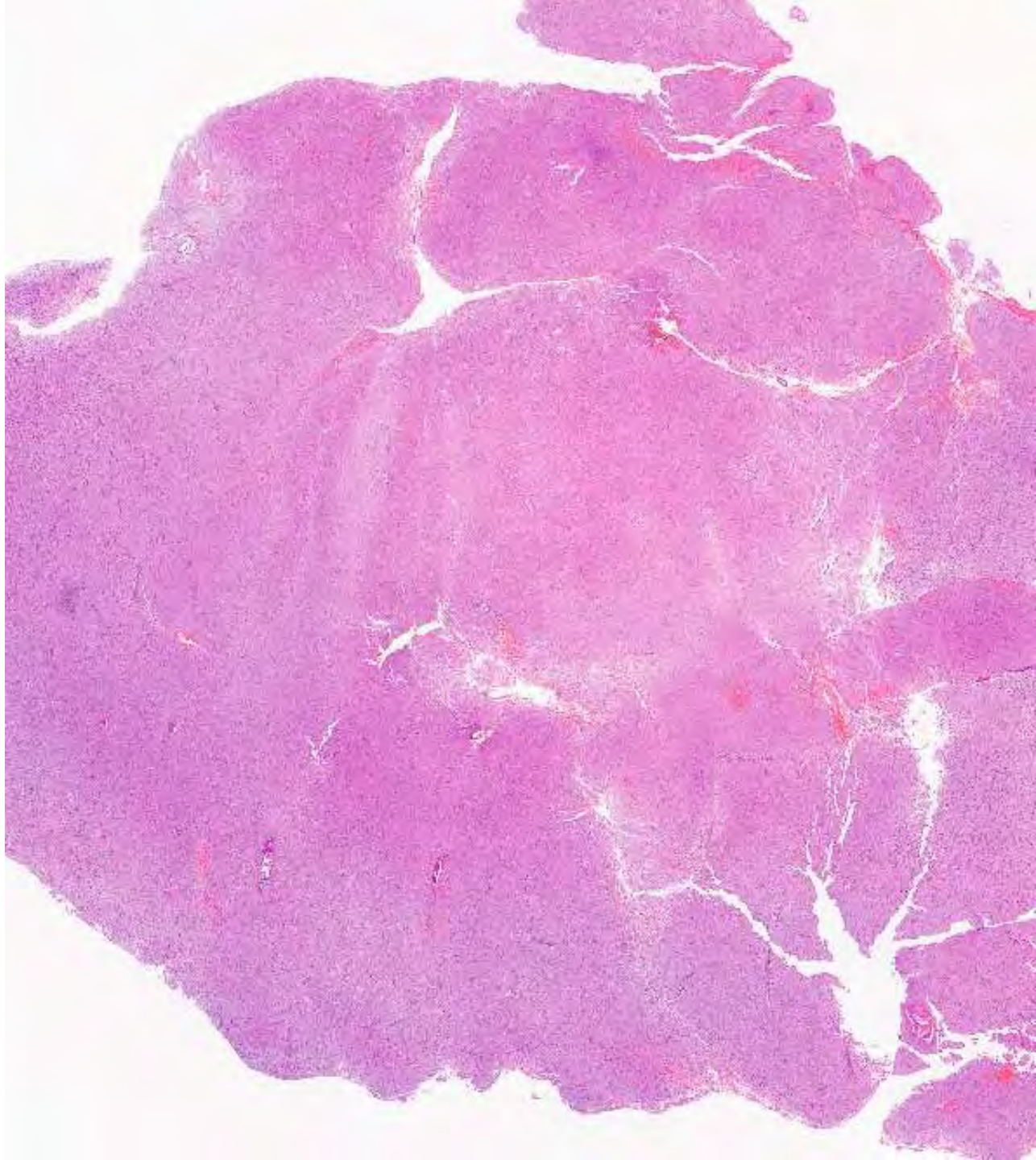
T1 +C

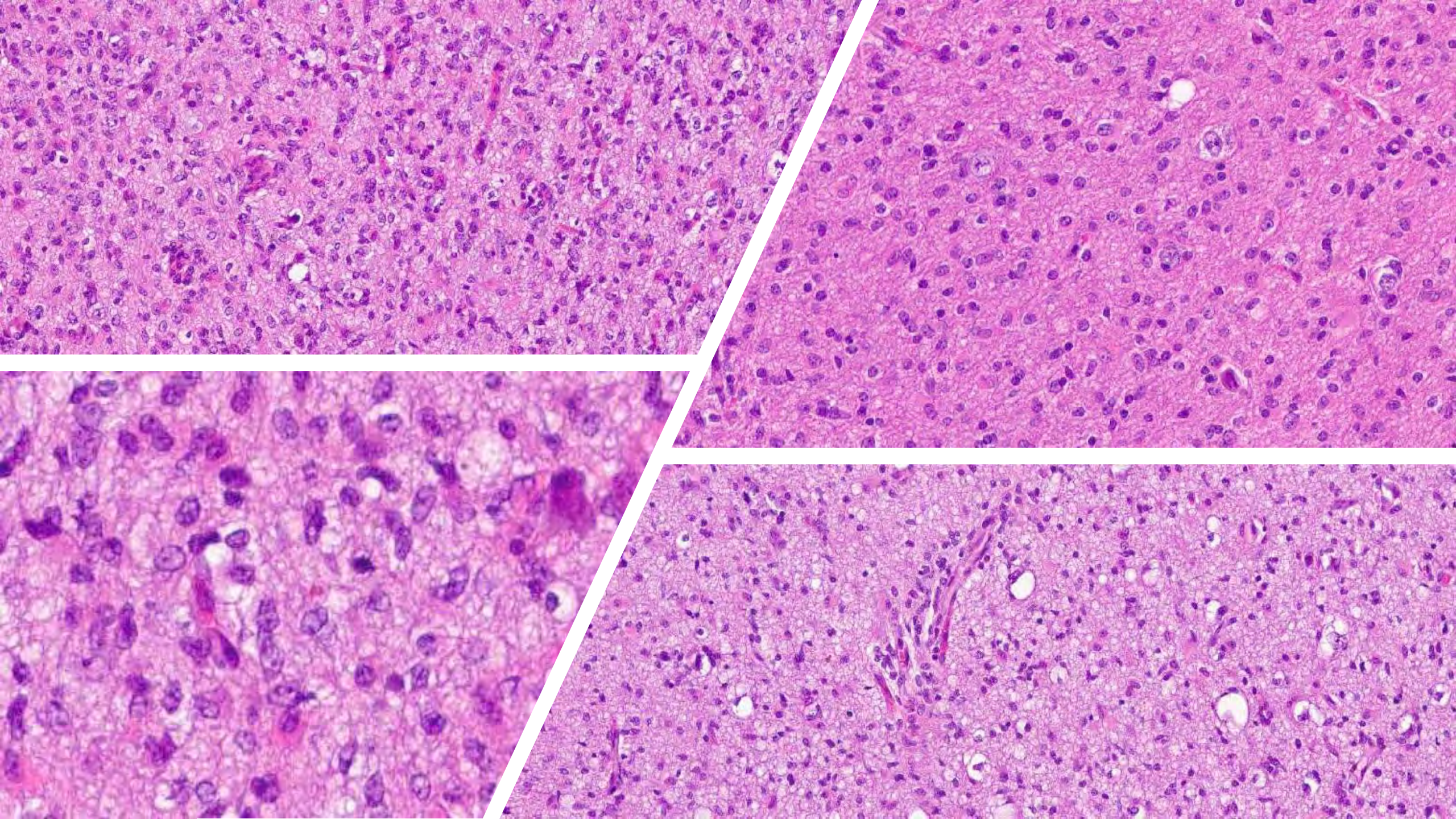
Post-operative MRI – contrast-enhancing area not sampled



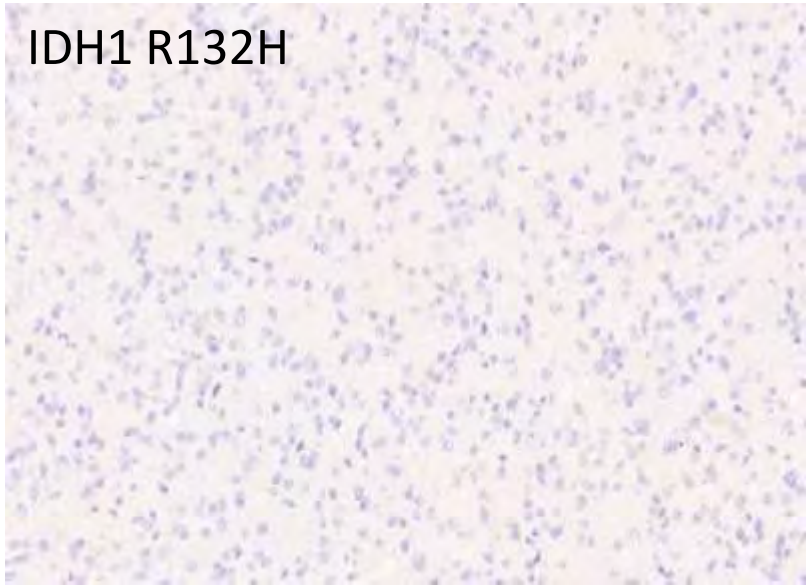
T1 +C



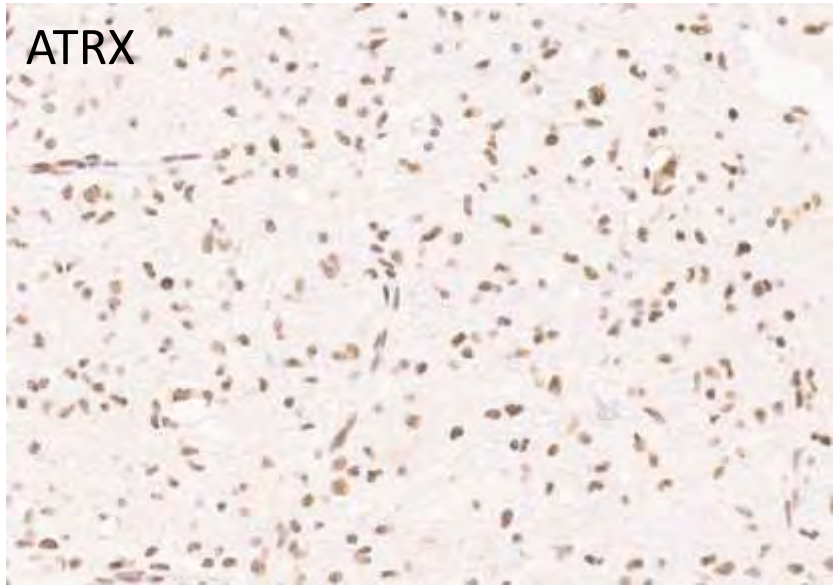




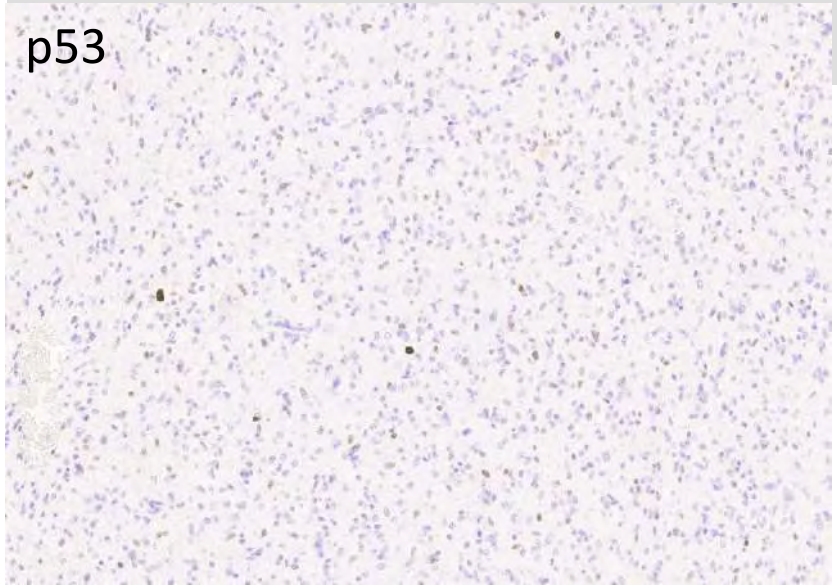
IDH1 R132H



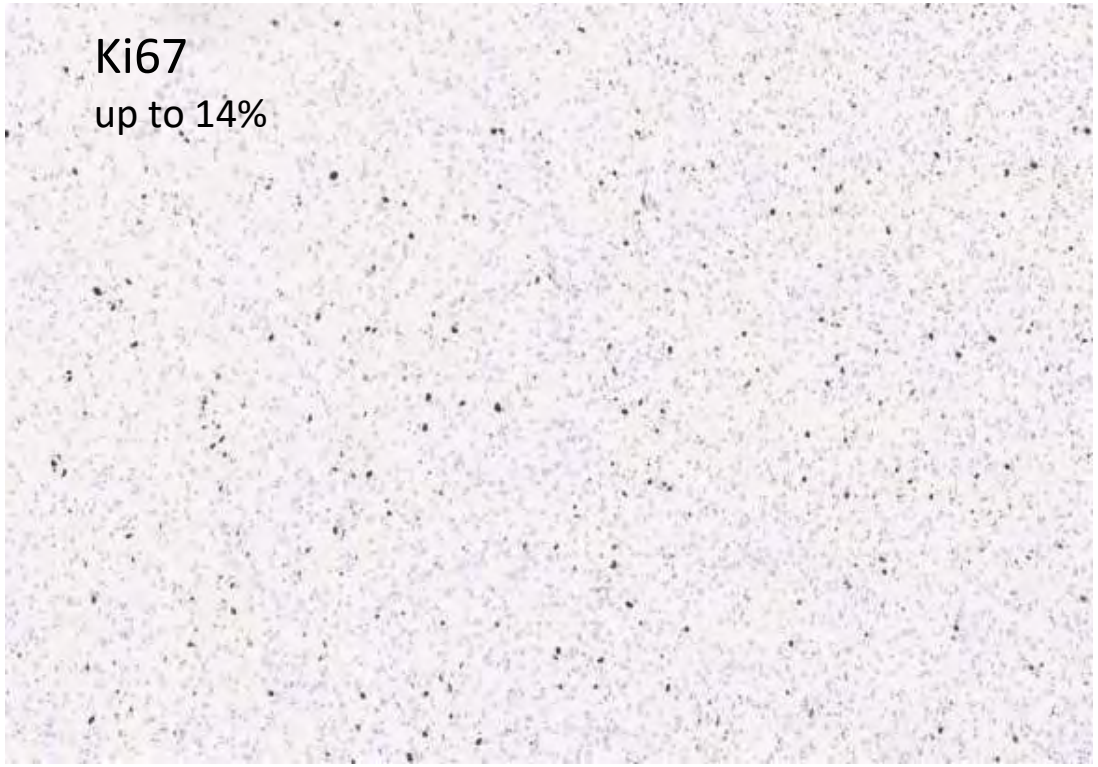
ATRX



p53

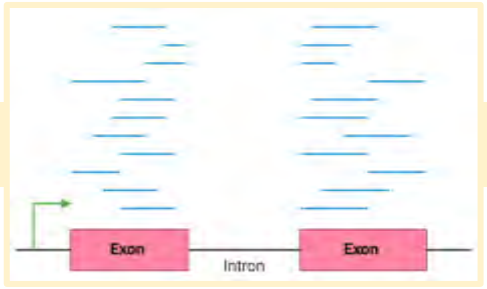


Ki67
up to 14%



Mitoses – up to 4 per 10 HPF

Next-Generation Sequencing Panel:



Copy Number Variations

CDK4	Amplification	12q14.1
EGFR	Amplification	7p11.2
MDM4	Amplification	1q32.1

Somatic Mutations

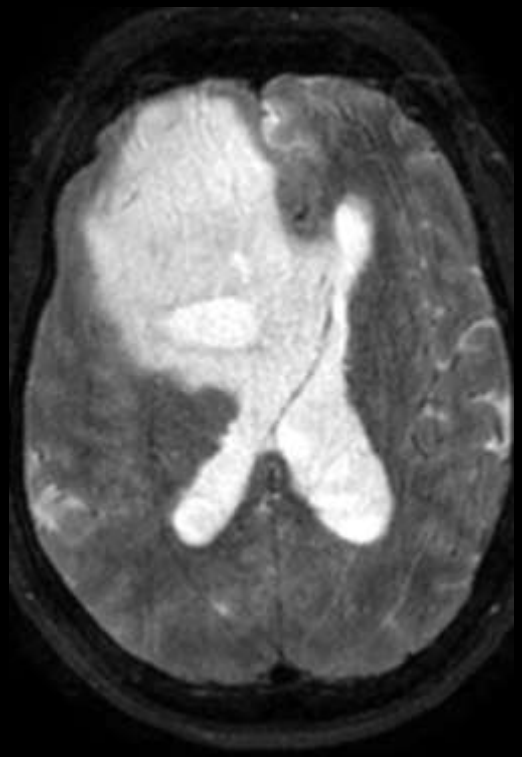
EGFR	p.R108K	(pathogenic)
TERT	c.-124C>T	(pathogenic)

Brain, left temporal lobe, awake craniotomy with resection:

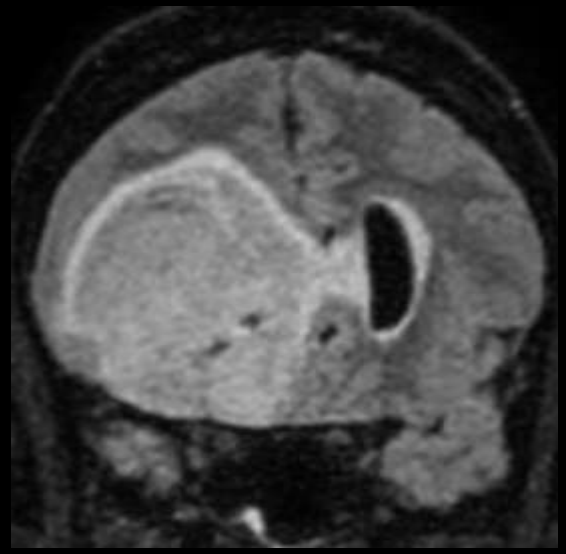
Glioblastoma, IDH-wildtype
CNS WHO grade 4

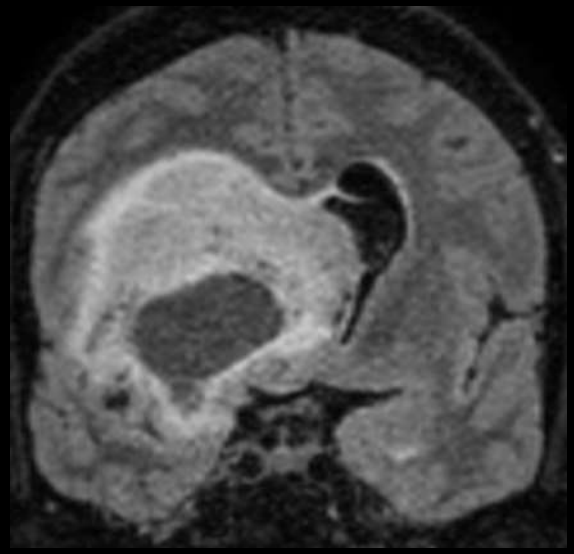
IDH1/2 (NGS): Negative for mutations
TERT (NGS): POSITIVE for c.-124C>T mutation
EGFR (NGS): POSITIVE for amplification and p.R108K mutation
CDK4 (NGS): Positive for amplification
MDM4 (NGS): Positive for amplification

59F who presented with altered mental status over the past few days



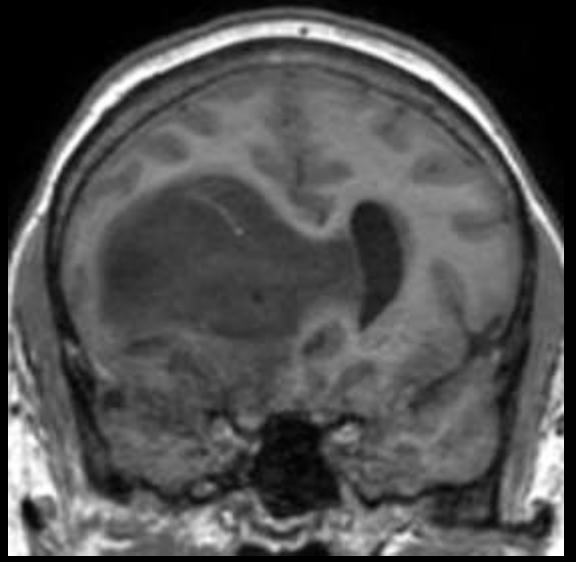
T2

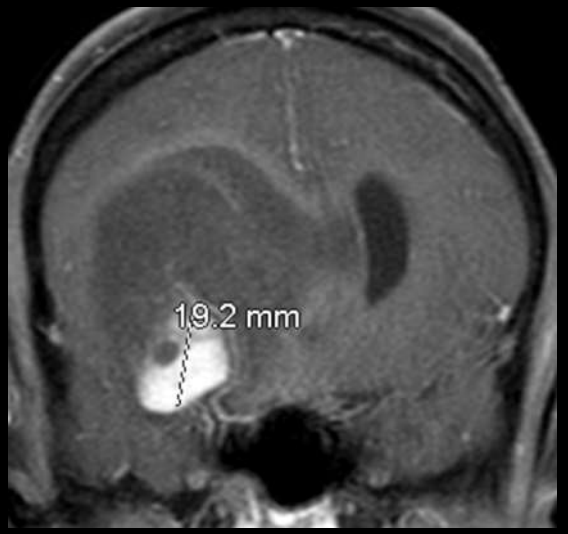




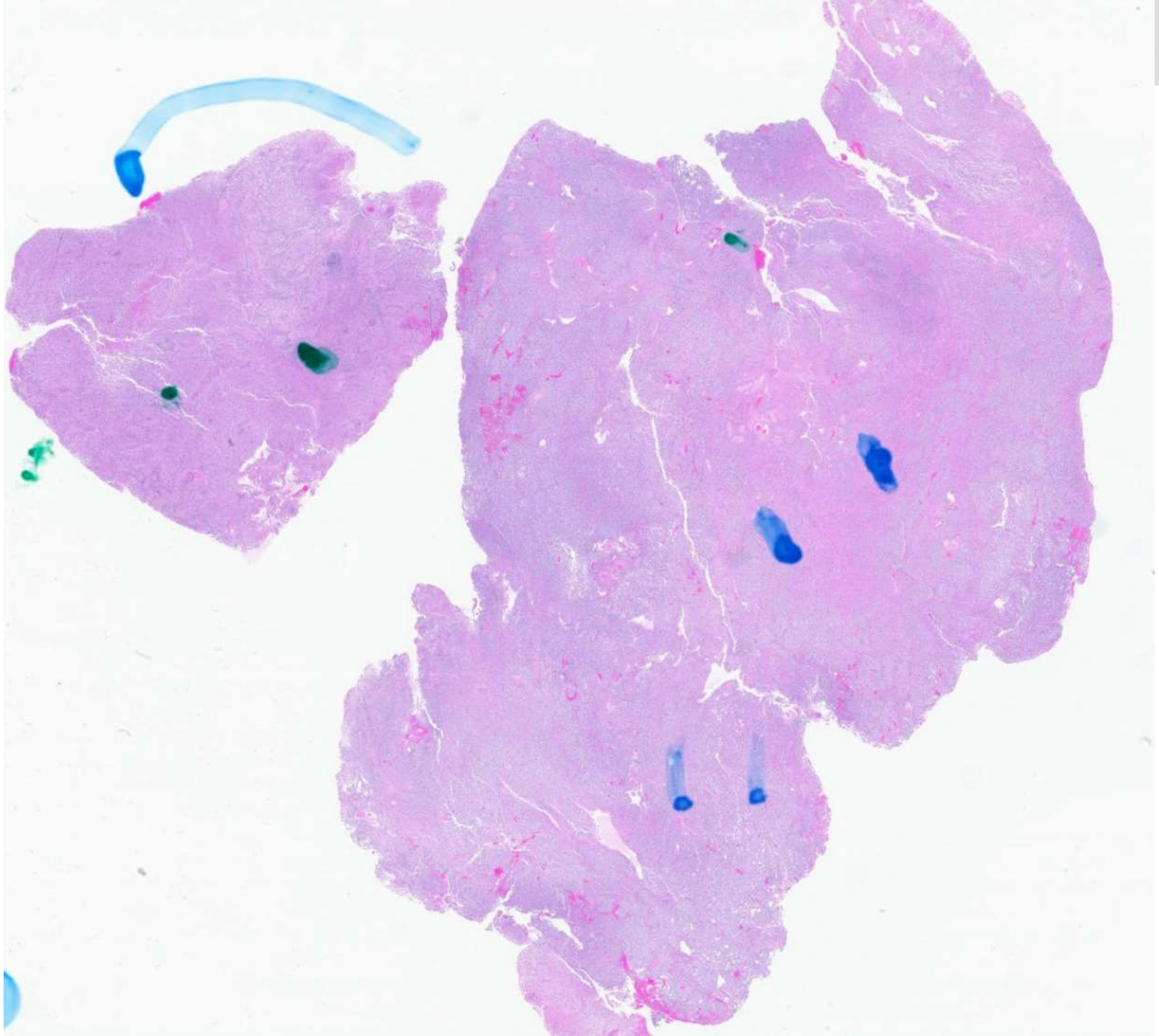
T2 FLAIR

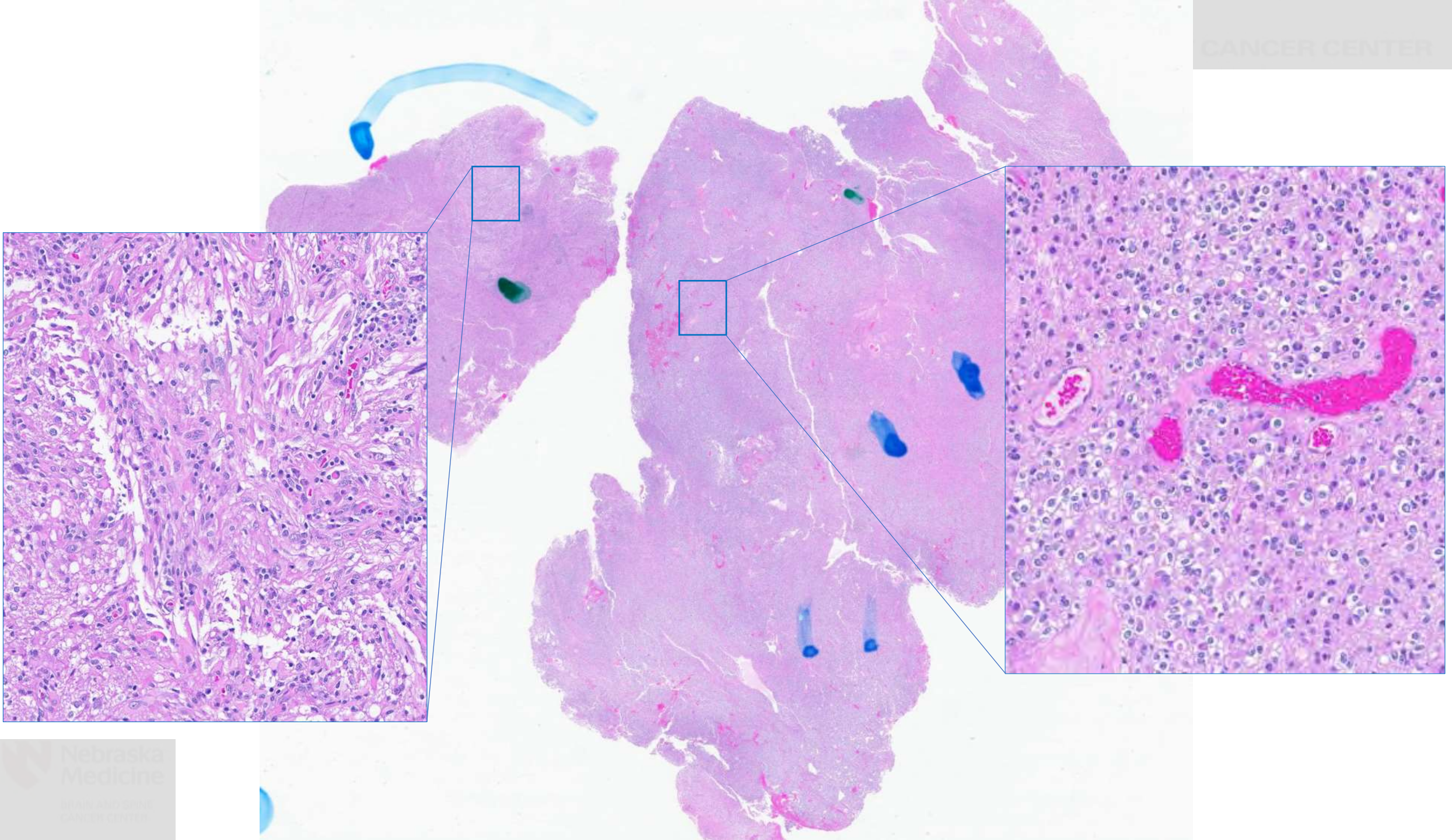
T1

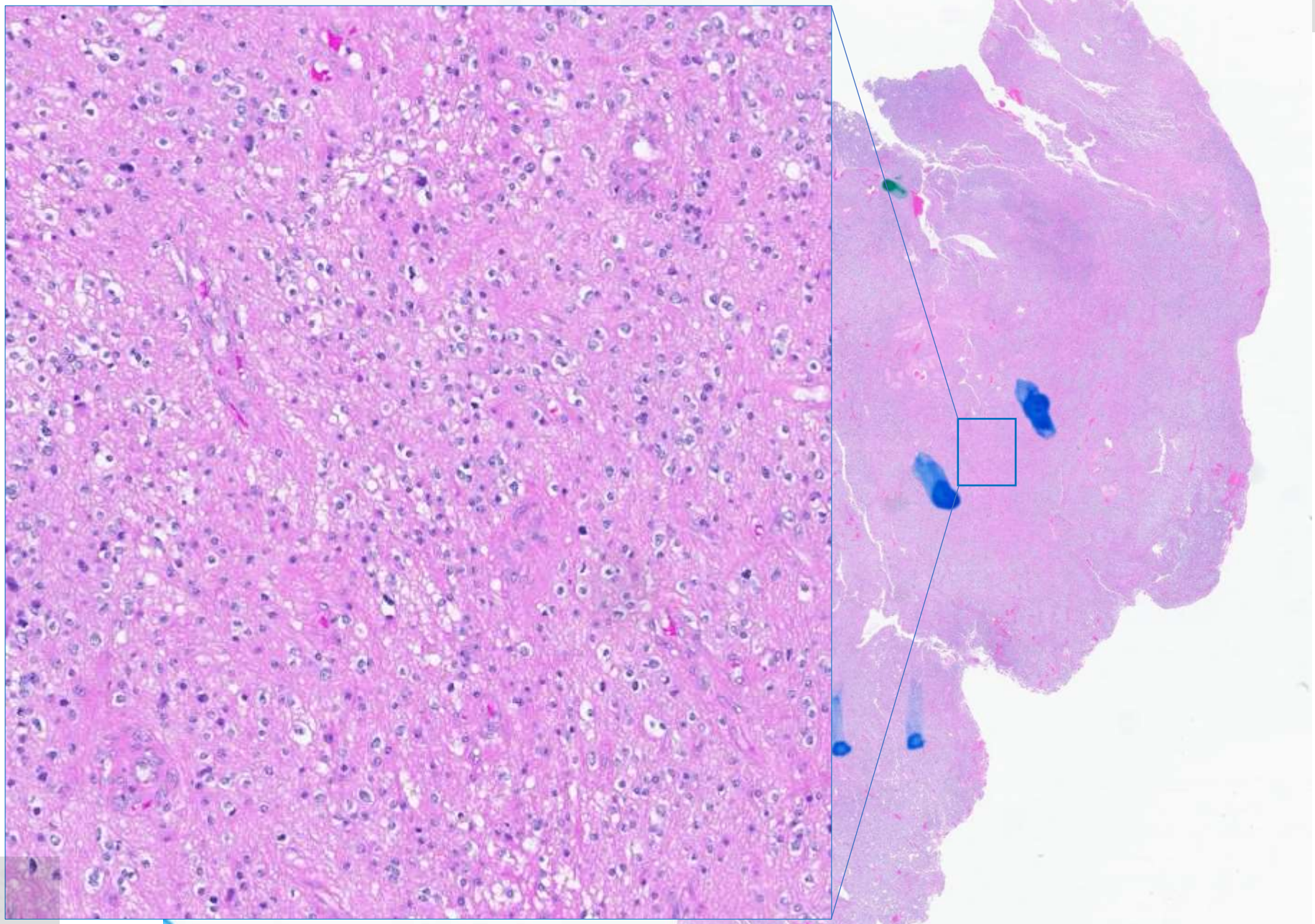


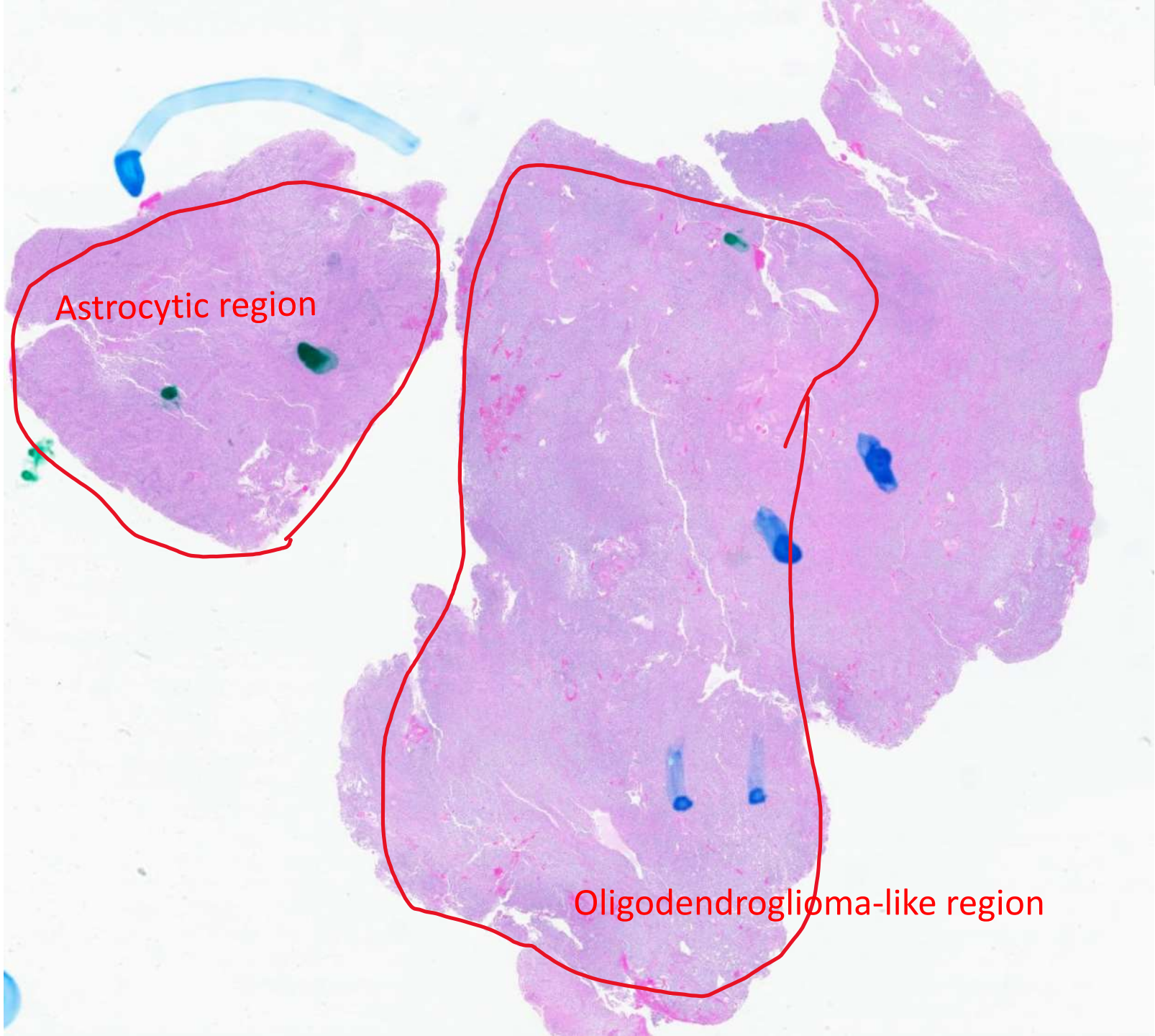


T1 +C

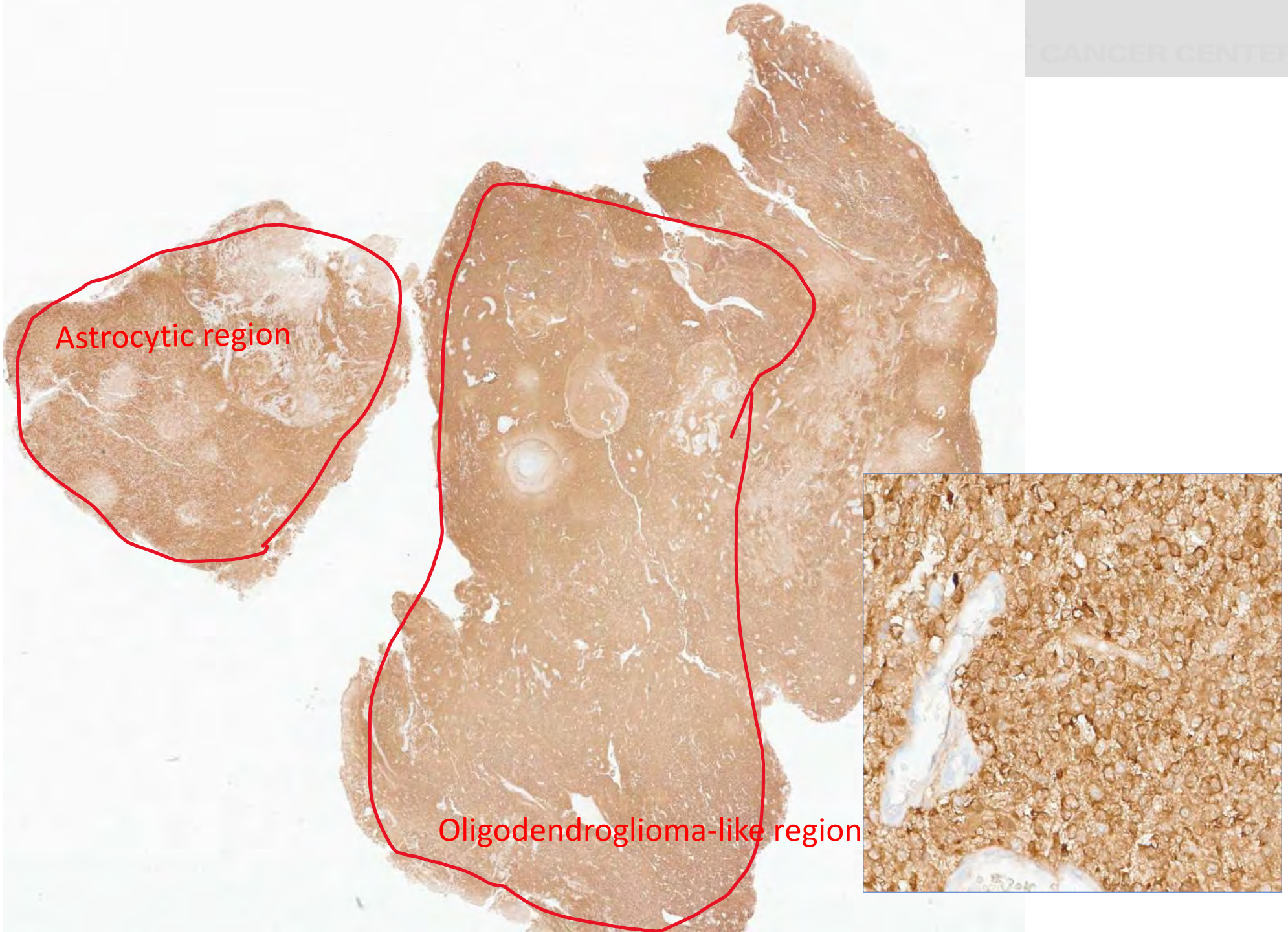






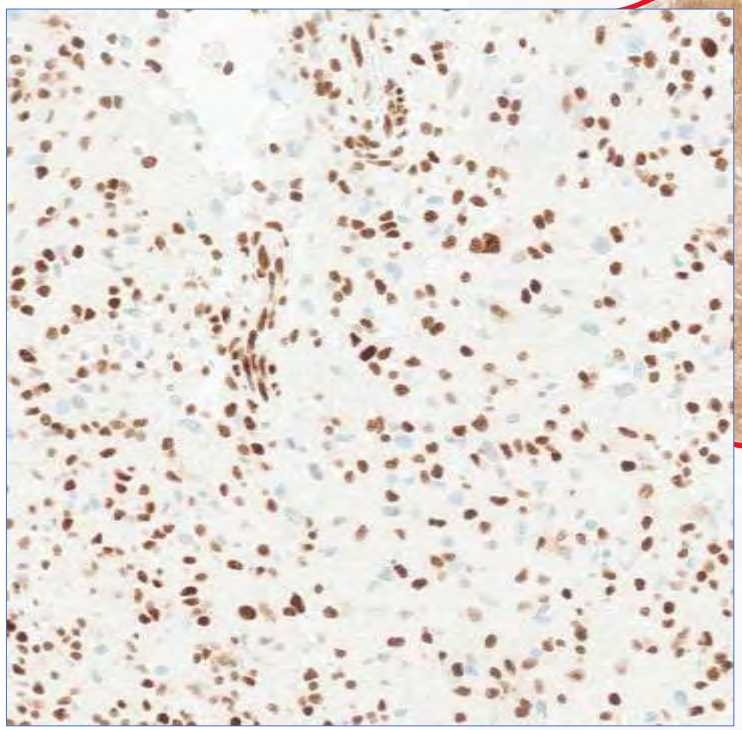

Astrocytic region
Oligodendroglioma-like region

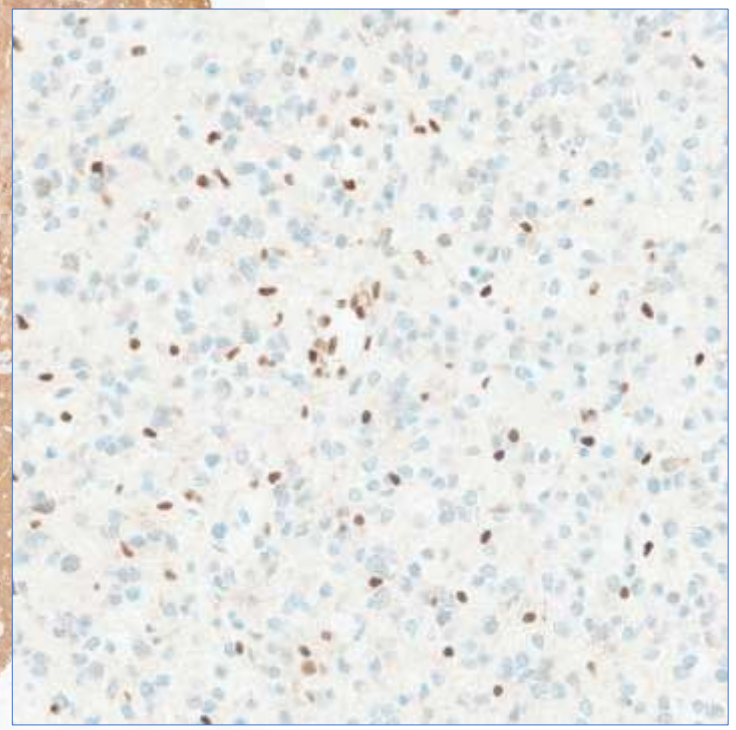
IDH1 p.R132H



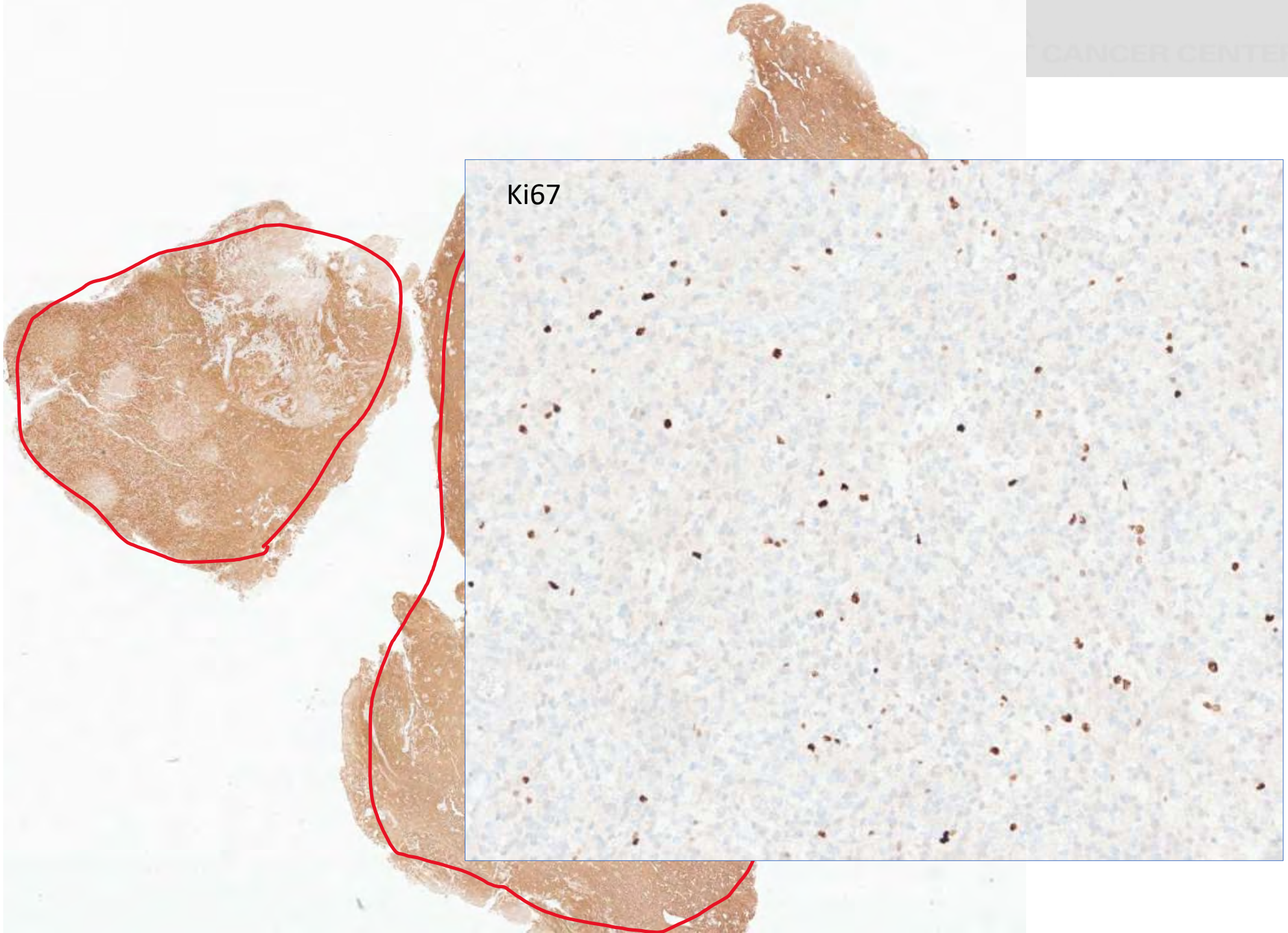
IDH1 p.R132H

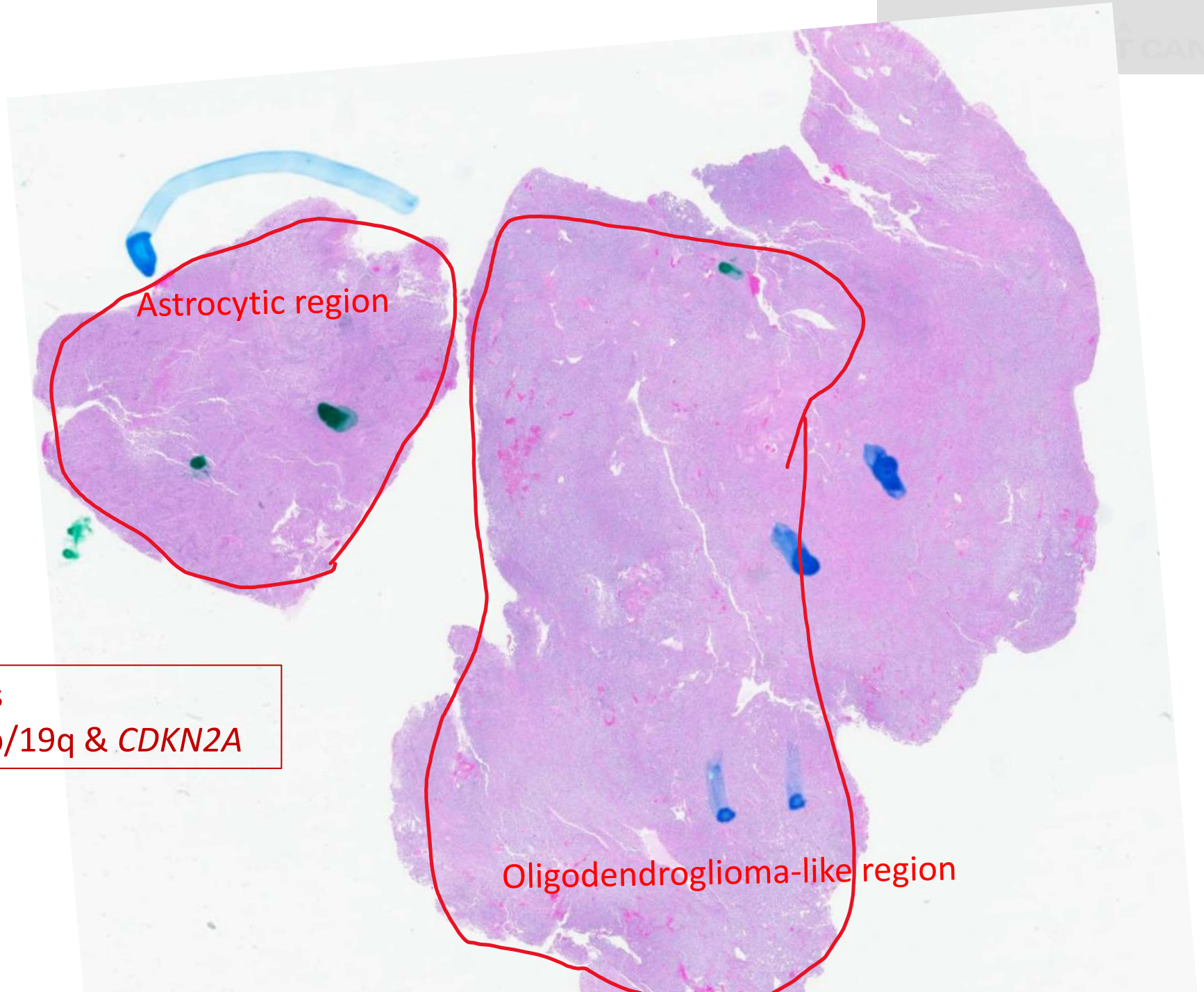
ATRX





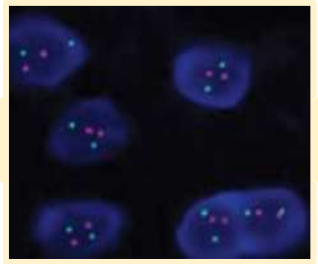
IDH1 p.R132H





Marked slides
→ FISH for 1p/19q & *CDKN2A*

Fluorescent In Situ Hybridization (*CDKN2A*, 1p/19q):



Astrocytic Morphology Area

POSITIVE for homozygous deletion of the *CDKN2A* (9p21) locus

NEGATIVE for 1p36 deletion

NEGATIVE for 19q13 deletion

Oligo-like Morphology Area

NEGATIVE for homozygous deletion of the *CDKN2A* (9p21 locus)

NEGATIVE for 1p36 deletion

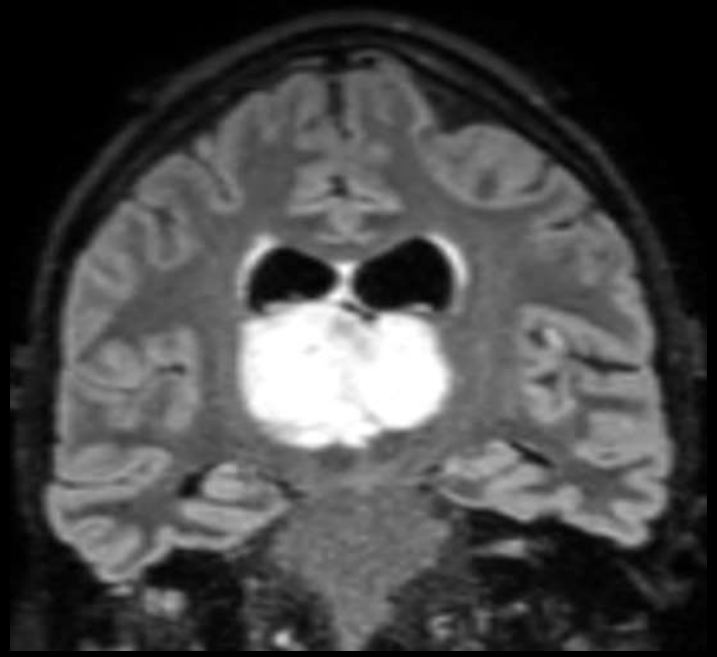
NEGATIVE for 19q13 deletion

Brain, right frontotemporal tumor, craniotomy with resection:

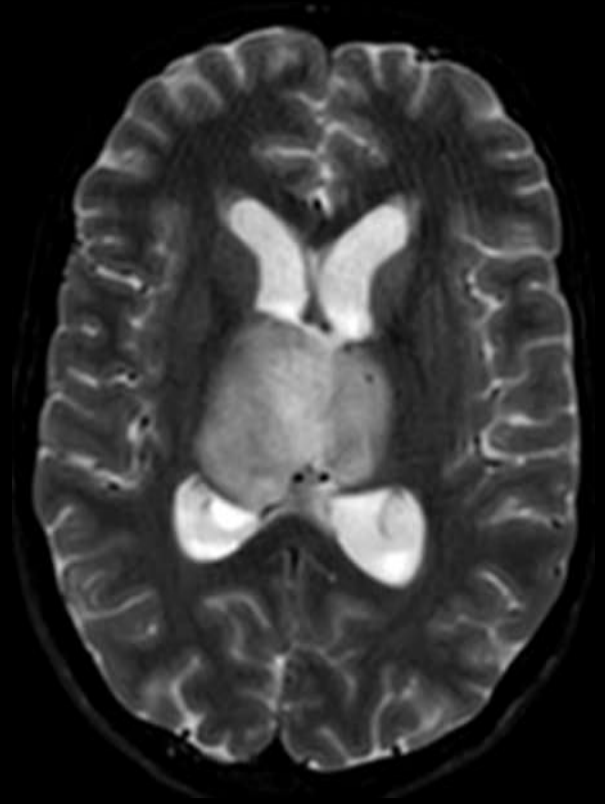
Astrocytoma, IDH-mutant
CNS WHO grade 4

IDH1 (IHC): POSITIVE for p.R132H mutant protein expression
ATRX (IHC): LOSS of nuclear expression, regional
CDKN2A (FISH): POSITIVE for homozygous deletion, regional
1p/19q (FISH): Negative for codeletion

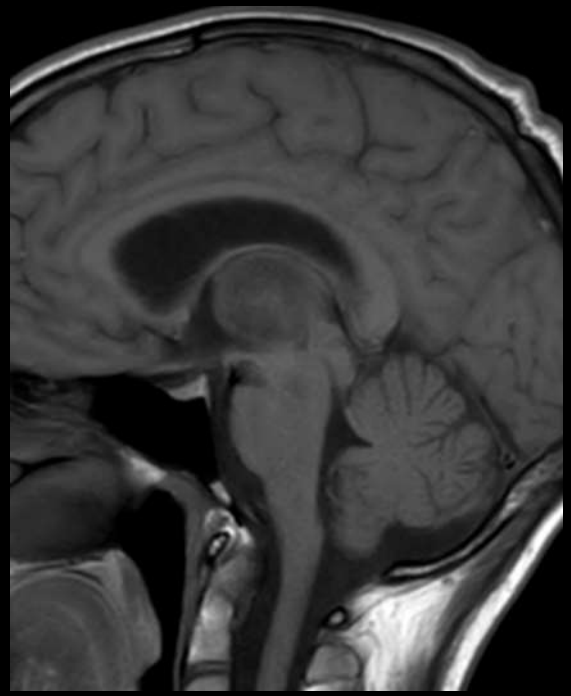
29M with diplopia found to have thalamic mass



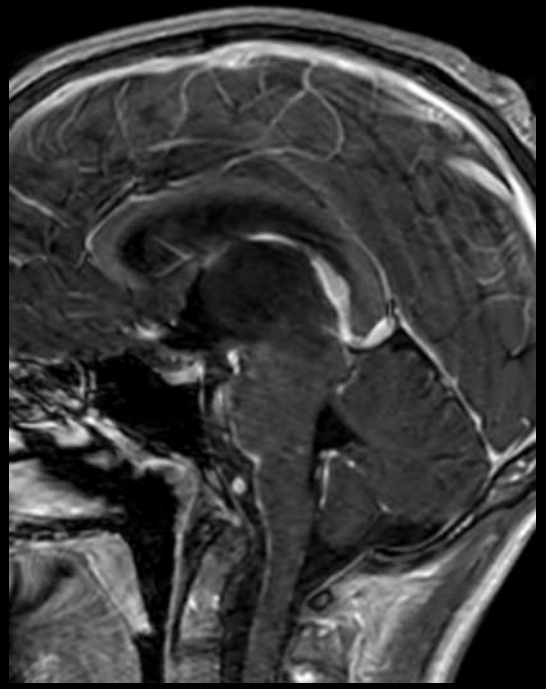
T2 FLAIR



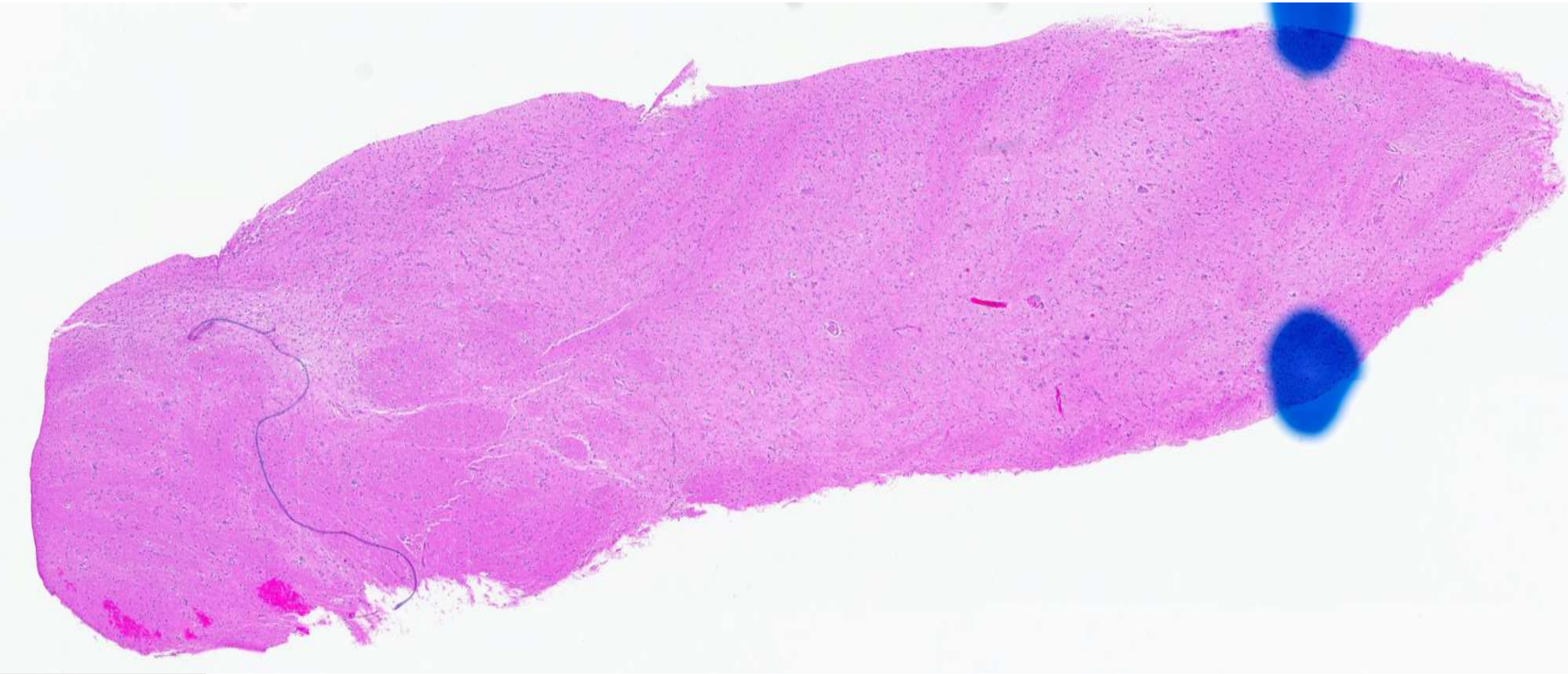
T2

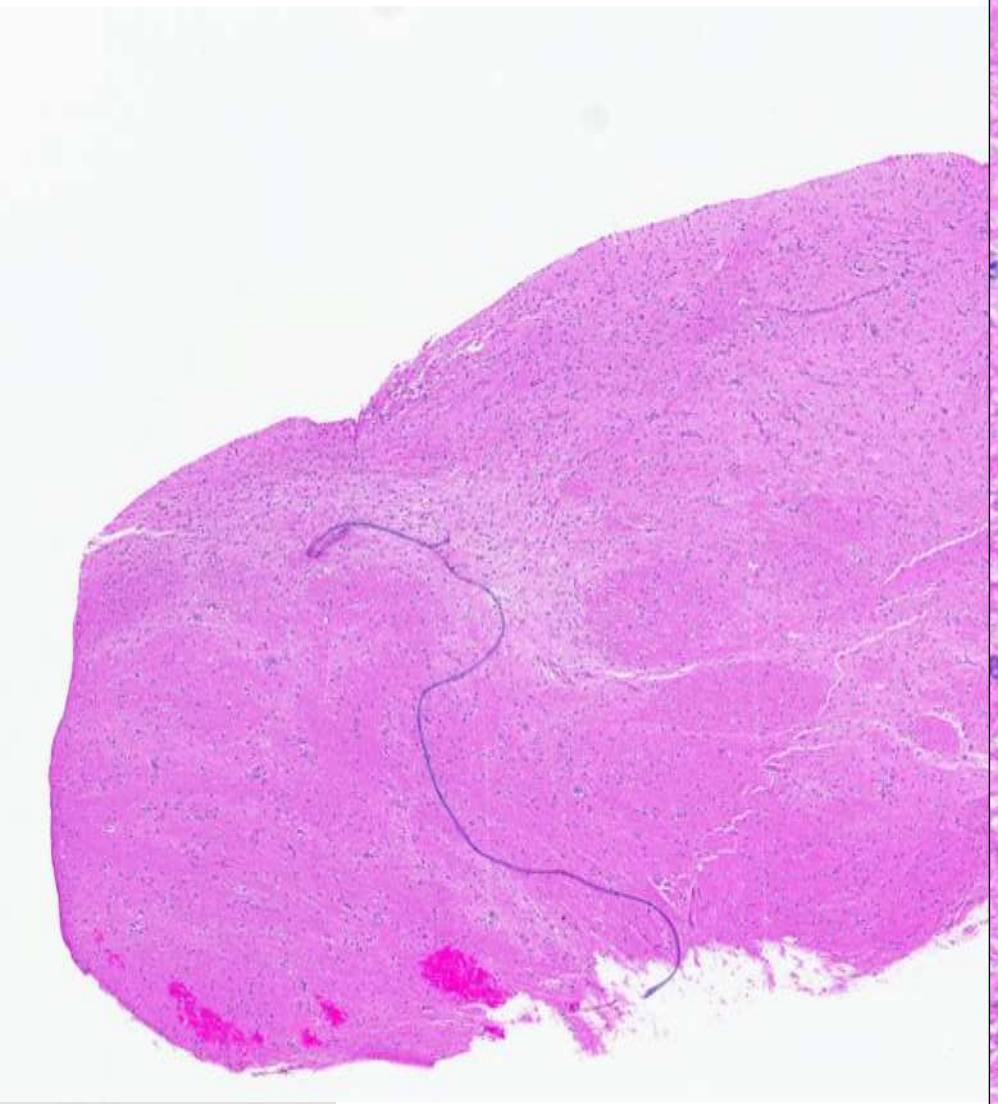


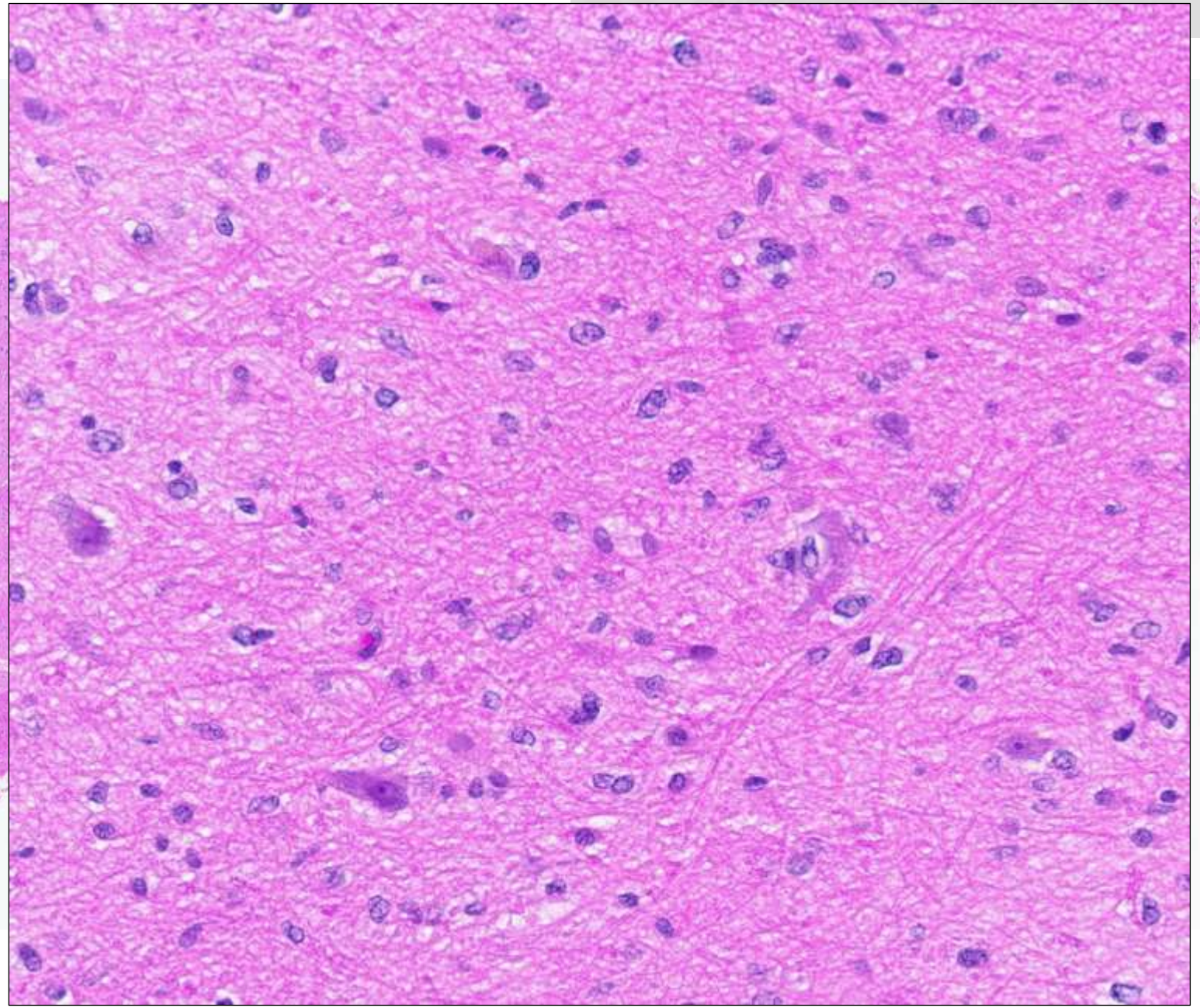
T1

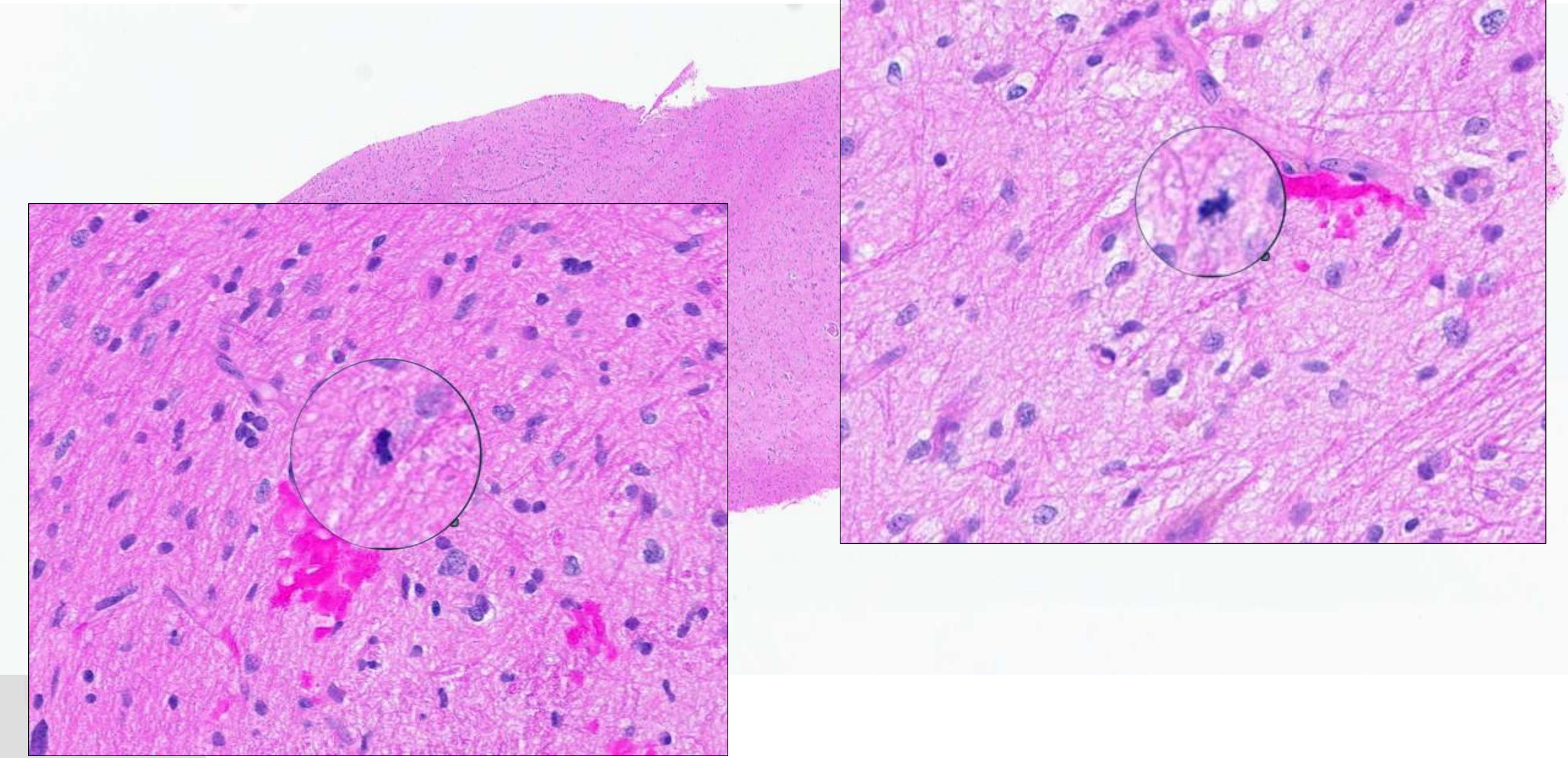


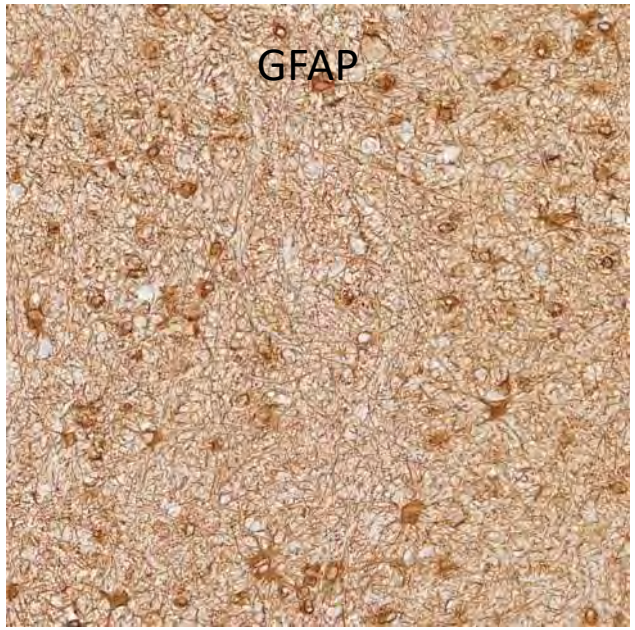
T1 +C

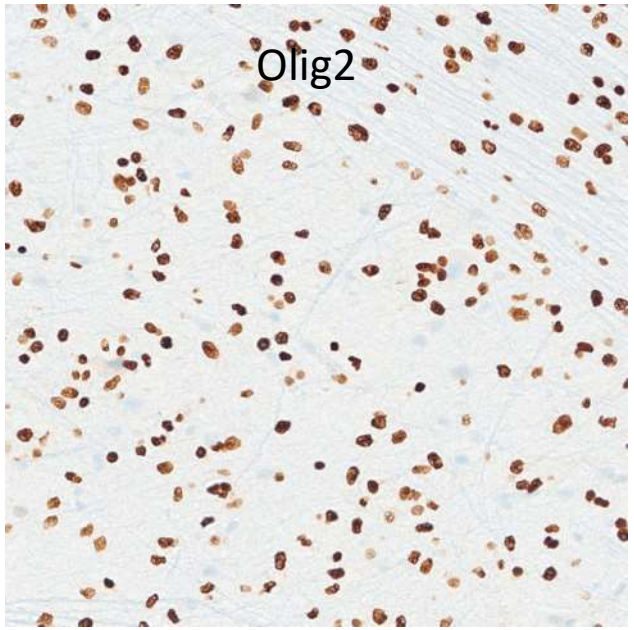


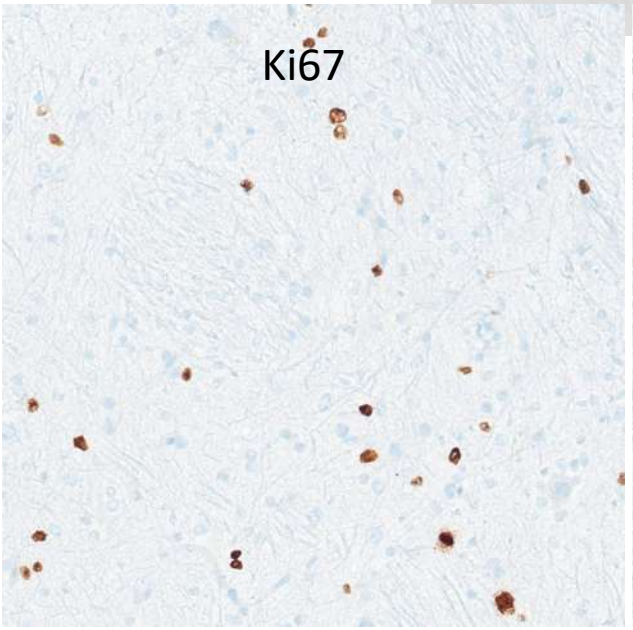


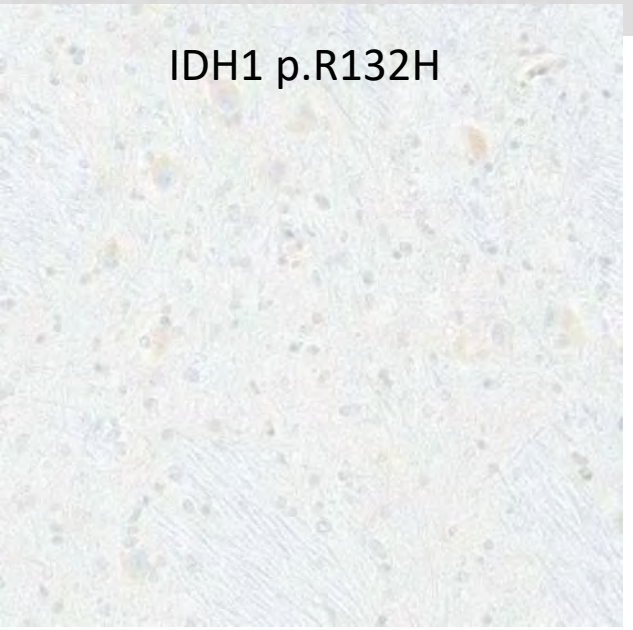


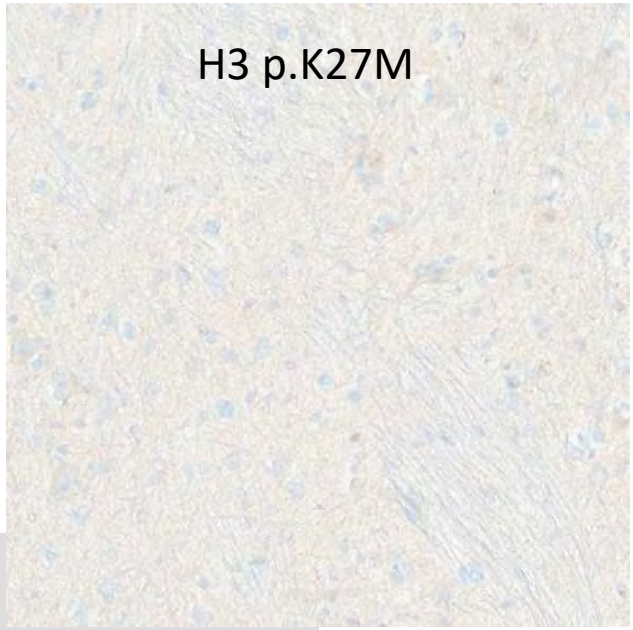


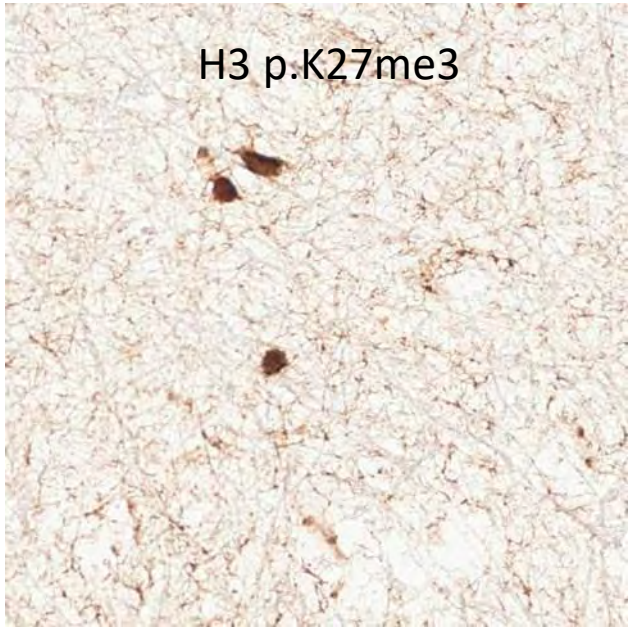

GFAP

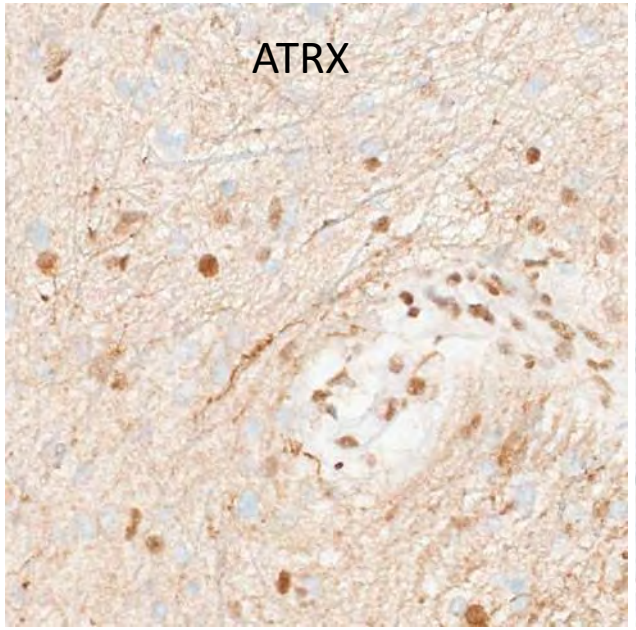

Olig2

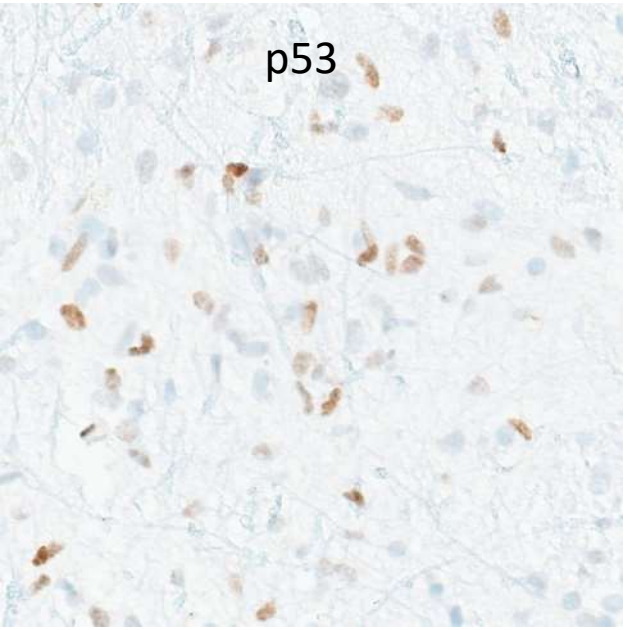

Ki67


IDH1 p.R132H

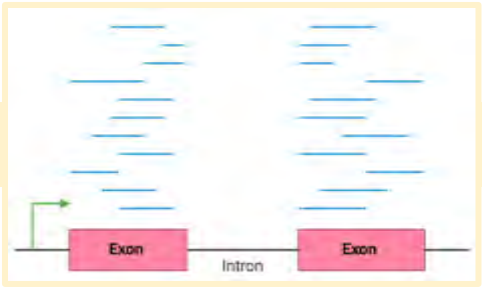

H3 p.K27M


H3 p.K27me3


ATRX


p53

Next-Generation Sequencing Panel:



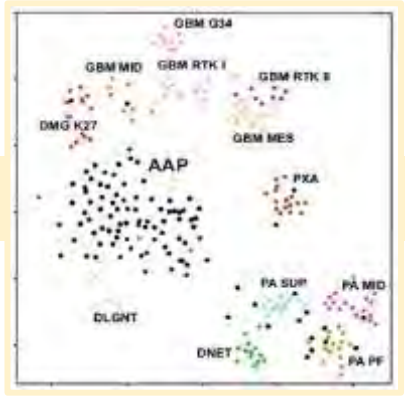
Copy Number Variations

CDKN2A	Homozygous deletion
CDKN2B	Homozygous deletion
NF1	Homozygous deletion

Somatic Mutations

SETD2	p.E1478*	21%	(pathogenic)
SETD2	p.L1804S	25%	(likely pathogenic)
ATRX	c.595-2A>G	50%	(likely pathogenic)

DNA Methylation-Based Tumor Classification:



Methylation Class Name	High-grade astrocytoma with piloid features
Methylation Class Confidence Score	High confidence
Methylation Class Description:	The “methylation class high-grade astrocytoma with piloid features” is mainly comprised of tumors with the histological diagnosis of anaplastic pilocytic astrocytoma or less commonly glioblastoma. The tumors mostly occur in the posterior fossa and rarely in the diencephalic/thalamic region; median age is 40 years (age range 24 to 75). Deletions of CDKN2A/B are very frequent (>70%). BRAF duplications are also observed in a fraction of cases. Around 50% of cases show an immunohistochemical loss of ATRX. Loss of chromosome 19q (total or partial) is observed in over 50% of cases.

Brain, thalamic tumor, stereotactic biopsy:

High-grade astrocytoma with piloid features (see comment)

Diagnosis comment:
The biopsy show an infiltrating astrocytoma with scattered mitotic figures and a high Ki67 labeling index (10-15%), morphologically consistent with a high-grade astrocytoma. NGS reveals a mutation in ATRX and homozygous deletions in CDKN2A/B and NF1. Methylation profiling reveals consensus match to High-grade astrocytoma with piloid features (HGAP) with a high confidence score. HGAP is a new tumor type in the 2021 WHO classification system with limited data available. A definitive WHO grade has not been established, although current data suggest a clinical behavior roughly corresponding to CNS WHO grade 3.

ORIGINAL PAPER

Anaplastic astrocytoma with piloid features, a novel molecular class of IDH wildtype glioma with recurrent MAPK pathway, CDKN2A/B and ATRX alterations

Annekathrin Reinhardt[1,2] · Damian Stichel[1,2] · Daniel Schrimpf[1,2] · Felix Sahm[1,2] · Andrey Korshunov[1,2] · David E. Reuss[1,2] · Christian Koelsche[1,2] · Kristin Huang[1,2] · Annika K. Wefers[1,2] · Volker Hovestadt[3,4] · Martin Sill[4,48] · Dorothee Gramatzki[29] · Joerg Felsberg[9] · Guido Reifenberger[9,30] · Arend Koch[7] · Ulrich-W. Thomale[35] · Albert Becker[8] · Volkmar H. Hans[10] · Marco Prinz[11,47] · Ori Staszewski[11] · Till Acker[12] · Hildegard Dohmen[12] · Christian Hartmann[13] · Wolf Mueller[14] · Muin S. A. Tuffaha[36] · Werner Paulus[15] · Katharina Heß[15] · Benjamin Brokinkel[15] · Jens Schittenhelm[16] · Camelia-Maria Monoranu[17] · Almuth Friederike Kessler[37] · Mario Loehr[37] · Rolf Buslei[18,19] · Martina Deckert[20] · Christian Mawrin[21] · Patricia Kohlhof[22] · Ekkehard Hewer[23] · Adriana Olar[24,25,26] · Fausto J. Rodriguez[27] · Caterina Giannini[28] · Amulya A. NageswaraRao[28] · Uri Tabori[38,39,40,41] · Nuno Miguel Nunes[40,41] · Michael Weller[29] · Ute Pohl[31] · Zane Jaunmuktane[32] · Sebastian Brandner[32] · Andreas Unterberg[42] · Daniel Hänggi[43] · Michael Platten[44,45] · Stefan M. Pfister[4,5,6,48] · Wolfgang Wick[33,4] · Christel Herold-Mende[34] · David T. W. Jones[4,48,49] · Andreas von Deimling[1,2,4] · David Capper[1,2,46,50]

Acta Neuropathologica (2018) 136:273–291
https://doi.org/10.1007/s00401-018-1837-8

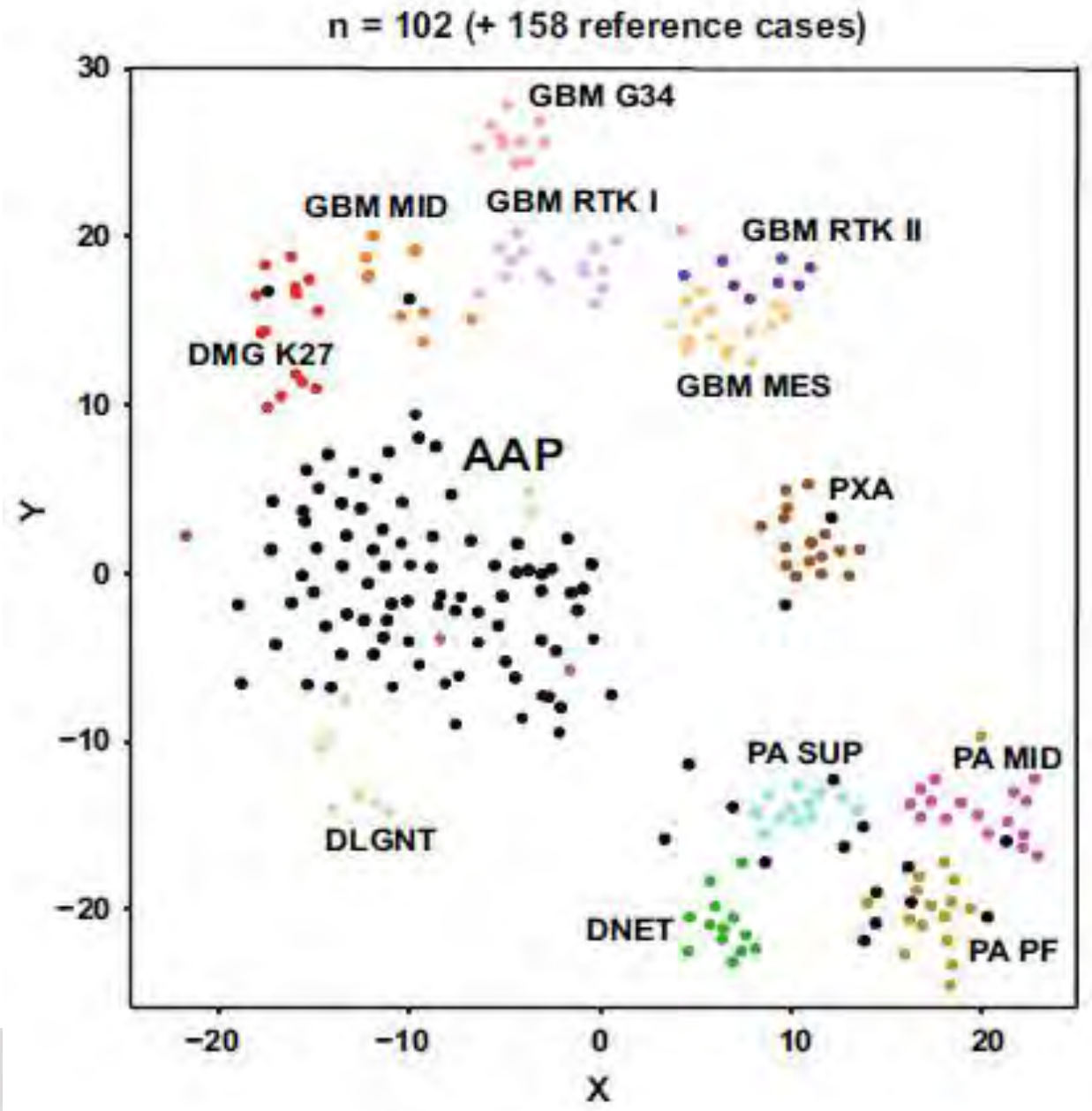


Fig. 1 t-SNE analysis of 102 cases with histological features compatible with the diagnosis of anaplastic pilocytic astrocytoma, indicated in black, and 158 reference cases of established glioma methylation classes, indicated in different colors. Tumors of the same class are depicted in one color. For this analysis, the 20,000 most variably methylated CPG sites were used. 83 of the histologically

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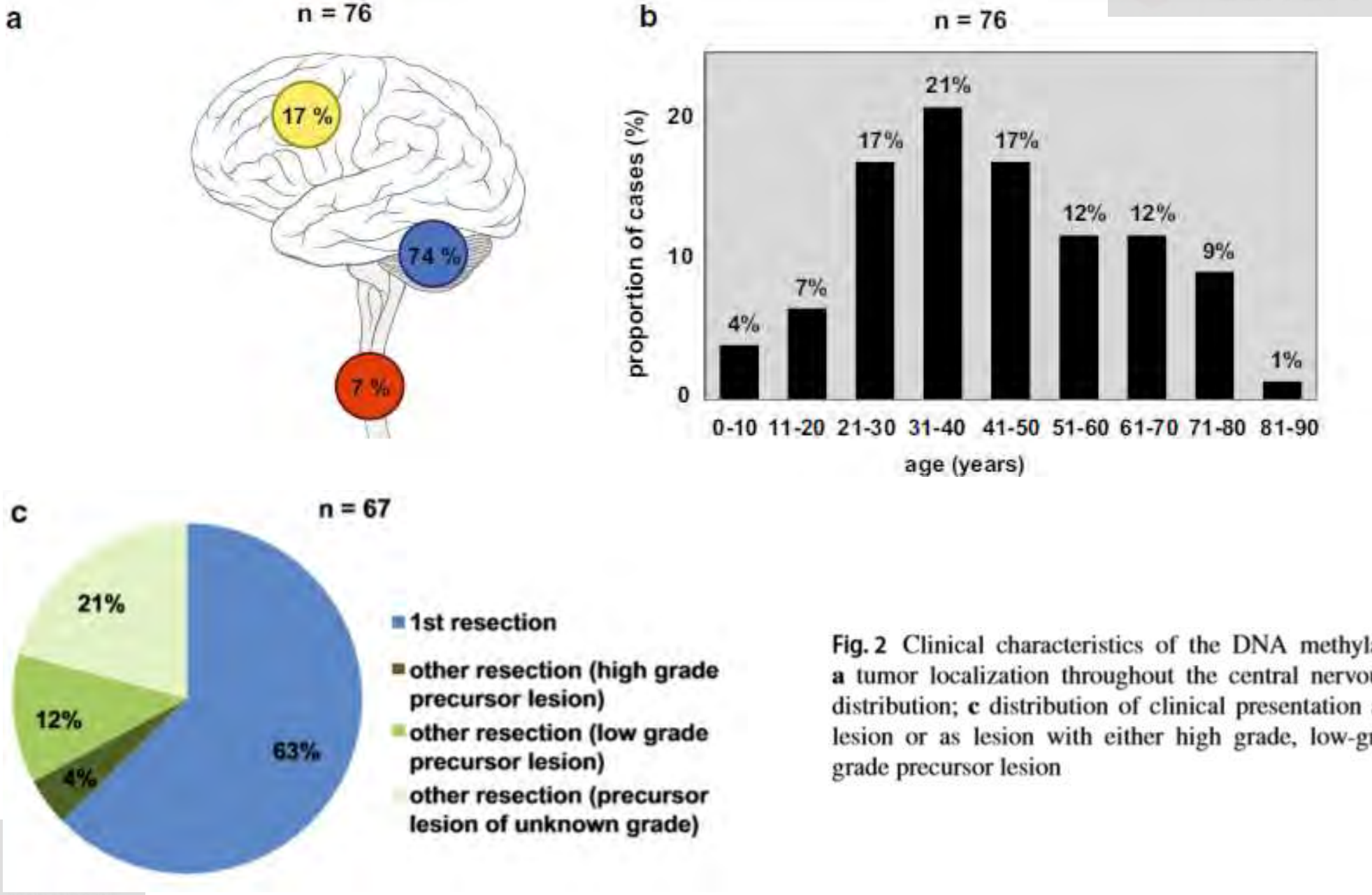

Fig. 2 Clinical characteristics of the DNA methylation class AAP: **a** tumor localization throughout the central nervous system; **b** age distribution; **c** distribution of clinical presentation as either primary lesion or as lesion with either high grade, low-grade or unknown grade precursor lesion

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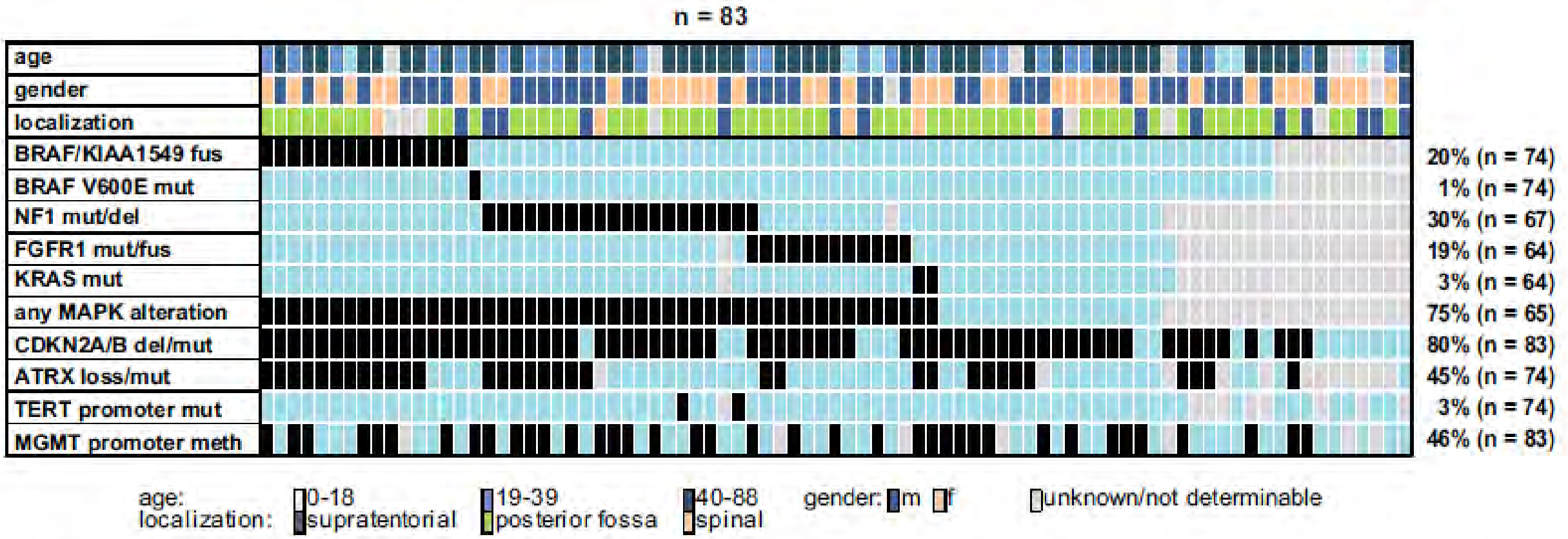

Fig. 6 Summary of molecular alterations and patient characteristics for the methylation class anaplastic astrocytoma with piloid features. For molecular alterations, black fields indicate the presence and light blue fields the absence of the respective alteration. Grey fields indicate that the lesion was not tested for the specific alteration or that the respective parameter was not determinable. *mut* mutation, *del* deletion, *fus* fusion, *meth* methylated

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Meningioma, CNS WHO grade 1-3

WHO grade 1
Meningothelial
Fibrous (fibroblastic)
Transitional (mixed)
Psammomatous
Angiomatous
Secretory
Lymphoplasmacyte-rich
Metaplastic
Rhabdoid (?)

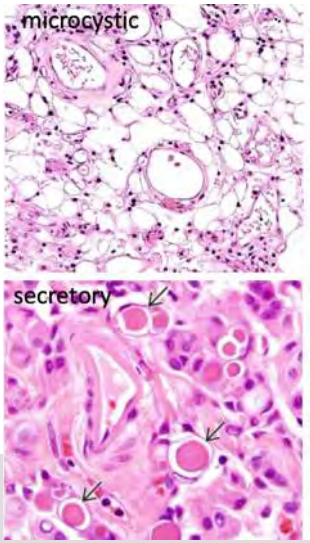
WHO grade 2
Chordoid
Clear cell

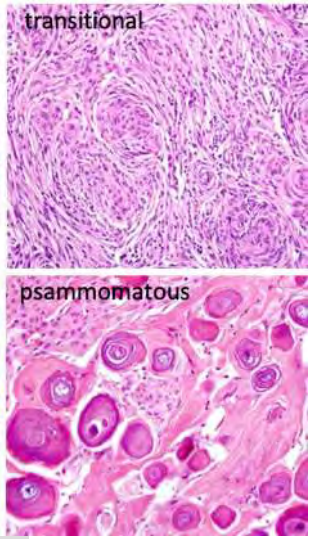
Atypical meningioma
Brain invasion
(or)
≥2.5mitosis/mm^2
(or)
At least 3 of the following:
increased cellularity
small cells with high N:C
prominent nucleoli
sheeting
spontaneous necrosis

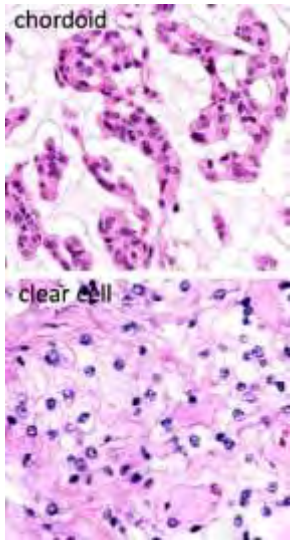
WHO grade 3
Papillary (?)
Rhabdoid (?)

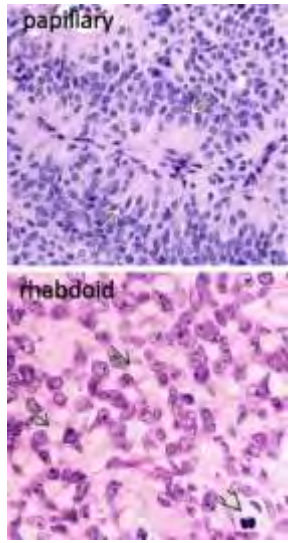
Anaplastic meningioma
Overtly malignant (resembling carcinoma, melanoma, high-grade sarcoma)
(and/or)
≥12.5mitosis/mm^2
(and/or)
Molecular features:
*TERT*p mutation
CDKN2A/B loss

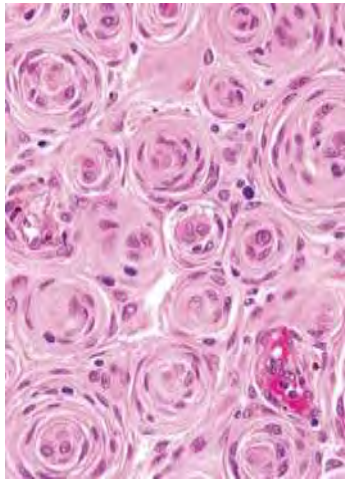
Recurrence risk: 7-25% 29-52% 50-94%

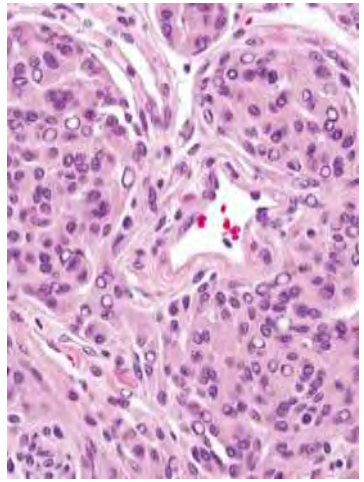


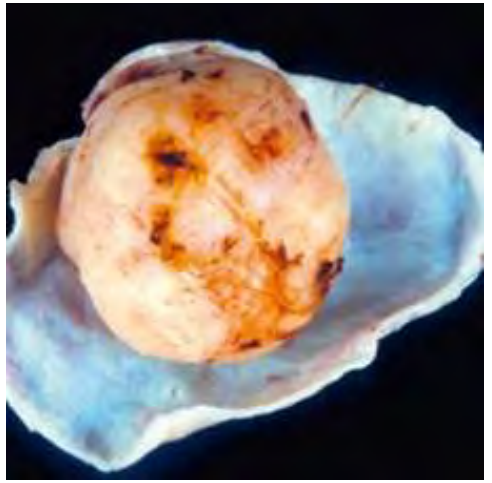


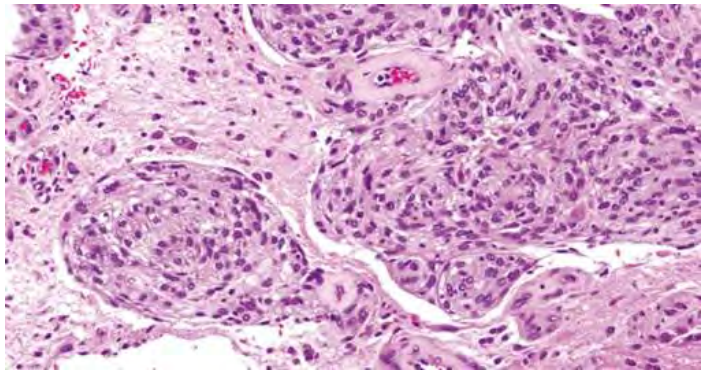


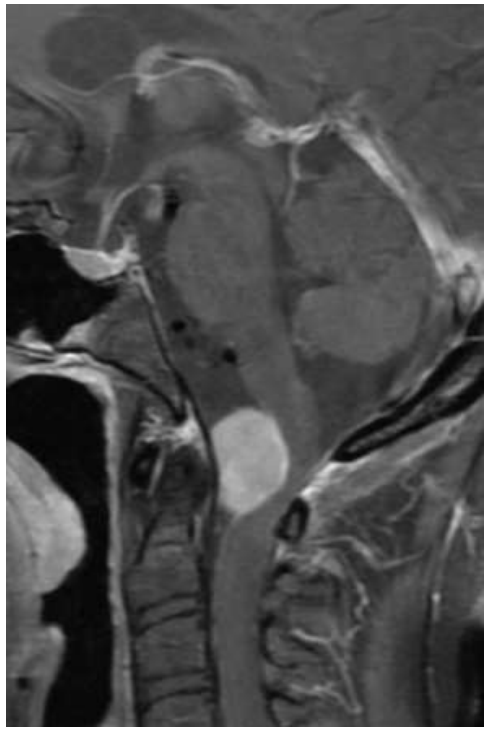


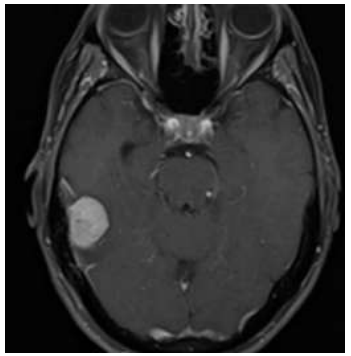


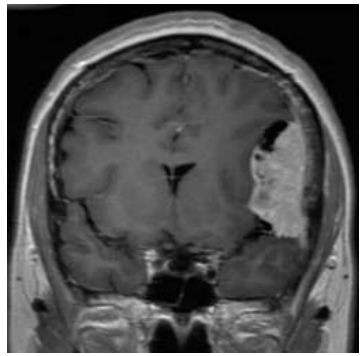












Additional proposed gliomas supported by tumor methylation profiling since WHO CNS 2021 publication:

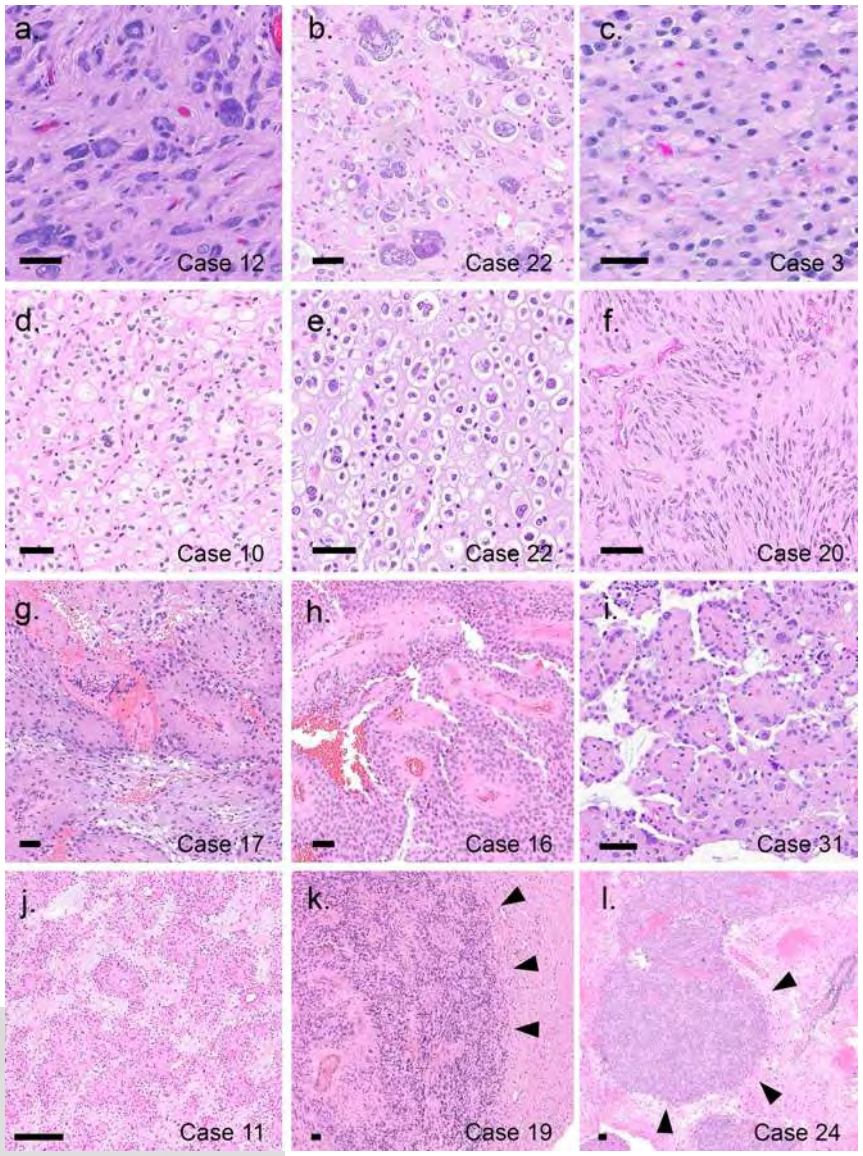
- High-grade glioma with pleomorphic and pseudopapillary features (HPAP)
- Neuroepithelial tumor with *PATZ1* fusion
- Glial tumor with *BCOR* fusion

Additional proposed gliomas supported by tumor methylation profiling since WHO CNS 2021 publication:

High-grade glioma with pleomorphic and pseudopapillary features (HPAP)

Neuroepithelial tumor with *PATZ1* fusion

Glial tumor with *BCOR* fusion

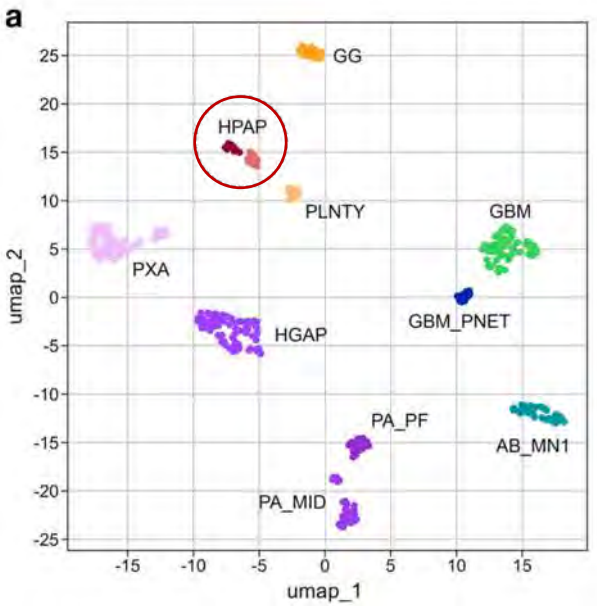


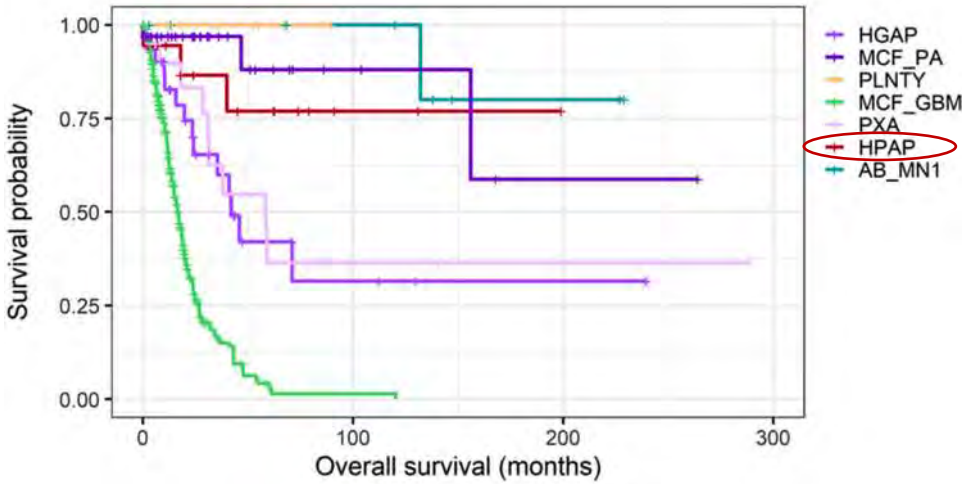
Acta Neuropathologica (2022) 143:403–414
https://doi.org/10.1007/s00401-022-02404-9

ORIGINAL PAPER

High-grade glioma with pleomorphic and pseudopapillary features (HPAP): a proposed type of circumscribed glioma in adults harboring frequent *TP53* mutations and recurrent monosomy 13

Drew Pratt[1] · Zied Abdullaev[1] · Antonios Papanicolau-Sengos[1] · Courtney Ketchum[1] · Pavalan Panneer Selvam[1]





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Thank you!

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