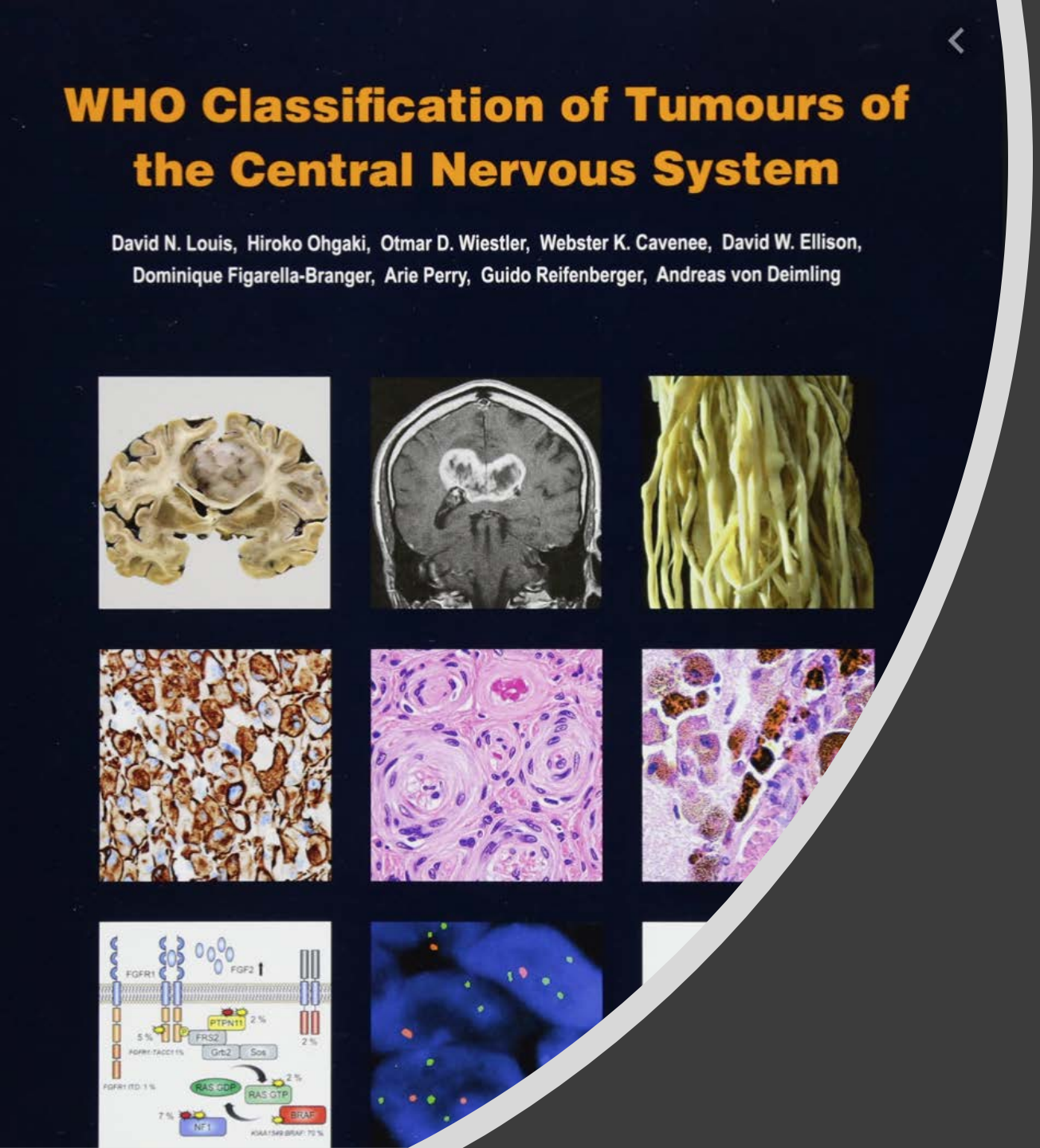



# Adult Gliomas and Cerebral Metastases

Dott. Giulio Ranazzi

Prof.ssa Antonella Stoppacciaro

# WHO classification of tumours of the central nervous system

| | |
|---|---|
| **Diffuse astrocytic and oligodendroglial tumours** | |
| Diffuse astrocytoma, IDH-mutant | 9400/3 |
| Gemistocytic astrocytoma, IDH-mutant | 9411/3 |
| *Diffuse astrocytoma, IDH-wildtype* | *9400/3* |
| Diffuse astrocytoma, NOS | 9400/3 |
| Anaplastic astrocytoma, IDH-mutant | 9401/3 |
| *Anaplastic astrocytoma, IDH-wildtype* | *9401/3* |
| Anaplastic astrocytoma, NOS | 9401/3 |
| Glioblastoma, IDH-wildtype | 9440/3 |
| Giant cell glioblastoma | 9441/3 |
| Gliosarcoma | 9442/3 |
| *Epithelioid glioblastoma* | *9440/3* |
| Glioblastoma, IDH-mutant | 9445/3* |
| Glioblastoma, NOS | 9440/3 |
| Diffuse midline glioma, H3 K27M–mutant | 9385/3* |
| Oligodendroglioma, IDH-mutant and 1p/19q-codeleted | 9450/3 |
| Oligodendroglioma, NOS | 9450/3 |
| Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted | 9451/3 |
| *Anaplastic oligodendroglioma, NOS* | *9451/3* |
| *Oligoastrocytoma, NOS* | *9382/3* |
| *Anaplastic oligoastrocytoma, NOS* | *9382/3* |
| **Other astrocytic tumours** | |
| Pilocytic astrocytoma | 9421/1 |
| Pilomyxoid astrocytoma | 9425/3 |
| Subependymal giant cell astrocytoma | 9384/1 |
| Pleomorphic xanthoastrocytoma | 9424/3 |
| Anaplastic pleomorphic xanthoastrocytoma | 9424/3 |
| **Ependymal tumours** | |
| Subependymoma | 9383/1 |
| Myxopapillary ependymoma | 9394/1 |
| Ependymoma | 9391/3 |
| Papillary ependymoma | 9393/3 |
| Clear cell ependymoma | 9391/3 |
| Tanycytic ependymoma | 9391/3 |
| Ependymoma, *RELA* fusion–positive | 9396/3* |
| Anaplastic ependymoma | 9392/3 |
| **Other gliomas** | |
| Chordoid glioma of the third ventricle | 9444/1 |
| Angiocentric glioma | 9431/1 |
| Astroblastoma | 9430/3 |
| **Choroid plexus tumours** | |
| Choroid plexus papilloma | 9390/0 |
| Atypical choroid plexus papilloma | 9390/1 |
| Choroid plexus carcinoma | 9390/3 |

| | |
|---|---|
| **Neuronal and mixed neuronal-glial tumours** | |
| Dysembryoplastic neuroepithelial tumour | 9413/0 |
| Gangliocytoma | 9492/0 |
| Ganglioglioma | 9505/1 |
| Anaplastic ganglioglioma | 9505/3 |
| Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease) | 9493/0 |
| Desmoplastic infantile astrocytoma and ganglioglioma | 9412/1 |
| Papillary glioneuronal tumour | 9509/1 |
| Rosette-forming glioneuronal tumour | 9509/1 |
| *Diffuse leptomeningeal glioneuronal tumour* | |
| Central neurocytoma | 9506/1 |
| Extraventricular neurocytoma | 9506/1 |
| Cerebellar liponeurocytoma | 9506/1 |
| Paraganglioma | 8693/1 |
| **Tumours of the pineal region** | |
| Pineocytoma | 9361/1 |
| Pineal parenchymal tumour of intermediate differentiation | 9362/3 |
| Pineoblastoma | 9362/3 |
| Papillary tumour of the pineal region | 9395/3 |
| **Embryonal tumours** | |
| Medulloblastomas, genetically defined | |
| Medulloblastoma, WNT-activated | 9475/3* |
| Medulloblastoma, SHH-activated and *TP53*-mutant | 9476/3* |
| Medulloblastoma, SHH-activated and *TP53*-wildtype | 9471/3 |
| Medulloblastoma, non-WNT/non-SHH | 9477/3* |
| *Medulloblastoma, group 3* | |
| *Medulloblastoma, group 4* | |
| Medulloblastomas, histologically defined | |
| Medulloblastoma, classic | 9470/3 |
| Medulloblastoma, desmoplastic/nodular | 9471/3 |
| Medulloblastoma with extensive nodularity | 9471/3 |
| Medulloblastoma, large cell / anaplastic | 9474/3 |
| Medulloblastoma, NOS | 9470/3 |
| Embryonal tumour with multilayered rosettes, C19MC-altered | 9478/3* |
| *Embryonal tumour with multilayered rosettes, NOS* | *9478/3* |
| Medulloepithelioma | 9501/3 |
| CNS neuroblastoma | 9500/3 |
| CNS ganglioneuroblastoma | 9490/3 |
| CNS embryonal tumour, NOS | 9473/3 |
| Atypical teratoid/rhabdoid tumour | 9508/3 |
| *CNS embryonal tumour with rhabdoid features* | *9508/3* |
| **Tumours of the cranial and paraspinal nerves** | |
| Schwannoma | 9560/0 |
| Cellular schwannoma | 9560/0 |
| Plexiform schwannoma | 9560/0 |

| | |
|---|---|
| Melanotic schwannoma | 9560/1 |
| Neurofibroma | 9540/0 |
| Atypical neurofibroma | 9540/0 |
| Plexiform neurofibroma | 9550/0 |
| Perineurioma | 9571/0 |
| Hybrid nerve sheath tumours | |
| Malignant peripheral nerve sheath tumour | 9540/3 |
| Epithelioid MPNST | 9540/3 |
| MPNST with perineurial differentiation | 9540/3 |
| **Meningiomas** | |
| Meningioma | 9530/0 |
| Meningothelial meningioma | 9531/0 |
| Fibrous meningioma | 9532/0 |
| Transitional meningioma | 9537/0 |
| Psammomatous meningioma | 9533/0 |
| Angiomatous meningioma | 9534/0 |
| Microcystic meningioma | 9530/0 |
| Secretory meningioma | 9530/0 |
| Lymphoplasmacyte-rich meningioma | 9530/0 |
| Metaplastic meningioma | 9530/0 |
| Chordoid meningioma | 9538/1 |
| Clear cell meningioma | 9538/1 |
| Atypical meningioma | 9539/1 |
| Papillary meningioma | 9538/3 |
| Rhabdoid meningioma | 9538/3 |
| Anaplastic (malignant) meningioma | 9530/3 |
| **Mesenchymal, non-meningothelial tumours** | |
| Solitary fibrous tumour / haemangiopericytoma** | |
| Grade 1 | 8815/0 |
| Grade 2 | 8815/1 |
| Grade 3 | 8815/3 |
| Haemangioblastoma | 9161/1 |
| Haemangioma | 9120/0 |
| Epithelioid haemangioendothelioma | 9133/3 |
| Angiosarcoma | 9120/3 |
| Kaposi sarcoma | 9140/3 |
| Ewing sarcoma / PNET | 9364/3 |
| Lipoma | 8850/0 |
| Angiolipoma | 8861/0 |
| Hibernoma | 8880/0 |
| Liposarcoma | 8850/3 |
| Desmoid-type fibromatosis | 8821/1 |
| Myofibroblastoma | 8825/0 |
| Inflammatory myofibroblastic tumour | 8825/1 |
| Benign fibrous histiocytoma | 8830/0 |
| Fibrosarcoma | 8810/3 |
| Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma | 8802/3 |
| Leiomyoma | 8890/0 |
| Leiomyosarcoma | 8890/3 |
| Rhabdomyoma | 8900/0 |
| Rhabdomyosarcoma | 8900/3 |
| Chondroma | 9220/0 |
| Chondrosarcoma | 9220/3 |
| Osteoma | 9180/0 |
| Osteochondroma | 9210/0 |
| Osteosarcoma | 9180/3 |
| **Melanocytic tumours** | |
| Meningeal melanocytosis | 8728/0 |
| Meningeal melanocytoma | 8728/1 |
| Meningeal melanoma | 8720/3 |
| Meningeal melanomatosis | 8728/3 |
| **Lymphomas** | |
| Diffuse large B-cell lymphoma of the CNS | 9680/3 |
| Immunodeficiency-associated CNS lymphomas | |
| AIDS-related diffuse large B-cell lymphoma | |
| EBV-positive diffuse large B-cell lymphoma, NOS | |
| Lymphomatoid granulomatosis | 9766/1 |
| Intravascular large B-cell lymphoma | 9712/3 |
| Low-grade B-cell lymphomas of the CNS | |
| T-cell and NK/T-cell lymphomas of the CNS | |
| Anaplastic large cell lymphoma, ALK-positive | 9714/3 |
| Anaplastic large cell lymphoma, ALK-negative | 9702/3 |
| MALT lymphoma of the dura | 9699/3 |
| **Histiocytic tumours** | |
| Langerhans cell histiocytosis | 9751/3 |
| Erdheim–Chester disease | 9750/1 |
| Rosai–Dorfman disease | |
| Juvenile xanthogranuloma | |
| Histiocytic sarcoma | 9755/3 |
| **Germ cell tumours** | |
| Germinoma | 9064/3 |
| Embryonal carcinoma | 9070/3 |
| Yolk sac tumour | 9071/3 |
| Choriocarcinoma | 9100/3 |
| Teratoma | 9080/1 |
| Mature teratoma | 9080/0 |
| Immature teratoma | 9080/3 |
| Teratoma with malignant transformation | 9084/3 |
| Mixed germ cell tumour | 9085/3 |
| **Tumours of the sellar region** | |
| Craniopharyngioma | 9350/1 |
| Adamantinomatous craniopharyngioma | 9351/1 |
| Papillary craniopharyngioma | 9352/1 |
| Granular cell tumour of the sellar region | 9582/0 |
| Pituicytoma | 9432/1 |
| Spindle cell oncocytoma | 8290/0 |
| **Metastatic tumours** | |

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [742A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O.
*Italics*: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone.*

2016 versus 2007 World Health Organization central nervous system tumors classifications and highlighting major changes in 2016 classification

| | 2016 | 2007 | Major changes in 2016 classification |
|---|---|---|---|
| Diffuse astrocytic and oligodendroglial tumors | Diffuse astrocytoma, IDH mutant<br>Gemistocytic astrocytoma, IDH mutant<br>Diffuse astrocytoma, IDH wild type<br>Diffuse astrocytoma, NOS<br>Anaplastic astrocytoma<br>IDH mutant<br>IDH wild type<br>NOS<br>Diffuse midline glioma, H3 K27M-mutant | Pilocytic astrocytoma<br>Pilomyxoid astrocytoma<br>Subependymal giant cell astrocytoma<br>Pleomorphic xanthoastrocytoma<br>Diffuse astrocytoma<br>Fibrillary astrocytoma<br>Gemistocytic astrocytoma<br>Protoplasmic astrocytoma<br>Anaplastic astrocytoma | Astrocytic, oligodendroglioma and glioblastoma tumors combined under one heading of diffuse glioma<br>Genetic classification of diffuse astrocytoma and anaplastic astrocytoma<br>Pilocytic astrocytoma, subependymal giant cell astrocytoma and pleomorphic xanthoastrocytoma included under different heading<br>Deletion<br>Protoplasmic and fibrillary astrocytoma<br>Addition<br>Diffuse midline glioma, H3 K27M-mutant and anaplastic pleomorphic Xanthoastrocytoma, WHO Grade III, instead of pleomorphic Xanthoastrocytoma with anaplastic features |
| Diffuse astrocytic and oligodendroglial tumors | Glioblastoma, IDH wild type<br>Giant cell glioblastoma<br>Gliosarcoma<br>Epithelioid glioblastoma<br>Glioblastoma, IDH mutant<br>Glioblastoma, NOS | Glioblastoma<br>Giant cell glioblastoma<br>Gliosarcoma<br>Gliomatosis cerebri | Classification of glioblastoma genetically<br>Addition of<br>Epithelioid glioblastoma<br>Glioblastoma with primitive neuronal component<br>Removal of gliomatosis cerebri |
| Diffuse astrocytic and oligodendroglial tumors | Oligodendroglioma<br>IDH mutant, and 1p19q co-deleted<br>NOS<br>Anaplastic oligodendroglioma<br>IDH mutant and 1p19q co-deleted<br>NOS | Oligodendroglioma<br>Anaplastic oligodendroglioma | Genetic-based classification |
| Diffuse astrocytic and oligodendroglial tumors | Oligoastrocytoma, NOS<br>Anaplastic oligoastrocytoma, NOS | Oligoastrocytoma<br>Anaplastic oligoastrocytoma | Addition of NOS: Use of the diagnosis "oligoastrocytoma" is now discouraged in favor of astrocytoma or oligodendroglioma |
| Other astrocytic tumors | Pilocytic astrocytoma<br>Pilomyxoid astrocytoma<br>Subependymal giant cell astrocytoma<br>Pleomorphic xanthoastrocytoma | | Different heading |

## Histological Grading of Central Nervous System Tumors

There are not many changes in WHO histological grading in 2016 update as compared to 2007 CNS tumor, only a new category "grade unknown" is added for diffuse leptomeningeal glioneuronal tumor. Grading of CNS tumors is mainly based on four morphologic criteria: cytological atypia, mitotic activity, microvascular proliferation (endothelial cell proliferation), and necrosis (St. Anne–Mayo grading system). According to above parameters, CNS tumors are classified in four grades.

- Grade I: Tumors do not meet any of the criteria. These tumors are slow growing, nonmalignant, and associated with long-term survival
- Grade II: Tumors meet only one criterion, i.e., only cytological atypia. These tumors are slow growing but recur as higher-grade tumors. They can be malignant or nonmalignant
- Grade III: Tumors meet two criteria, i.e., anaplasia and mitotic activity. These tumors are malignant and often recur as higher-grade tumors
- Grade IV: Tumors meet three or four of the criteria, i.e., showing anaplasia, mitotic activity with microvascular proliferation, and/or necrosis. These tumors reproduce rapidly and are very aggressive malignant tumors.

# World Health Organization histological grading of 2016 central nervous system tumors

| | I | II | III | IV | Grade unknown |
|---|---|---|---|---|---|
| Diffuse astrocytic and oligodendroglial tumors | | Diffuse astrocytoma<br>IDH mutant<br>IDH wild type<br>Oligodendroglioma<br>IDH mutant, and1p19q co-deleted | Anaplastic astrocytoma<br>IDH mutant<br>IDH wild type<br>Anaplastic oligodendroglioma, IDH mutant, and1p19q co-deleted | Diffuse midline glioma, H3 K27M-mutant<br>Glioblastoma, IDH wild type<br>Glioblastoma, IDH mutant | |
| Other astrocytic tumors | Pilocytic astrocytoma<br>Subependymal giant cell astrocytoma | Pleomorphic xanthoastrocytoma<br>Pilomyxoid astrocytoma | Anaplastic pleomorphic xanthoastrocytoma | | |

| Tumors | Molecular marker |
| --- | --- |
| Astrocytoma | IDH1/2,TP53,ATRX |
| Oligodendroglioma | IDH1/2,1p/19q co-deletion, TERT |
| Glioblastoma | IDH1/2,TERT,MGMT methylation |
| Diffuse midline glioma | H3 K27M-mutant |

LEGEND:
IDH:isocitrate dehydrogenase
Tp53:tumor protein p53
ATRX: Alpha-thalassemia/mental retardation syndrome X-linked
MGMT: $O^6$ Methylguanine-DN-methyltransferase

# Molecular markers

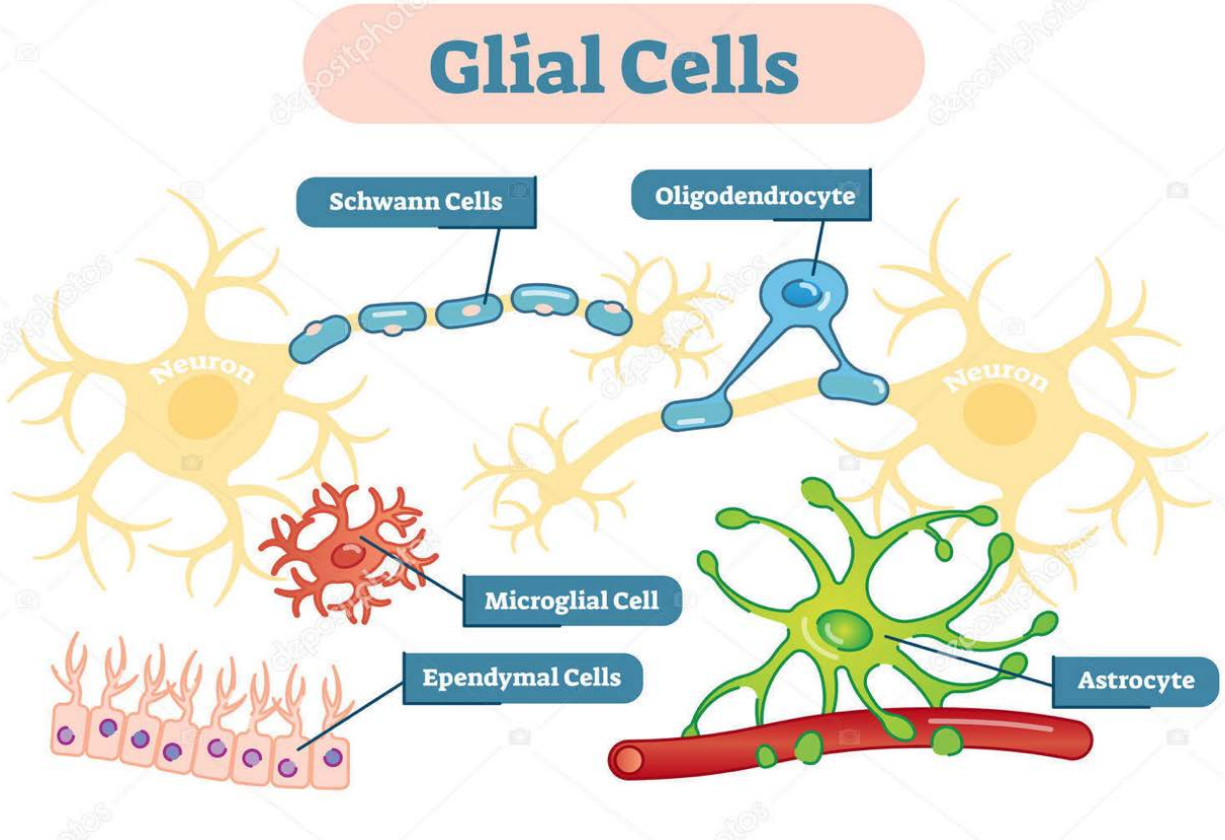
**IDH1 and IDH2 -** Enzymes in Krebs cycle that convert isocytrate to alpha-ketoglutarate. Mutations of these enzymes result in abnormal production of hydroxyglutarate which causes histone and DNA methylation, hence promoting tumorigenesis.

**1p/19 q codeletion –** Deletion of short arm of chromosome 1 and long arm of chromosome 19. Demonstrated by FISH. Diagnostic for Grade II and Grade III (anaplastic) oligodendroglioma and strong prognostic factor with improve survival

**MGMT methylation-** MGMT is a DNA repair enzyme and nullify the alkylating effect of temozolomide. When the promoter region is hypermethylated, gene will be silenced and chemotherapy with temozolomide is more effective.

**H3K27M-** Mutation in H3F3A gene encoding for hystone H3.3. This mutation leads to a reduction of H3K27 trimethylation with epigenetic alterations and consequent tumorigenesis.

# Gliomas




Histochemistry of gliomas

**Glial fibrillary acidic protein** (**GFAP**) intermediate filament for astrocytes (normal, reactive, neoplastic)

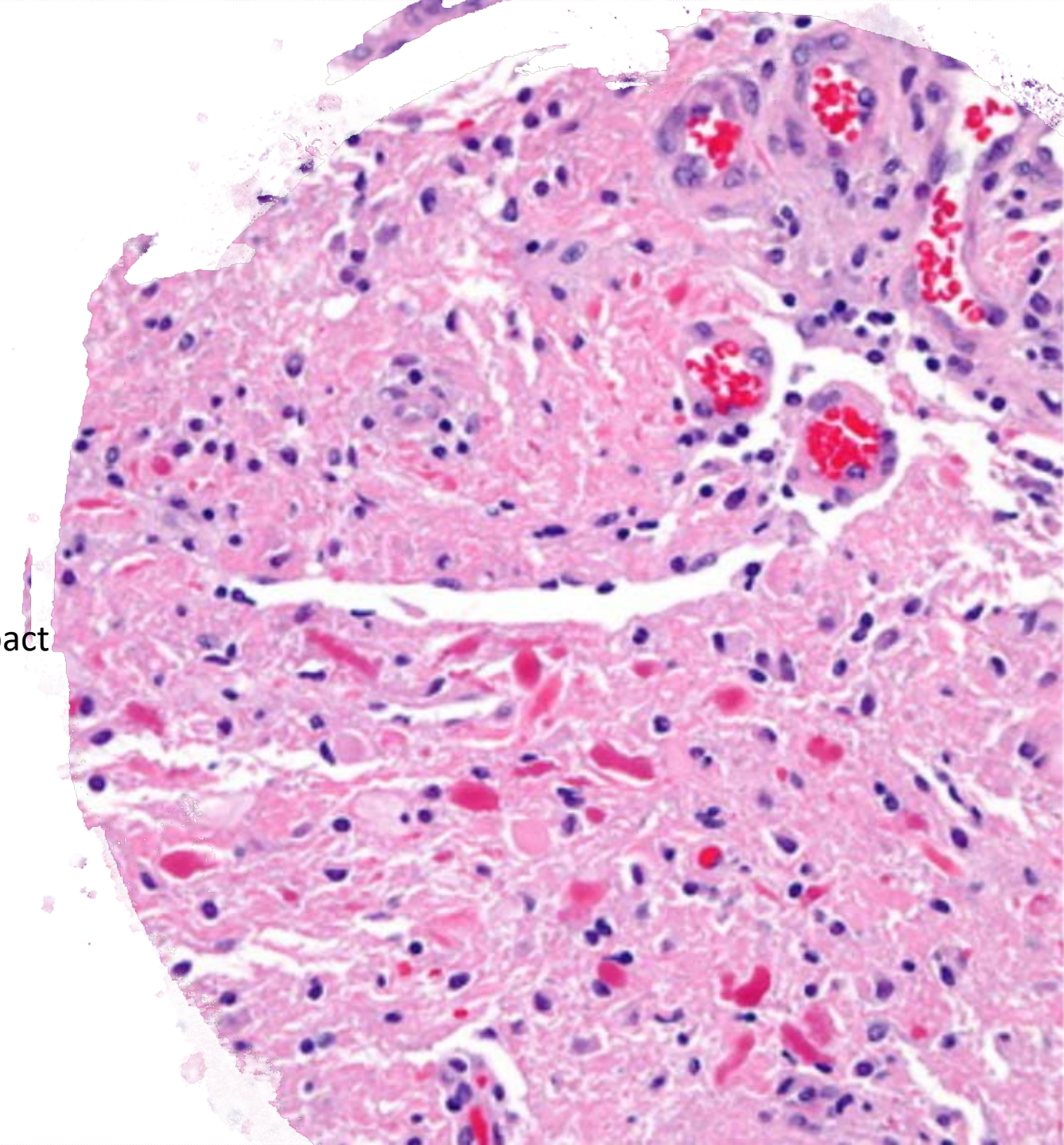
**Olig2** trascription factor expressed in astrocytes and oligodendrocytes

# Pilocytic Astrocytoma

WHO Grade I

- Most common glioma in children
- In adults mean age 22 yrs
- Localized throughout the neuroaxis
- Low to moderate cellularity with biphasic pattern (compact and loose texture)
- Rosenthal fibres and eosinophilic granular bodies
- Glomeruloid/multilayered vessels
- Rare anaplastic transformation

- **IDH –**

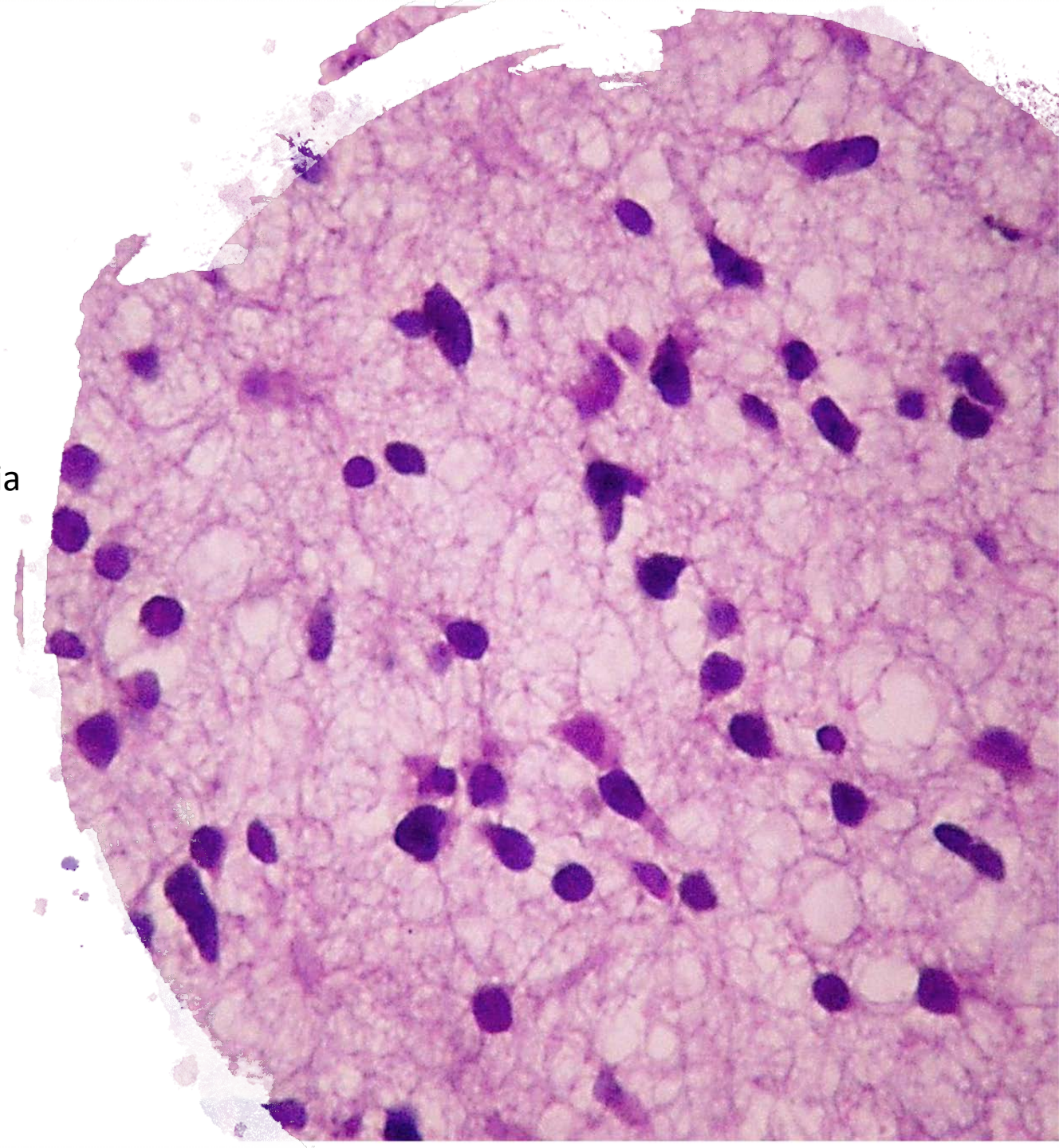


# Diffuse Astrocytoma IDH-mutant

WHO Grade II

- Mean age patient 35 yrs
- Commonly in cerebrum, frontal lobes
- Moderately increased cellularity/moderate nuclear atypia
- Mitotic activity absent
- No necrosis
- No microvascular proliferation

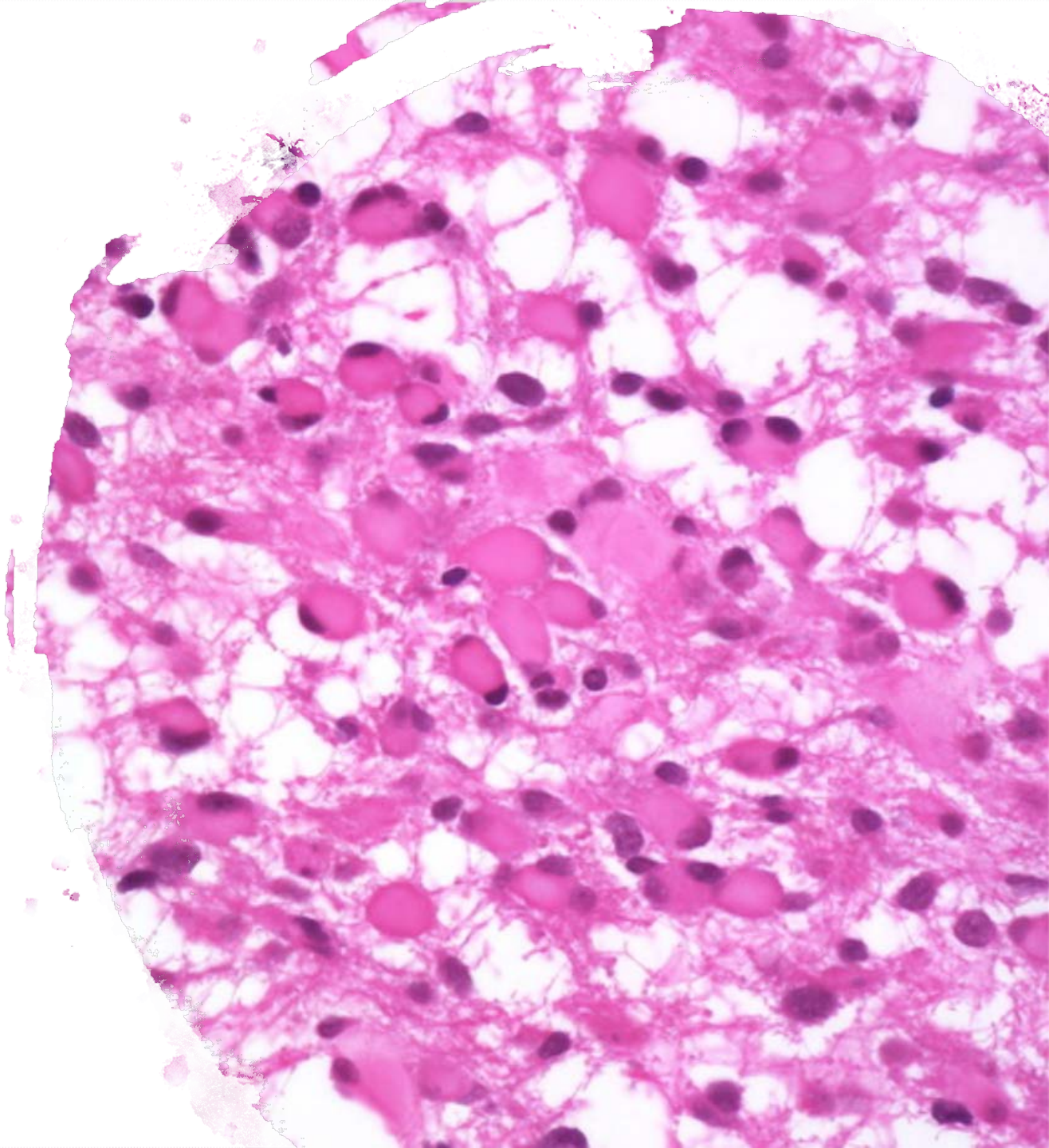
- **TP53 +**
- **IDH1 + (or IDH1/2 + evaluated by PCR)**
- **ATRX mutation +**
- **Ki67 < 4%**



# Gemistocytic Astrocytoma

Histologic variant of Diffuse Astrocytoma

- Abundant eosinophilic cytoplasm
- Nuclei displaced to the periphery
- Perivascular lymphocytic infiltrates
- Early progression and inferior outcome

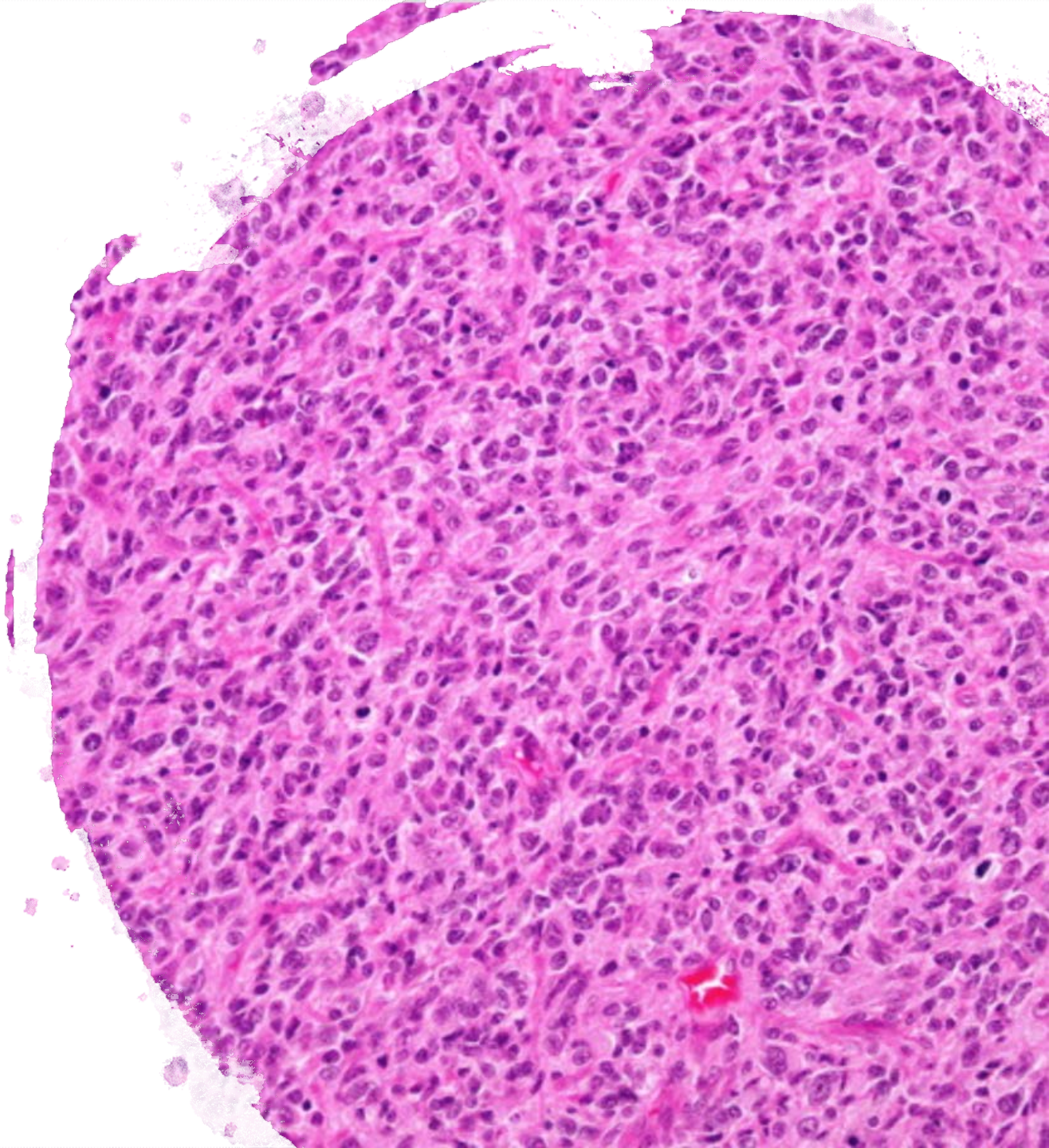


# Anaplastic Astrocytoma, IDH-mutant

WHO Grade III

- Mean age patient 37 yrs
- Commonly in cerebrum, frontal lobes
- High cellularity
- Distinct nuclear atypia
- Mitotic activity
- No microvascular proliferation
- No necrosis

- **ATRX mutation +**
- **Ki67 5-10%**

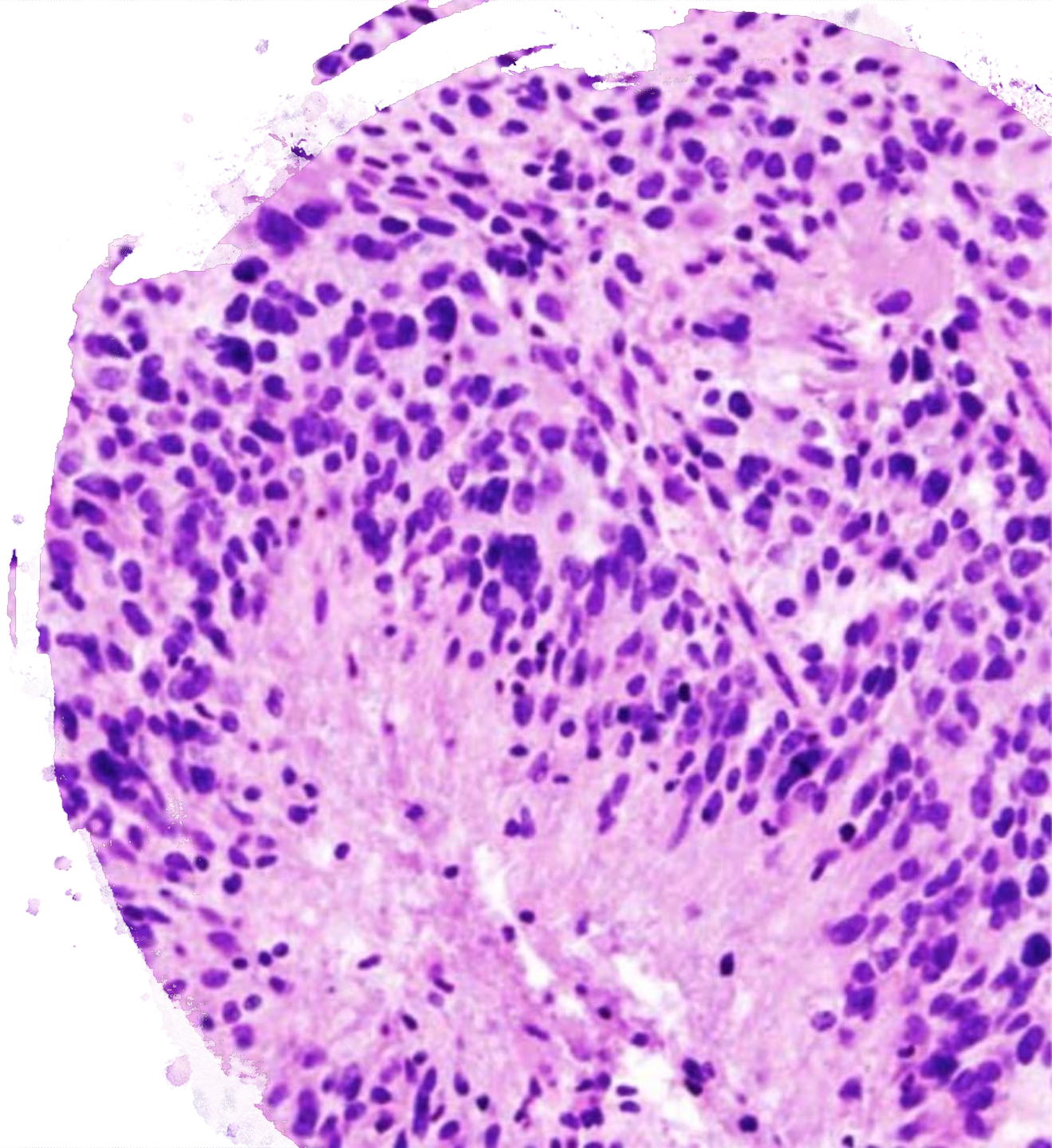


# Glioblastoma IDH-mutant

WHO Grade IV

- 10% of Glioblastomas
- Cerebral hemispheres
- Mean age patient: 44 yrs
- Pleomorphic tumor cells with nuclear atypia
- Different components (small, granular, lipidized cells)
- Microvascular proliferation
- Palisading necrosis
- Brisk mitotic activity

- **Ki67 >15%**
- **ATRX mutation +**



# Glioblastoma IDH-wild type

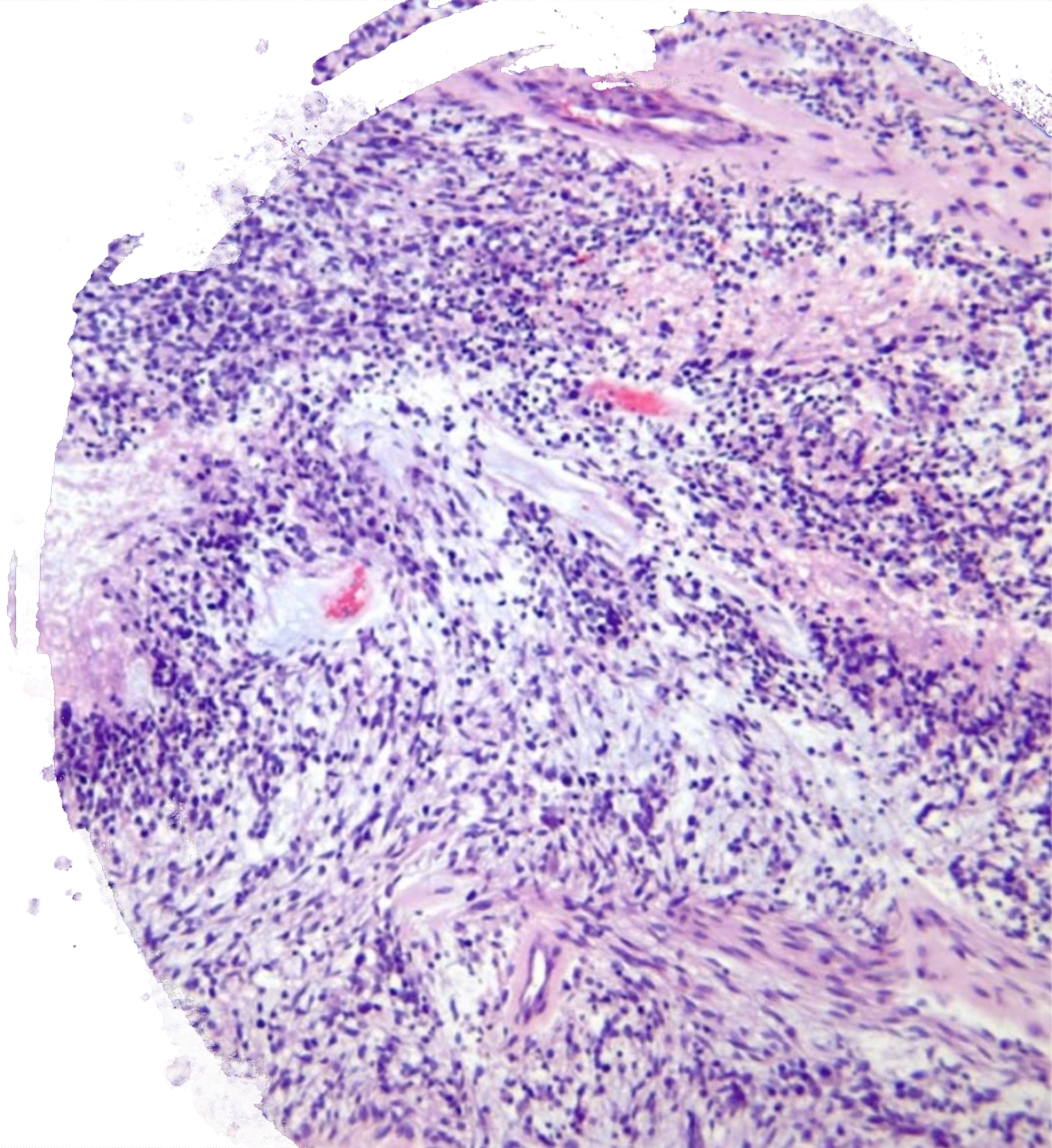
WHO Grade IV

- 90% of glioblastomas
- Mean age patient 62 yrs
- Same histology as glioblastoma IDH-mutant

- **ATRX mutation -**
- **MGMT methylation**

Hystological variants:

1. Giant cell Glioblastoma
2. Gliosarcoma
3. Epithelioid Glioblastoma

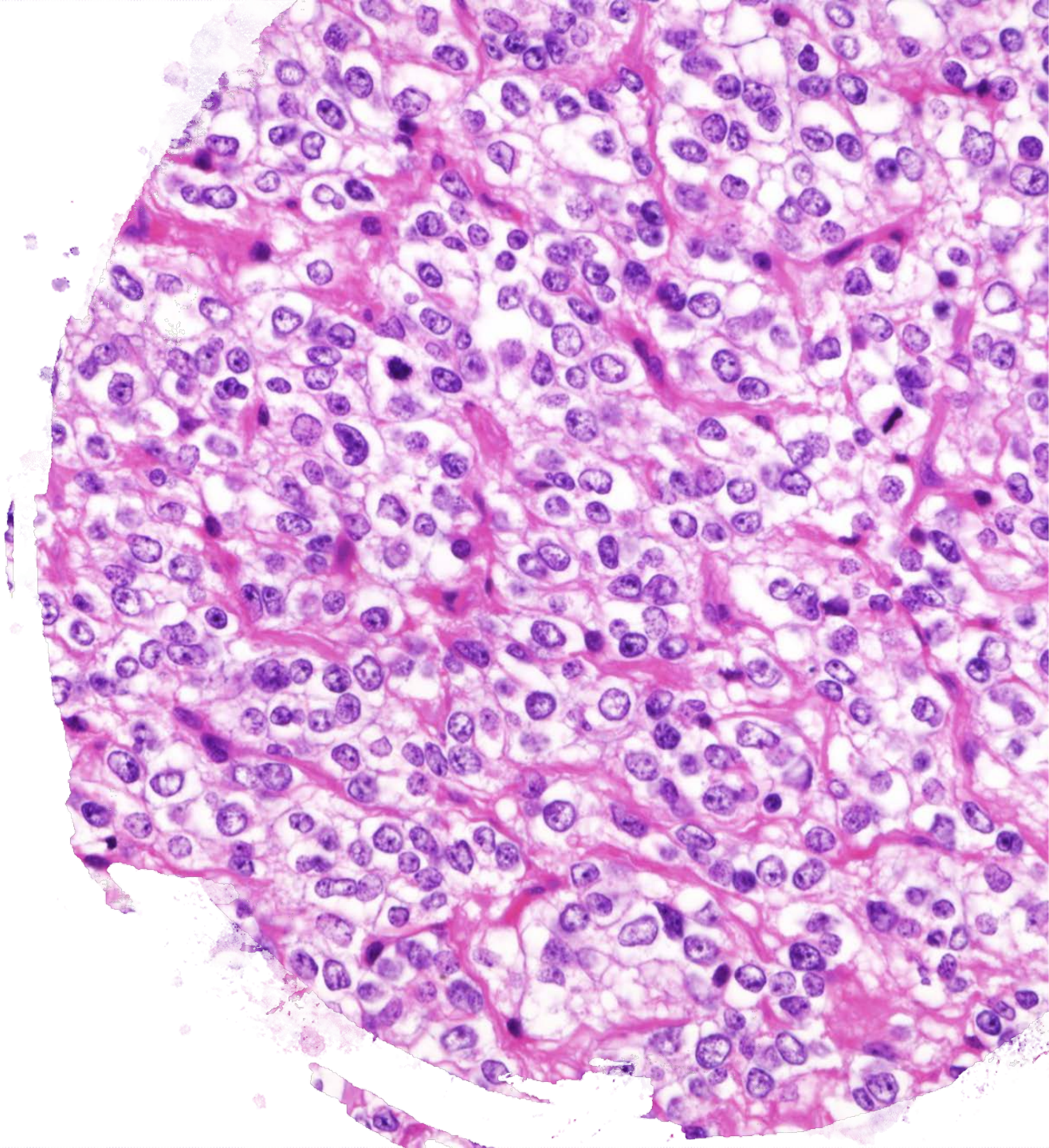


# Oligodendroglioma IDH- mutant and 1p/19q codeleted

WHO Grade II

- Mean age patient 44 yrs
- Commonly in cerebral hemispheres, frontal lobes
- Moderate cellularity
- Clear perinuclear halo
- Central spherical nucleus
- Delicate branching capillaries
- Low or absent mitotic activity
- No microvascular proliferation
- No necrosis

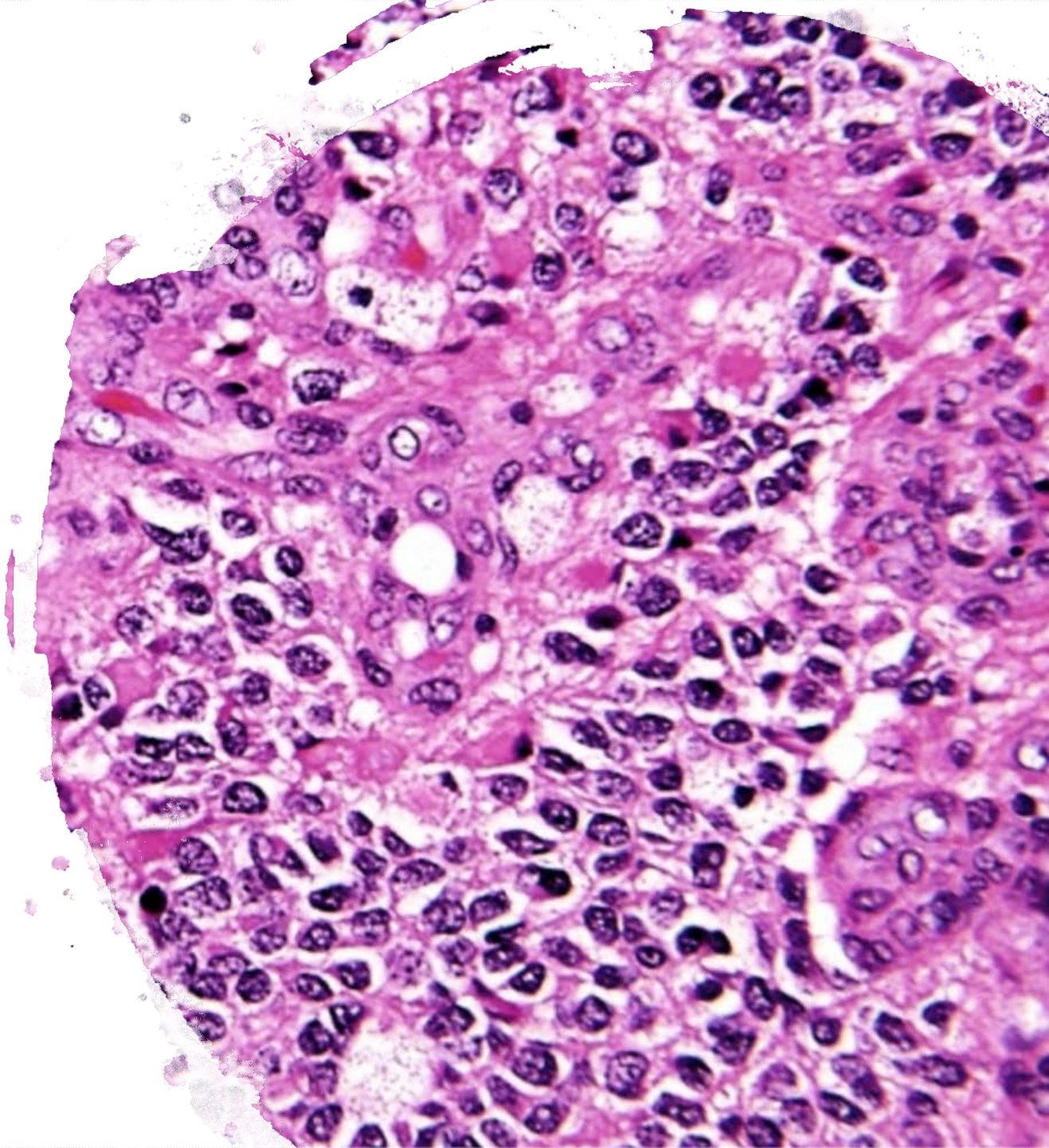
- **KI67 <5%**
- **IDH1 + (or IDH1/2 by PCR)**
- **1p/19q codeletion iby FISH**



# Anaplastic oligodendroglioma IDH-mutant and 1p/19q codeleted

WHO Grade III

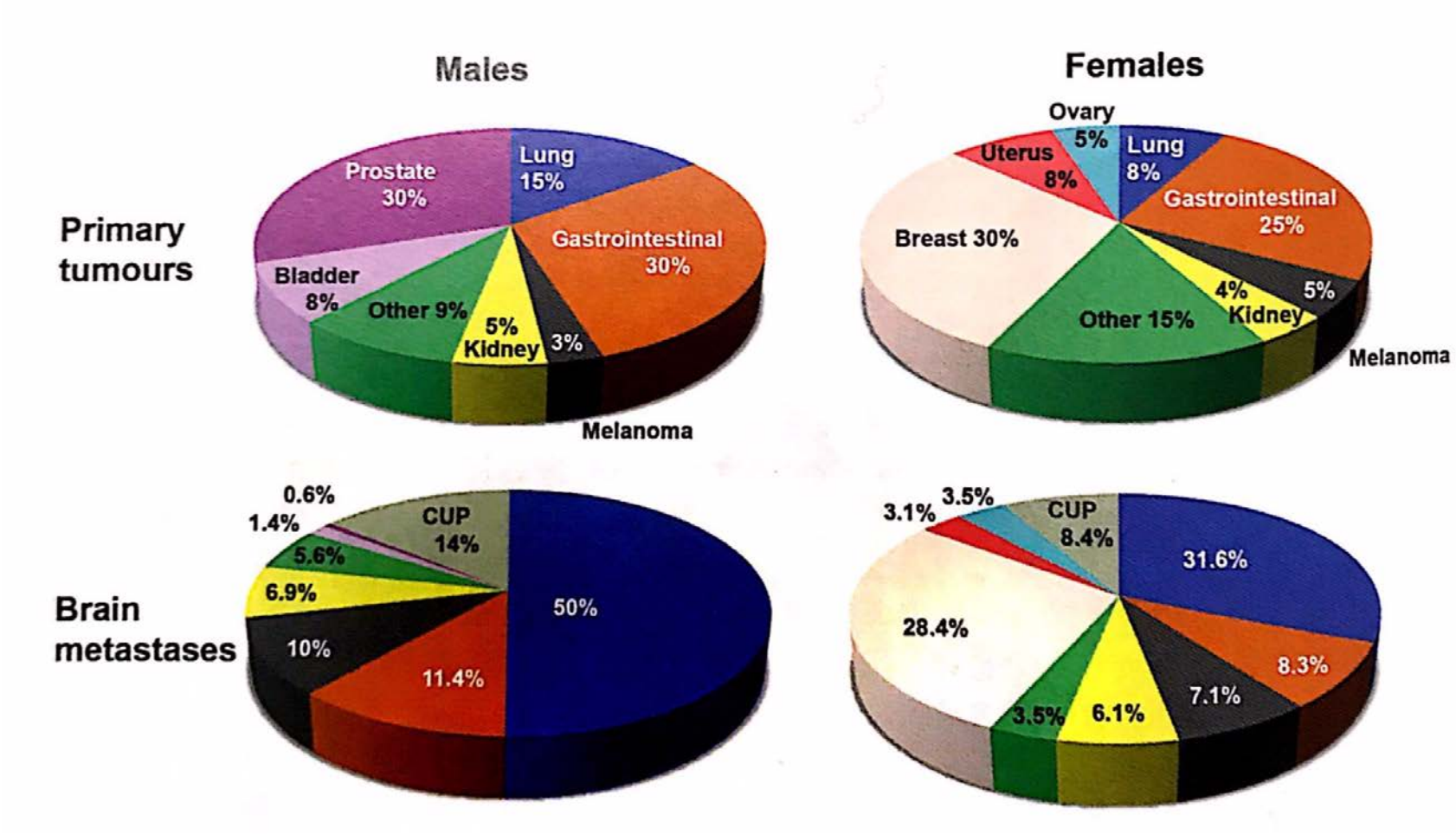
- Mean age patient 49 yrs
- Cerebral hemispheres, frontal lobes.
- High cellularity
- Distinct cellular atypia
- Brisk mitotic activity
- Microvascular proliferation
- Necrosis



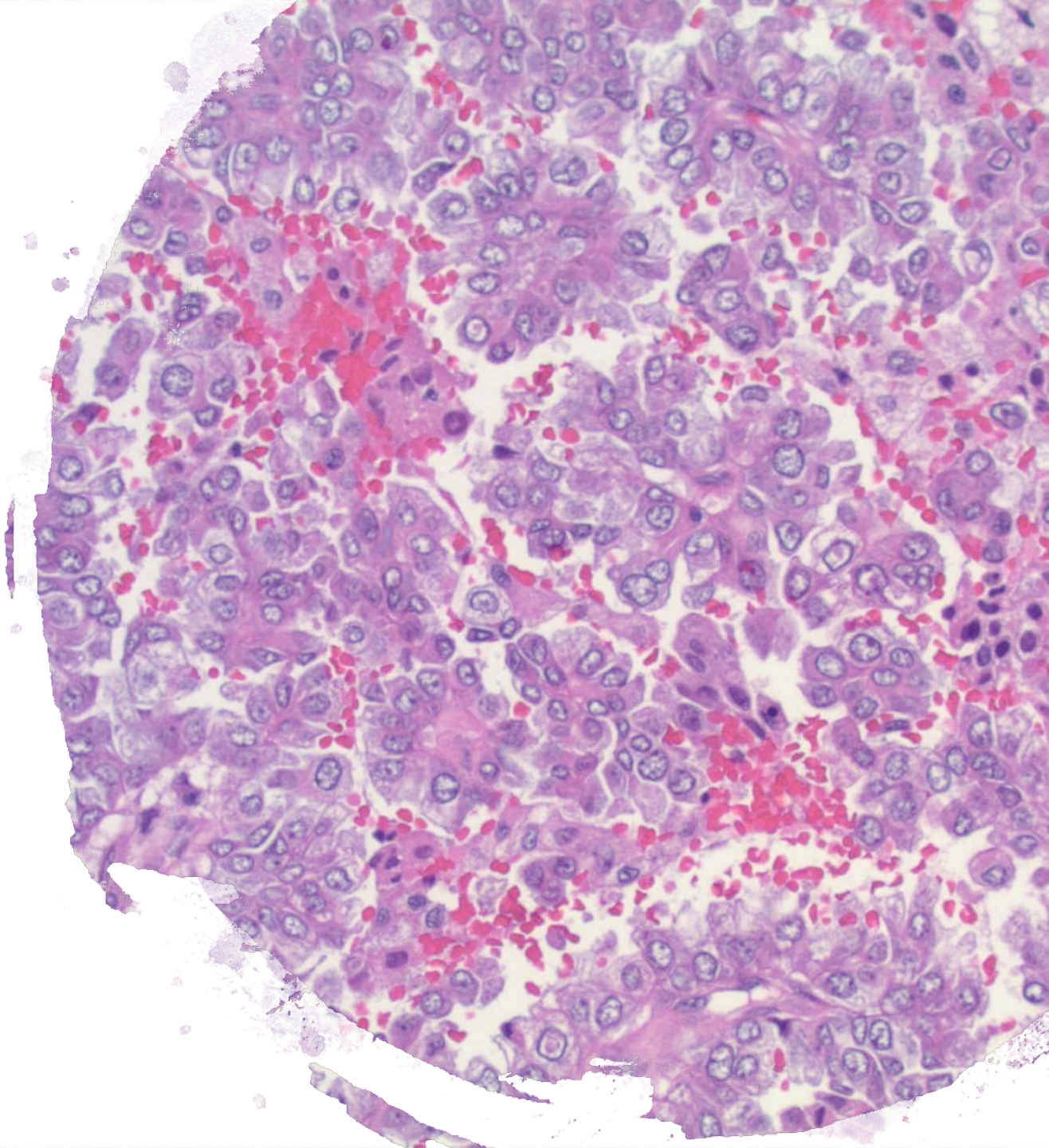
- **Ki67 >5%**
- **IDH1 + (or IDH1/2 by PCR)**
- **1p/19q codeletion by FISH**

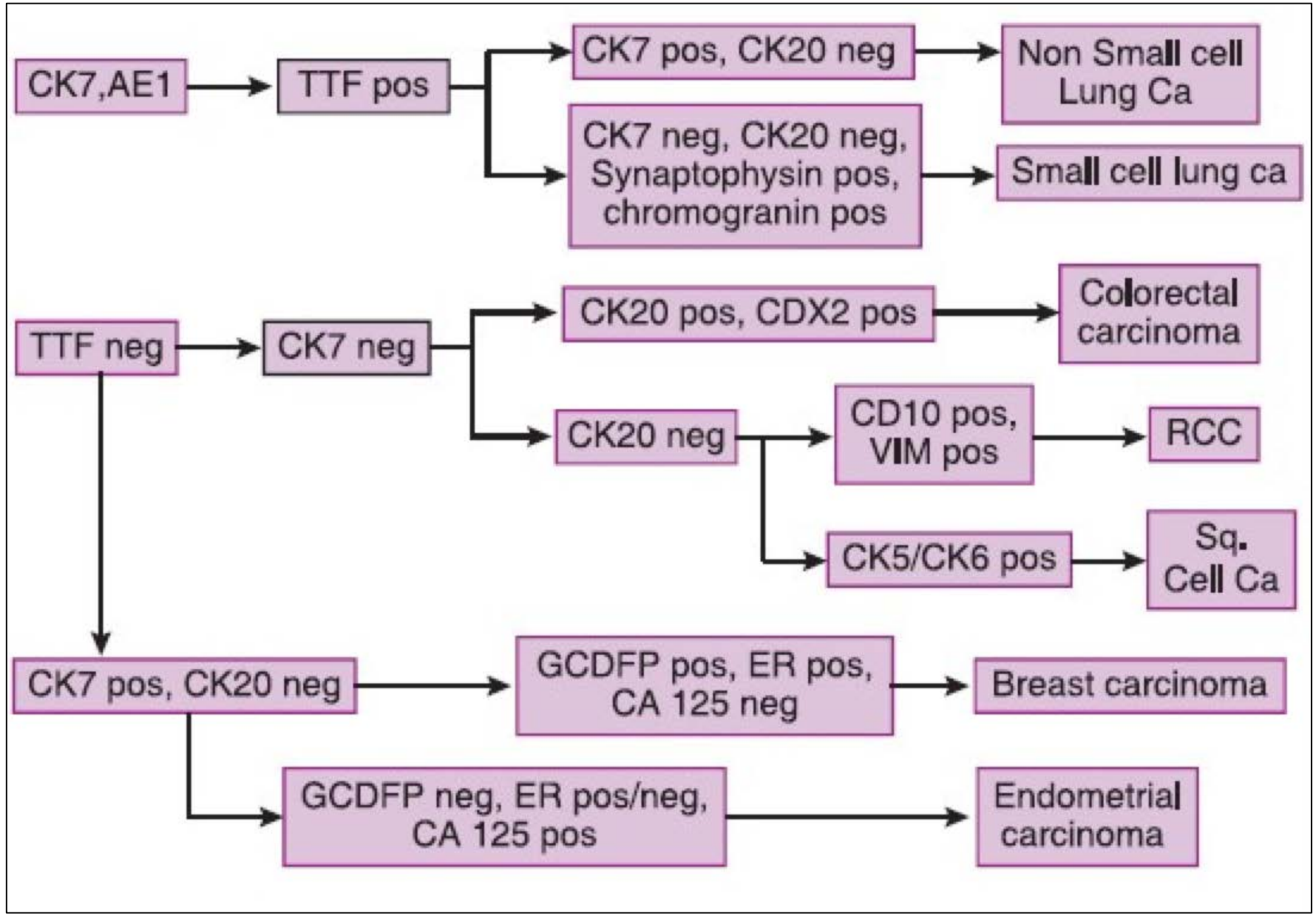
# CNS metastases

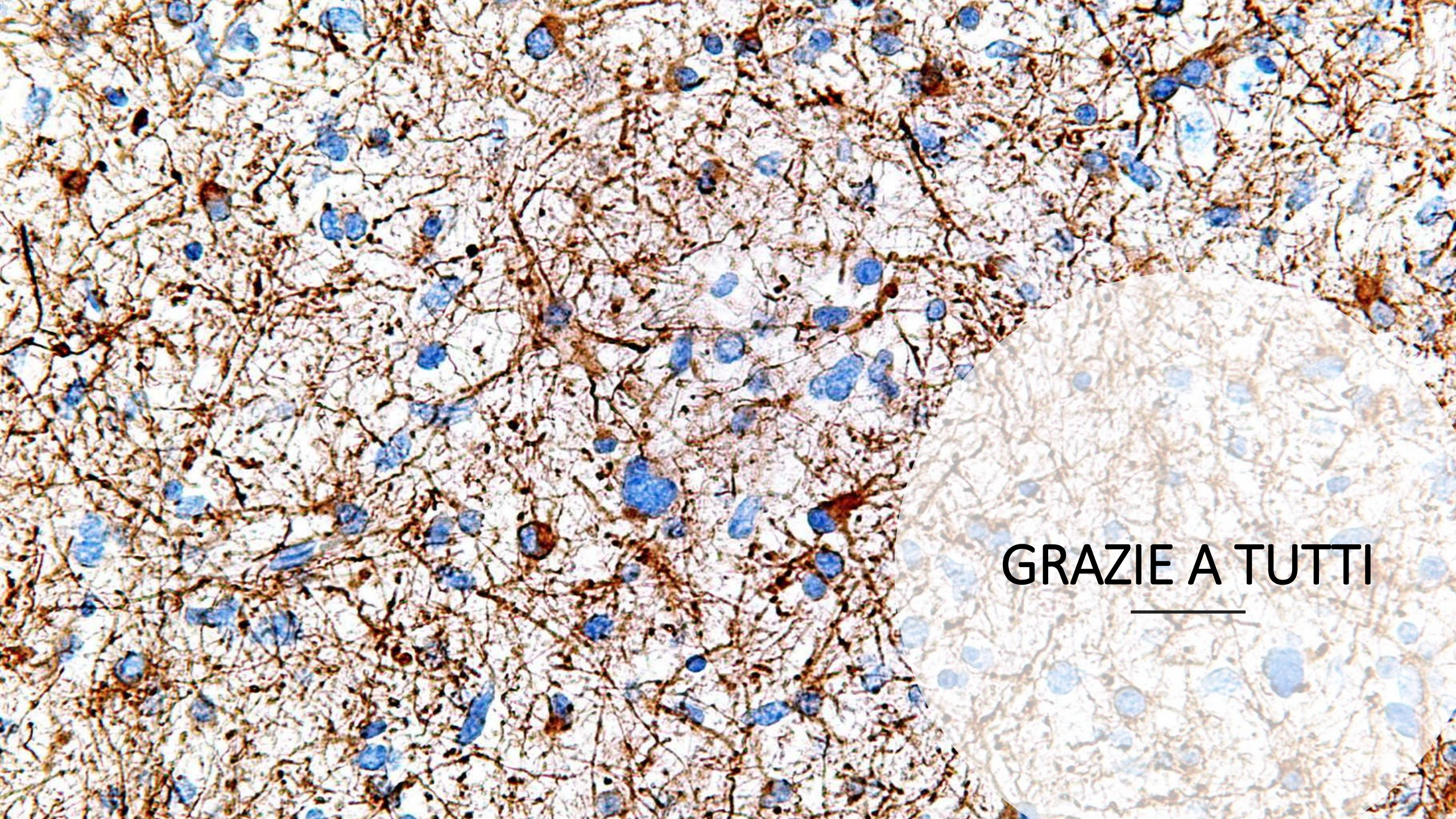
- More than primary tumors
- Localization in hemispheres (80%); 15% in the cerebellum; 5% brain stem
- More than half are multiple



- Well defined and rounded greyish-white with central necrosis
- Haemorrhagic and brown to black in pigmented melanoma
- Perivascular growth, gliosis, oedema in the adiacent CNS tissue
- Central tumor necrosis with tumor tissue at the periphery and around blood vessels
- Morphology similar to high grade glioma but GFAP -, Olig2 -
- Proliferation index (Ki67) maybe higher than in the primary tumors




CK7,AE1
TTF pos
CK7 pos, CK20 neg
Non Small cell Lung Ca
CK7 neg, CK20 neg, Synaptophysin pos, chromogranin pos
Small cell lung ca
TTF neg
CK7 neg
CK20 pos, CDX2 pos
Colorectal carcinoma
CK20 neg
CD10 pos, VIM pos
RCC
CK5/CK6 pos
Sq. Cell Ca
CK7 pos, CK20 neg
GCDFP pos, ER pos, CA 125 neg
Breast carcinoma
GCDFP neg, ER pos/neg, CA 125 pos
Endometrial carcinoma


GRAZIE A TUTTI