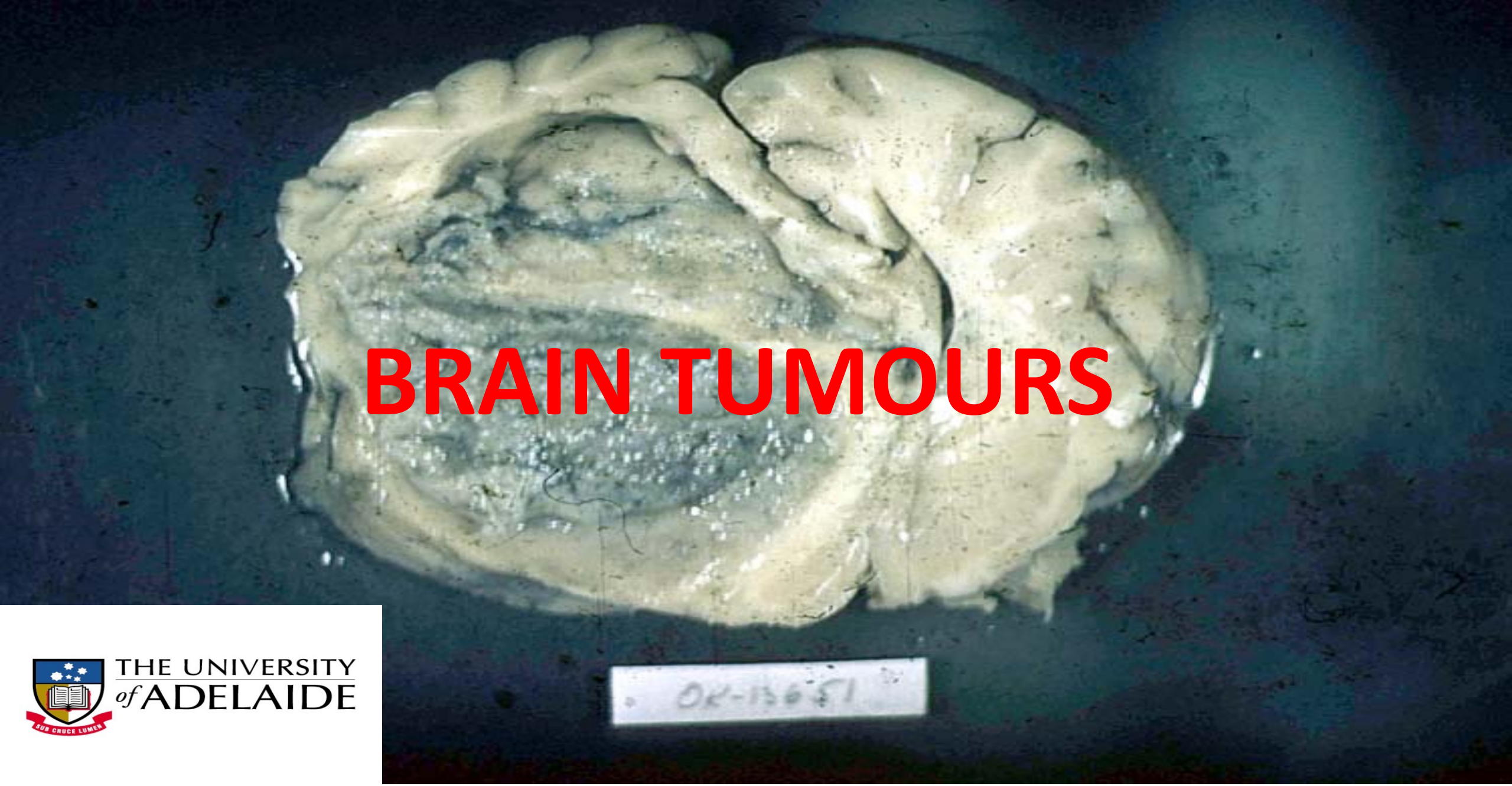

THE UNIVERSITY of ADELAIDE

A/Professor John Finnie

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Benign tumours

Well-differentiated with a similar structure to tissue of origin

Little or no anaplasia (cellular atypia)

Slow progressive expansion

Mitotic figures rare

No invasion, but cohesive, expansile growth

Often encapsulated; no metastasis

Malignant tumours

Lack some differentiation and their structure is often atypical

Variable anaplasia

Slow-to-rapid, erratic growth

Mitotic figures often numerous and sometimes atypical

Local infiltration

Usually not encapsulated

Often contain necrotic areas (where growth exceeds the capacity of the blood supply to sustain tumour)

Frequent metastasis (but those of the CNS very rarely metastasise, but are notably invasive)

Account for <2% of all malignant neoplasms, but are the second most common tumour of children after leukaemia

Of all intracranial tumours, ~60% are of neuroepithelial origin, 30% meningeal, 5% from cranial and spinal nerves, 4% lymphomas, and 1% germ cell tumours

The WHO classification lists ~120 different types and subtypes of nervous system tumours and incidence, location, age and sex distribution, biological behaviour and patient survival differ greatly for most of these neoplasms

It is therefore likely that aetiologies and biological underpinnings of many CNS tumours are varied

Mortality rates are highly dependent on the type of tumour – some lesions (WHO grade I) can be relatively benign and others (WHO grades II-IV) showing different degrees of malignancy, with type IV typically having survival times <2 years from time of diagnosis

Mortality rates are also influenced by the effectiveness of diagnostic and therapeutic measures and highly related to the location in the nervous system with some amenable to removal and others having debilitating side-effects

Females have a lower incidence of gliomas, but a higher predilection to develop meningiomas

Age distribution is bimodal, with the first peak in children and a second, larger peak in adults 45-70 years of age, mainly due to glioblastomas

Some geographic variation in brain tumour incidence, being higher in developed, industrialised countries

Variability in genes across populations could predispose certain individuals to brain tumours and affect their response to therapy (pharmacogenomics)

Also complex interactions between race, genetic constitution, tumour genotype, age and gender

Aetiology of brain tumours is largely unknown, with therapeutic X-ray irradiation the sole environmental factor associated with increased risk of developing brain tumours

Classification and grading of brain tumours

Tumours of the nervous system present with a wide variety of histological appearances

Classifications have been based variously on morphological features, biological behaviour, cells of origin, histological resemblances, expression of particular molecules, and genetic abnormalities

The World Health Organisation (WHO) classification uses primarily histological appearance, abetted by genetic and immunohistochemical features

Grading attempts to assign a numerical value to expected biological behaviour, ranging from benign (grade 1) to malignant (grade IV)

Grading and classification

From a clinical perspective, the following information is required: patient age and gender, location of tumour, neuroradiological findings, and past medical history

The patient's age and tumour location narrows the differential diagnosis to a remarkable degree, abetted by neuroradiology

Immunohistochemistry (IHC) is very useful for identifying lines of differentiation (e.g. GFAP in glial tumours and cytokeratins in epithelial tumours) and tumour grading by proliferation markers

Grading and classification

Electron microscopy has been largely superseded by IHC and is only used to define poorly differentiated tumours

Molecular genetics is also important to characterise some tumours and is useful to determine some treatment decisions (e.g. type of chemotherapy or radiation therapy)

Multi-step theory of tumourigenesis in gliomas

Tendency for neoplasms to evolve to higher states of biological aggressiveness (malignant progression), especially gliomas, where >50% progress to higher grades of malignancy

Also regional morphological variations in a given glioma grade, providing additional evidence of the dynamic nature of the oncogenic process operative in individual tumours

Most malignant tumours are derived from the accumulation of multiple genetic alterations, including amplification of some oncogenes and loss of certain suppressor genes (e.g. p53)

Oncogenes

An oncogene is any DNA sequence which encodes a protein capable of transforming cells in culture o inducing cancer in animals

Cellular oncogenes are termed proto-oncogenes and are present in the genome of every cell and are required for normal growth and differentiation

Proto-oncogenes can be mutated by a variety of genetic mechanisms to form oncogenes and overexpression of oncogenes plays an important role in the genesis of cancers by interacting with growth regulating mechanisms

Oncogenesis

In oncogenesis, disruption of the cellular balance between positive and negative growth regulating mechanisms leads to a transformed phenotype

Enhanced positive regulation by oncogenes is important in mediating tumour progression

In the multi-step paradigm of carcinogenesis, there is a predictable and progressive rise in cytogenetic aberrations acquired by gliomas during their evolution to increasing grades of malignancy – in low-grade astrocytomas, there are only subtle karyotypic abnormalities, whereas GBM's represent the most extensive form of cytogenetic deviation

Brain tumours and ICP

Ability of primary brain tumours to disrupt the blood-brain barrier (BBB), induce vasogenic cerebral oedema, increase intracranial pressure (ICP) and generate seizures is a common feature of virtually all brain tumours

Tumour-associated oedema is an important factor in brain tumour morbidity and mortality

Monro-Kellie doctrine:

Because the brain is encased in a rigid skull, any volumetric change to one of the intracranial constituents (brain, CSF or blood) must be compensated for by a reciprocal and equivalent volume reduction in the other constituents

Brain tumours and ICP

The ICP will only rise when these compensatory mechanisms are exhausted

Brain tumours generate a raised ICP by 2 main mechanisms:

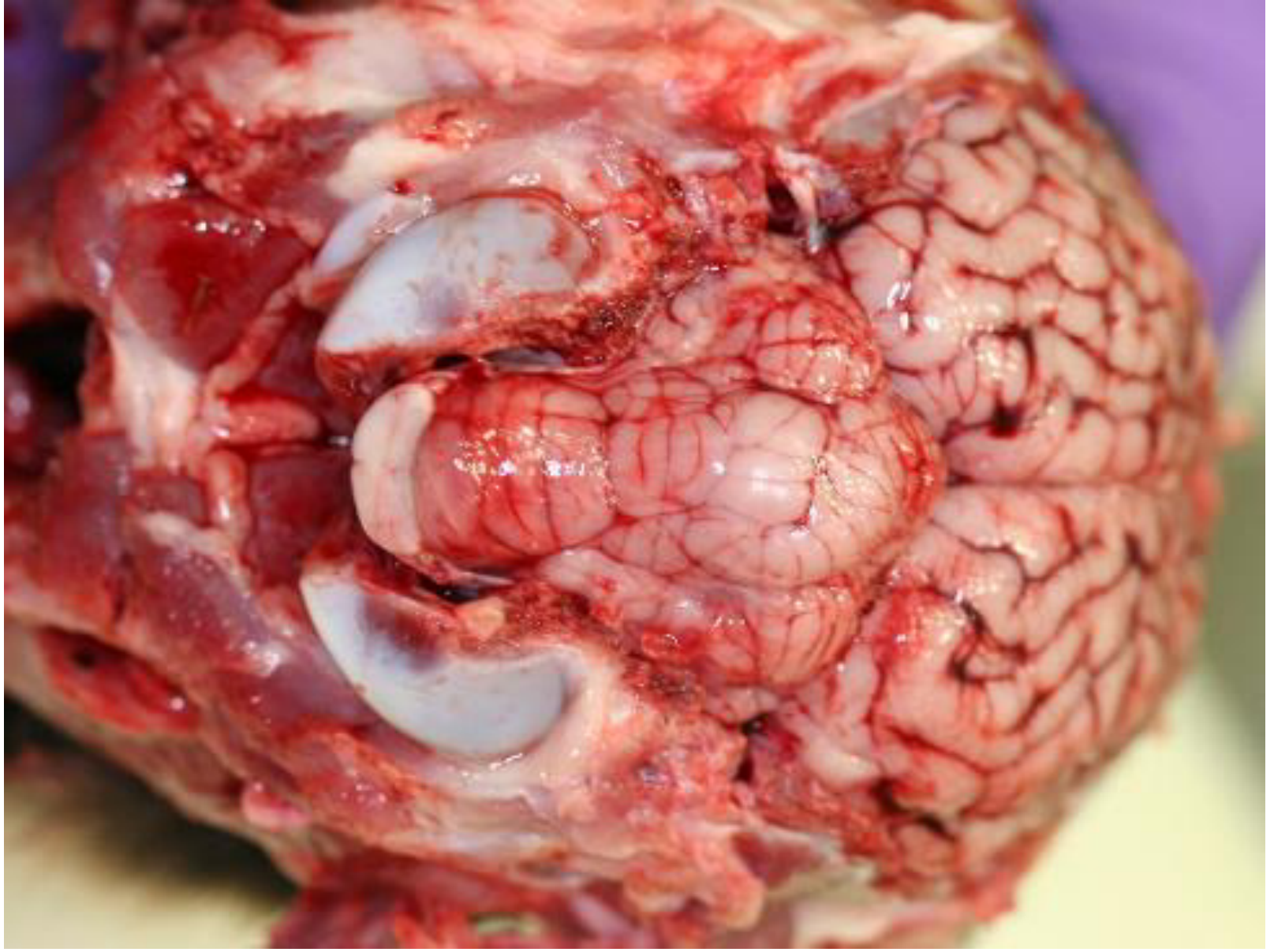
1. **Volumetric addition of the relentlessly expanding, space-occupying tumour mass, often supplemented by substantial peritumoural vasogenic oedema and sometimes haemorrhage**
2. **2. CSF obstruction and resultant hydrocephalus**

Brain tumours and ICP

Eventually a marked reduction in cerebral perfusion, brainstem compression and herniation will ensue

Cranial cavity is compartmentalised by the falx cerebri (between hemispheres) and tentorium cerebelli (between hemispheres and cerebellum) and only available exit from the cranial cavity is the foramen magnum

Posterior cranial space is less tolerant to expanding tumours than the supratentorial compartment, commonly leading to downward protrusion and impaction of cerebellar tonsils, which descend through the foramen magnum into the spinal canal ("cerebellar coning")



Herniation of the cerebellar tonsils through the foramen magnum into spinal canal (“cerebellar coning”)

Cerebellar coning with haemorrhagic necrosis of herniated cerebellar tonsils

Brain tumours and cerebral oedema

Brain oedema can contribute to headache, focal neurological signs, and depressed levels of consciousness

In gliomas, the dramatic clinical improvement with steroid therapy highlights the profound contribution of oedema to clinical signs

With brain tumours, increased ICP often proves to be the inevitable and frequently fatal complication of many intracranial tumours

Clinical signs of raised ICP

Headache – initial symptom in ~50% of brain tumour patients and will eventually occur in all. Caused by traction, distortion or irritation of pain-sensitive structures in intracranial compartment, especially dura and blood vessels. Characterised by rapid onset and progression, increasing in frequency, severity and duration and especially prominent in the early morning. May be diffuse and bilateral or more localising, reflecting the tumour site

Vomiting – especially in children

Alterations in consciousness – ranging from subtle to coma

Papilloedema – most common and reliable sign of raised ICP, which blocks axonal transport in optic nerve, leading to its swelling

Brain tumour neovascularisation

In brain tumours, the ability to acquire a new blood supply is critical to sustaining further growth and dissemination

Up to 1-2 mm in diameter, nutrients and oxygen can be obtained by diffusion from nearby blood vessels, but larger tumours need a new blood supply or they undergo necrosis

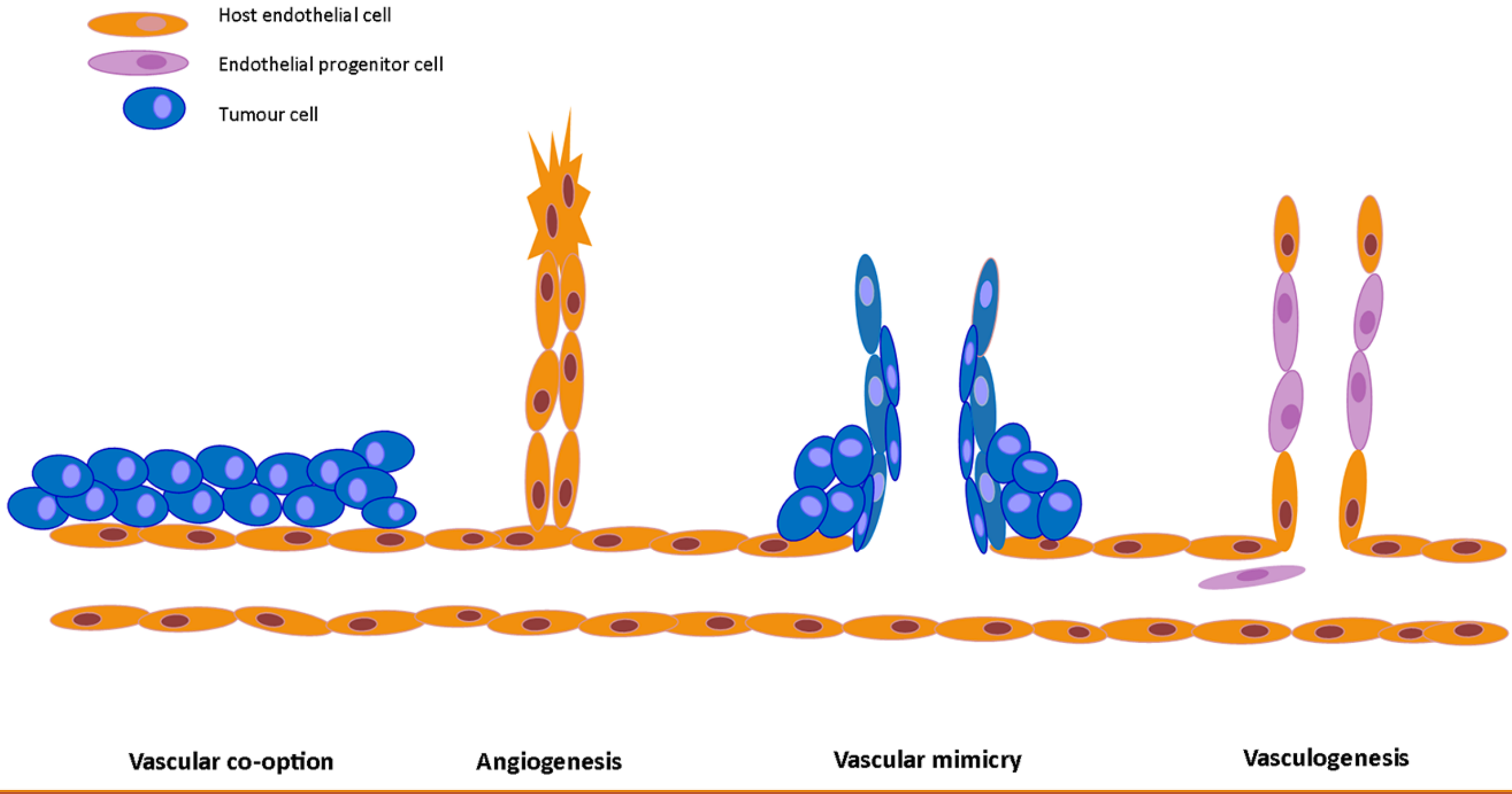
Necrosis is largely driven by intra-tumoral hypoxia (mediated by hypoxia-inducing factor or HIF) and tightly regulated by pro- (particularly vascular endothelial growth factor or VEGF) and anti-angiogenic growth factors

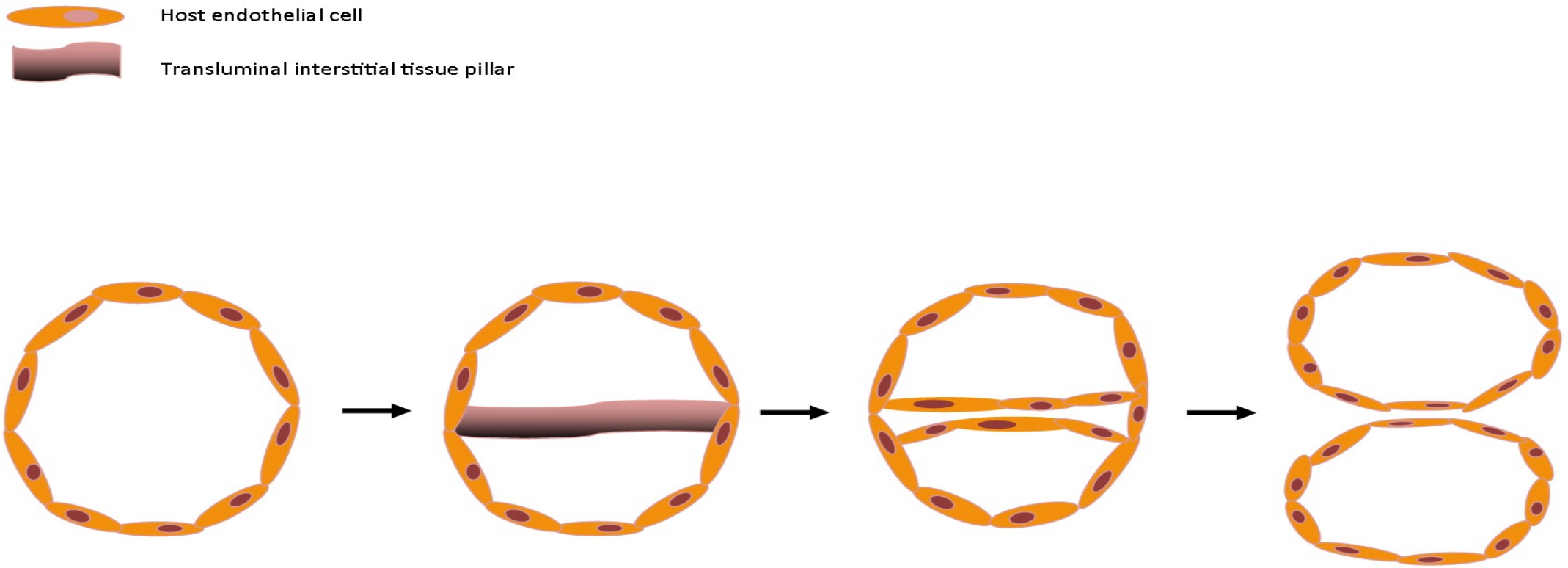
Brain tumour neovascularisation

Tumour-associated blood vessels are structurally anarchic (with disorganised, highly permeable walls, dilated lumina and endothelial cell proliferation), functionally aberrant, and prone to haemorrhage

Brain tumours can acquire a new vascular supply by a number of different mechanisms

1. **Vascular co-option: where nutrients and oxygen are obtained by co-opting nearby blood vessels**
2. **Sprouting angiogenesis: new vessels formed from pre-existing vessels (the principal mechanism)**
3. **Vascular mimicry: new vascular channels are lined by tumour, not endothelial, cells**
4. **Vasculogenesis: incorporation of endothelial, bone marrow-derived, progenitor and cancer stem-like cells into existing vessels to enlarge them**
5. **Intussusception: splitting of an existing capillary into 2 new vessels**


Host endothelial cell
Endothelial progenitor cell
Tumour cell
Vascular co-option
Angiogenesis
Vascular mimicry
Vasculogenesis


Host endothelial cell
Transluminal interstitial tissue pillar

Astrocytic tumours

Show astrocytic differentiation and most common primary tumours of cerebral hemispheres in adults

Most are diffusely distributed – comprised of diffuse astrocytomas (WHO grade II), anaplastic astrocytomas (WHO grade III), and glioblastomas (glioblastoma multiforme) (WHO grade IV)

Astrocytomas

2 cardinal characteristics:

1. **Diffuse infiltration of adjacent/distant brain regions**

2. **Tendency to progression to a more malignant phenotype by acquisition of genetic alterations**

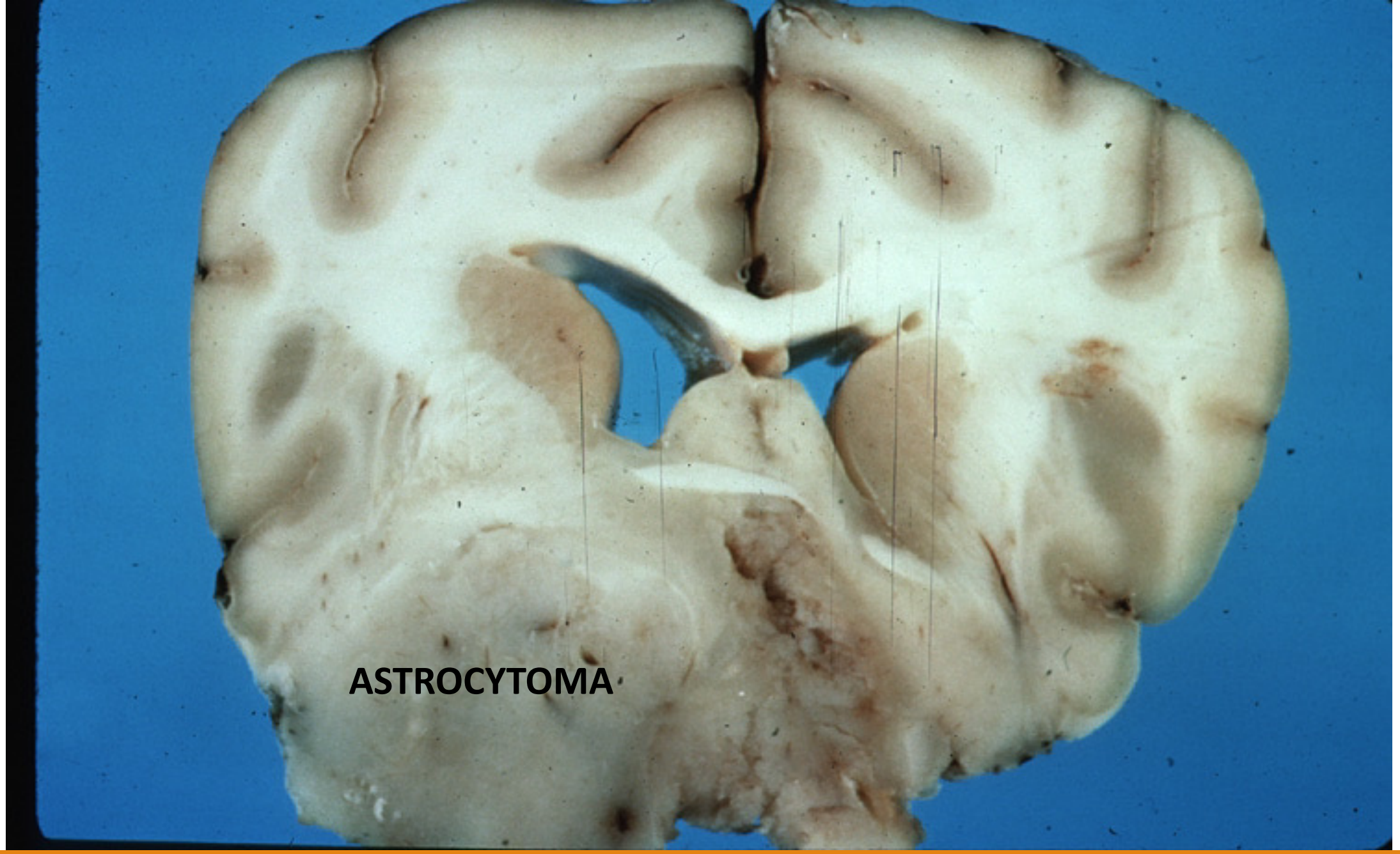
Astrocytomas

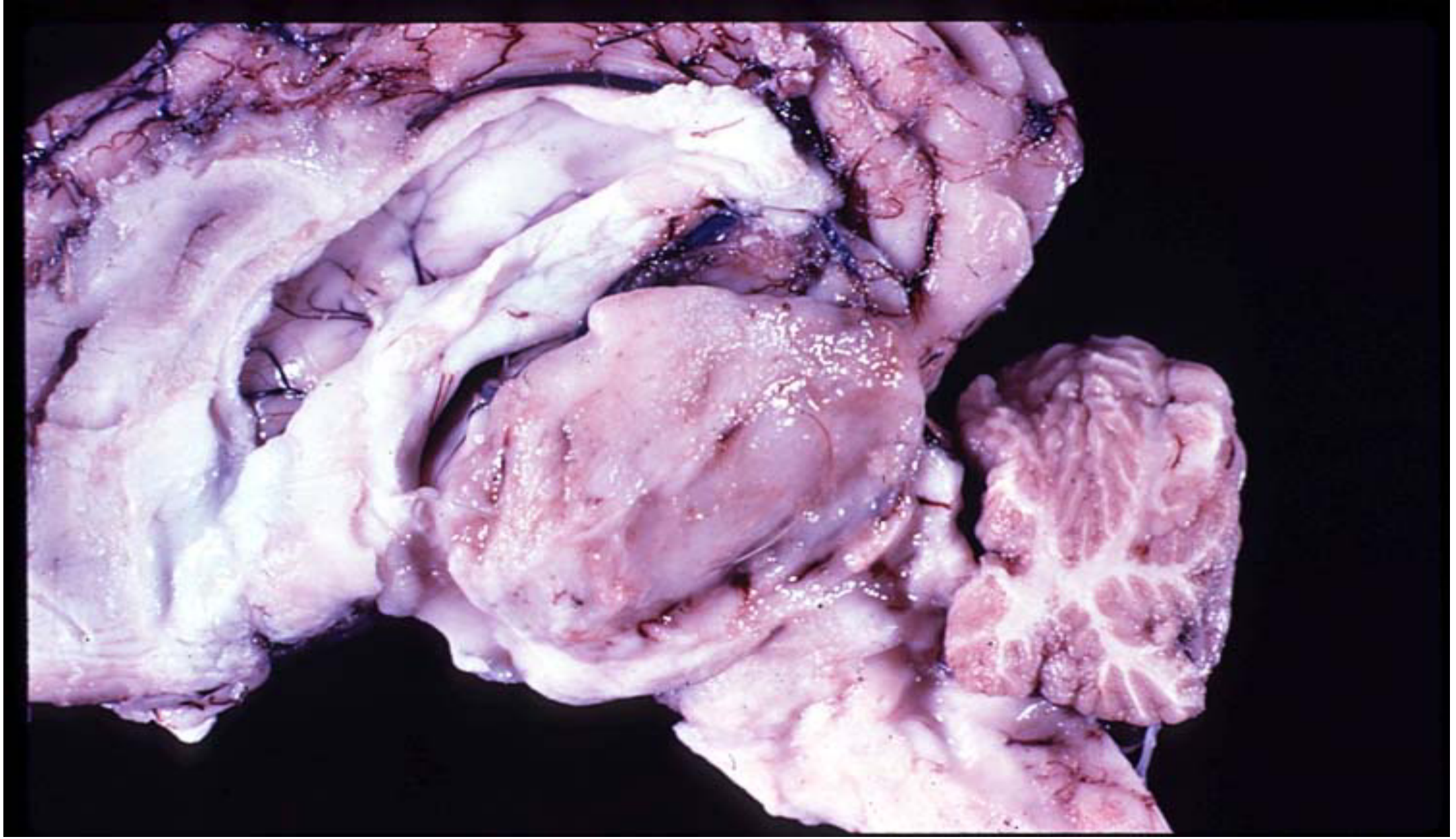
Also characteristic of these tumours are:

1. **Location at any site, but preferentially cerebral hemispheres, especially frontotemporal region, often in subcortical or deep white matter**

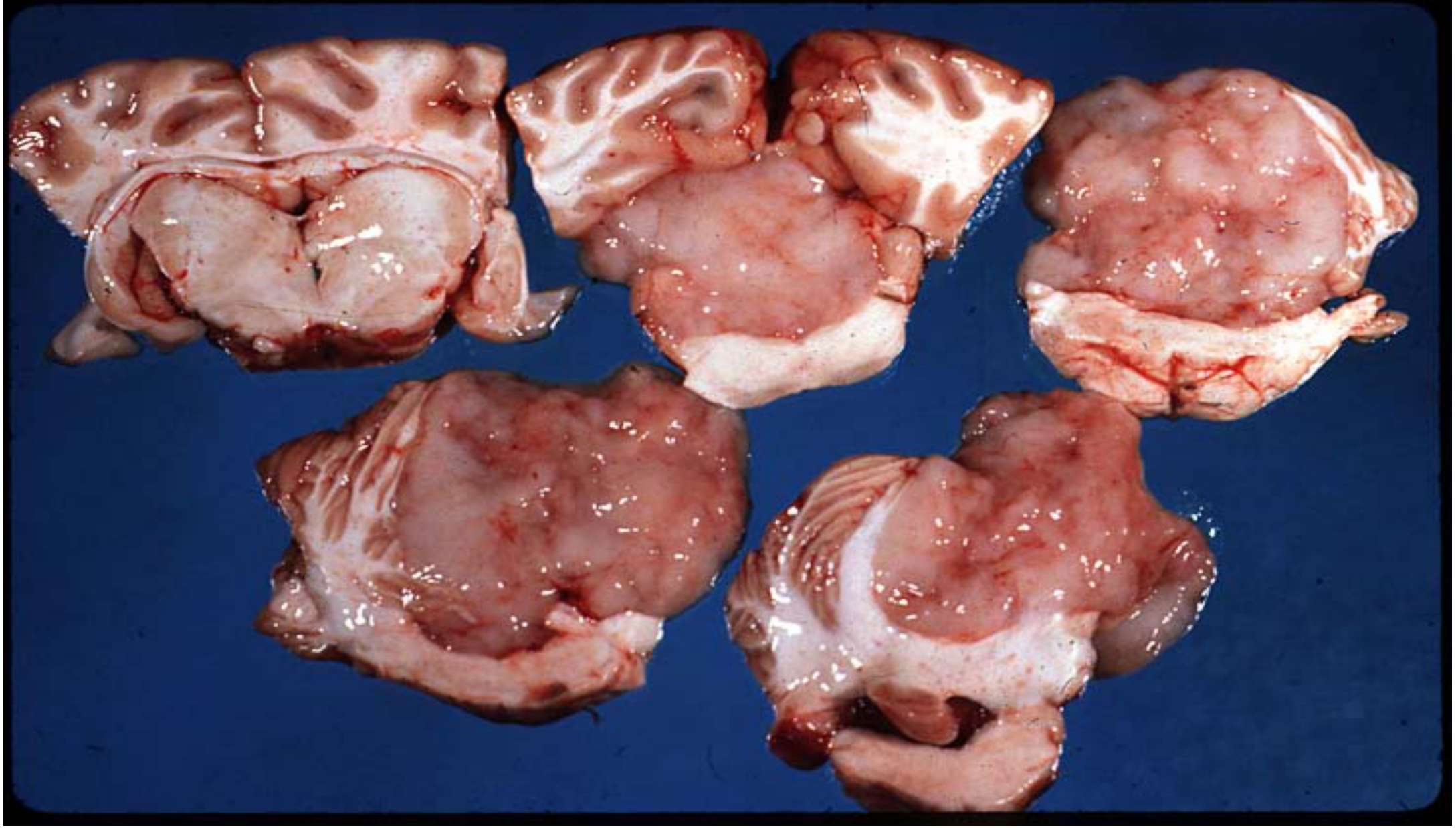
2. **Presentation in adults rather than children**

3. **Range of histopathological features, genetic alterations and biological behaviour**

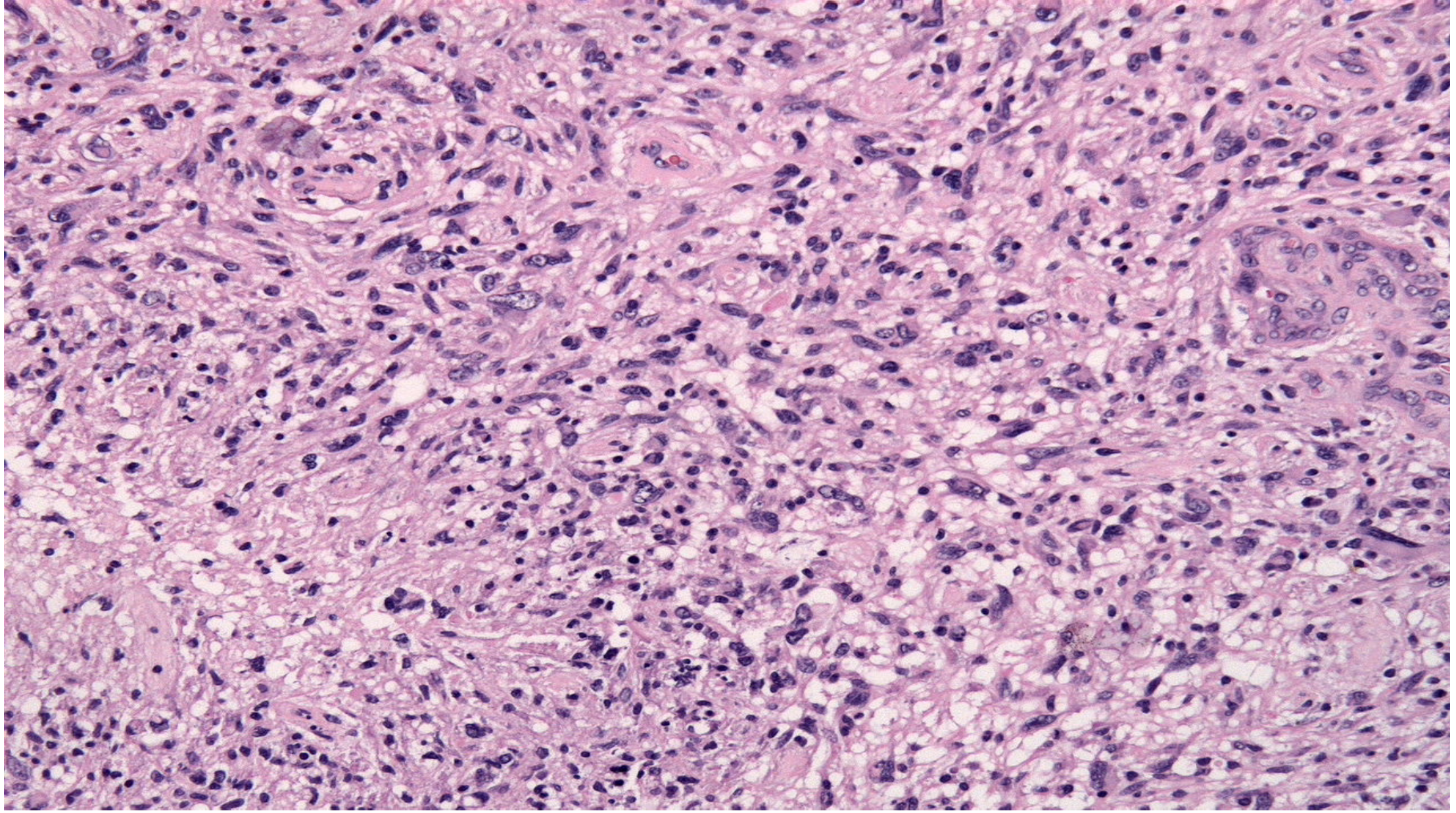

ASTROCYTOMA



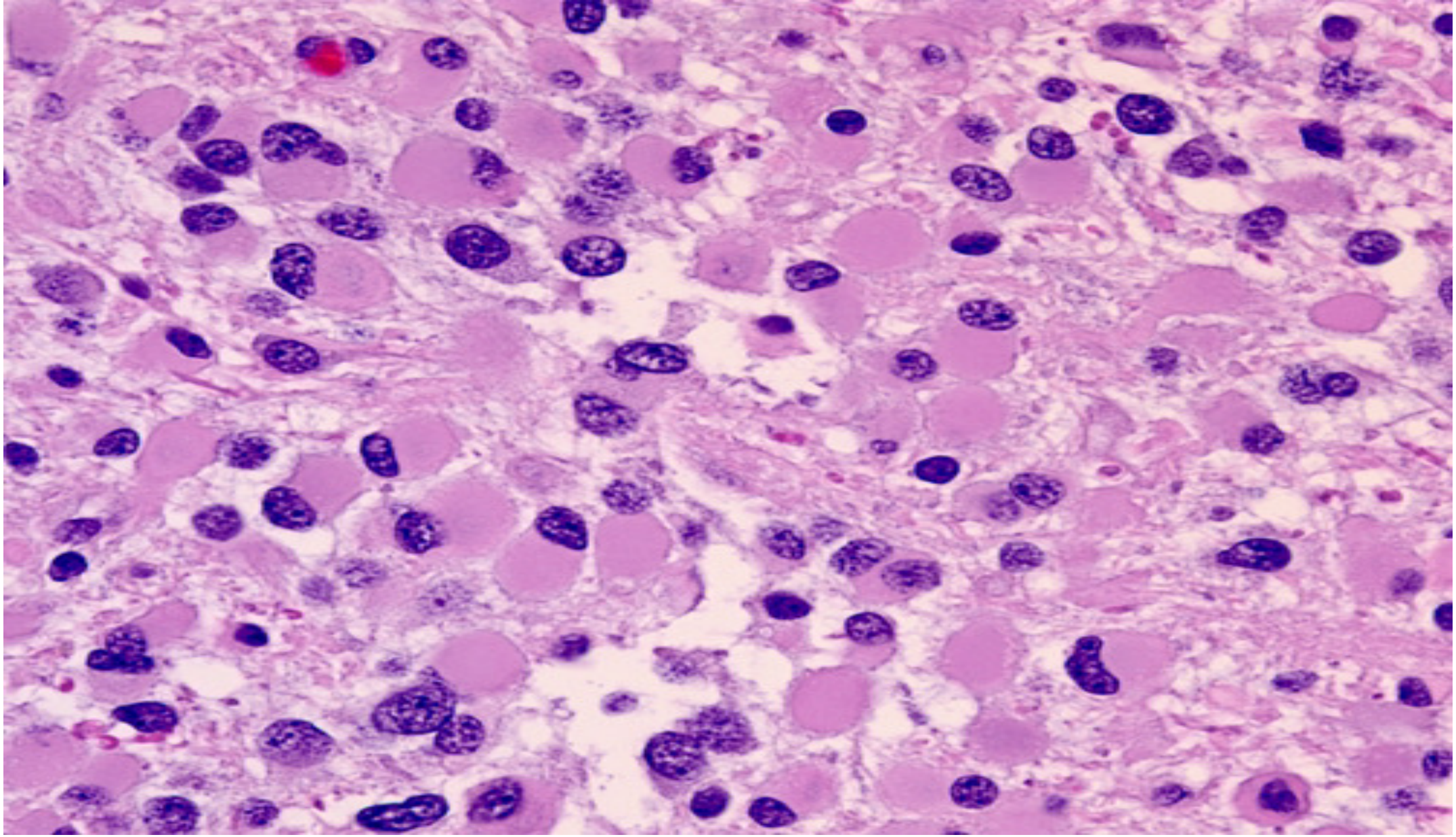
Astrocytoma – large mass between the cerebrum and cerebellum



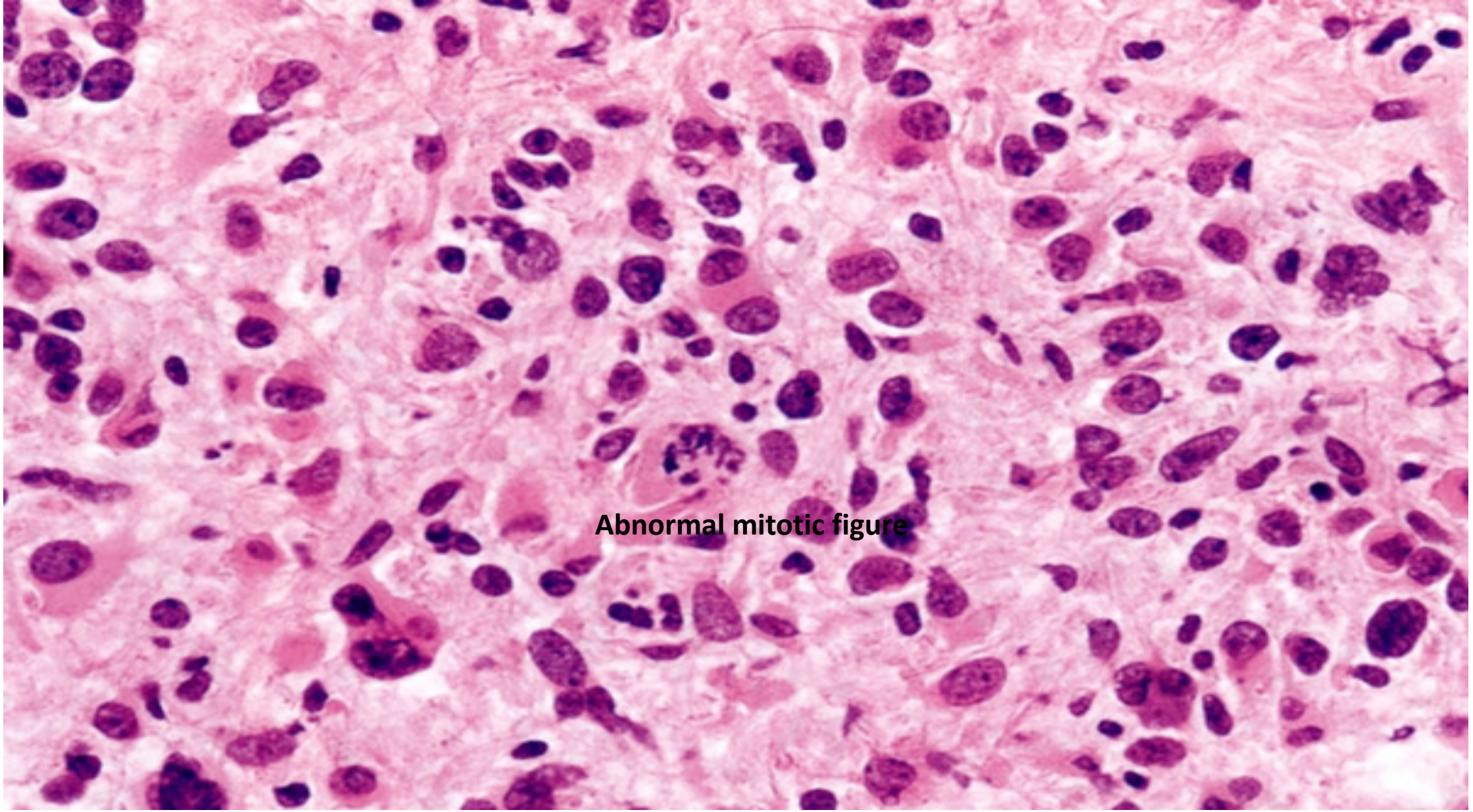
Astrocytoma with involvement of different brain regions



Histological appearance of an astrocytoma



Lower grade astrocytoma with tumour cells showing abundant cytoplasm (gemistocytic astrocytoma)



Anaplastic astrocytoma with nuclei showing marked pleomorphism and an abnormal mitotic figure

Astrocytomas

Most common CNS neoplasm, accounting for ~60% of all brain tumours

Low grade astrocytomas typically affect young adults, glioblastoma peaks in 6th decade, and anaplastic astrocytoma in intermediate ages

Males more commonly affected than females (1.5:1)

Initially, non-localising signs common (headaches, personality changes, seizures), but eventually patients develop increased ICP

Astrocytomas

Malignant gliomas probably arise from progenitor (stem) cells and genetic changes occur for progression from hyperplasia to dysplasia to malignancy

Gliomas have a remarkable tendency to infiltrate surrounding brain, frustrating therapy, especially along WM tracts. Invasion requires an ability to migrate and modulate the extracellular space

Gliomas in subsequent biopsies show increased malignant features and eventually vascular proliferation and necrosis

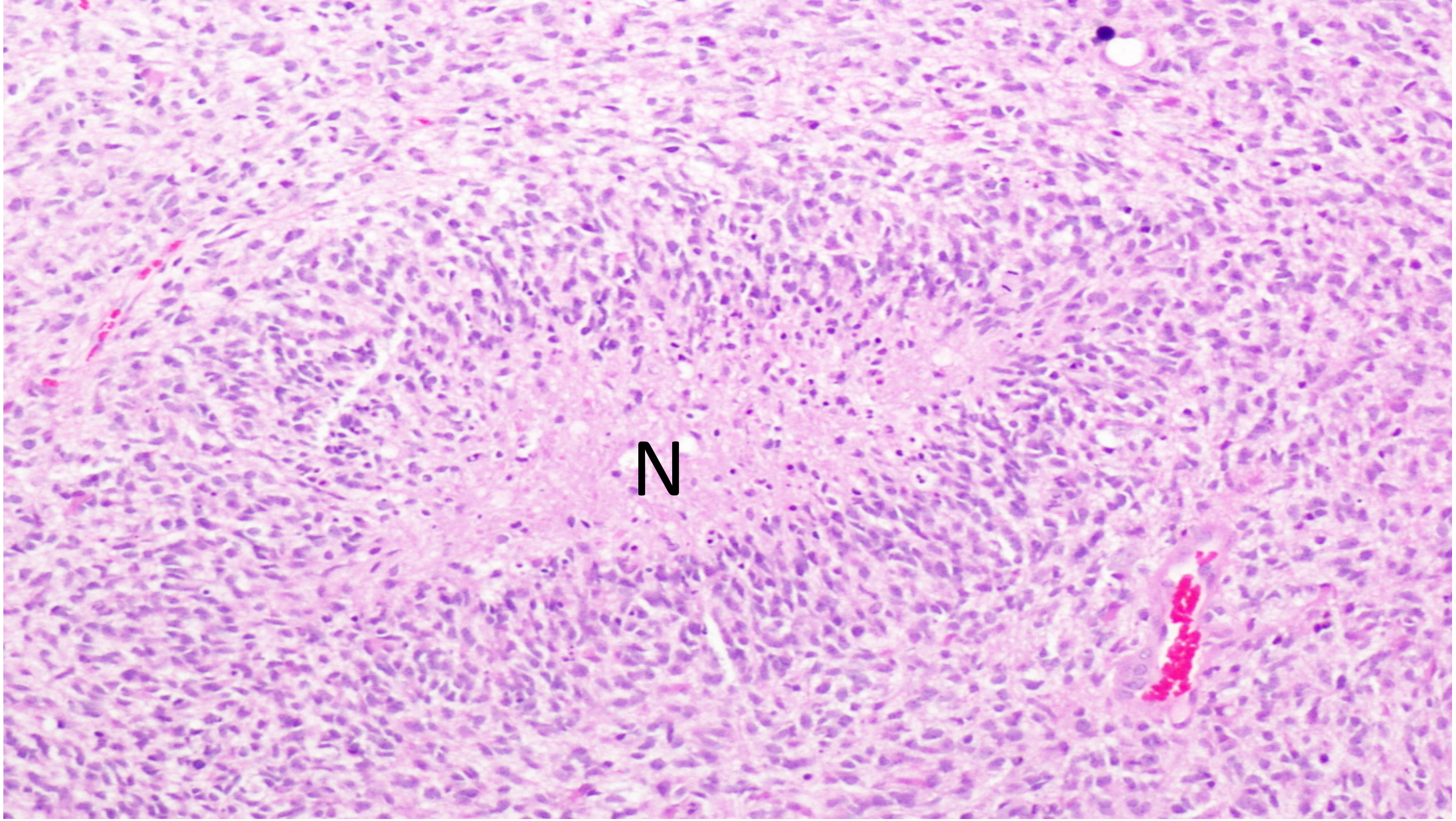
Astrocytomas

Necrosis is a hallmark of high grade astrocytic gliomas, sometimes occupying up to 90% of the tumour mass, and is a good predictor of aggressive behaviour

Necrosis occurs when metabolic demands of continued growth exceeds the vascular supply +/- thrombosis

Necrotic foci are typically surrounded by pseudopalisading glioma cells

Vascular proliferation is a hallmark feature, with characteristic **"glomeruloid tufts"**



Glioblastoma showing a central area of necrosis (N) and surrounding pseudopalisading glioma cells

Glioblastoma

Glioblastoma (formerly termed glioblastoma multiforme or GBM) is a grade IV astrocytoma, usually arising *de novo* after a brief clinical history rather than developing from low-grade or anaplastic astrocytomas

Most common brain tumour – 12-15% of all intracranial neoplasms and 50-60% of all astrocytomas

Notorious for their extensive and rapid invasion of surrounding brain and poor prognosis largely due to this extensive spread, especially along myelinated tracts, making complete surgical excision impossible

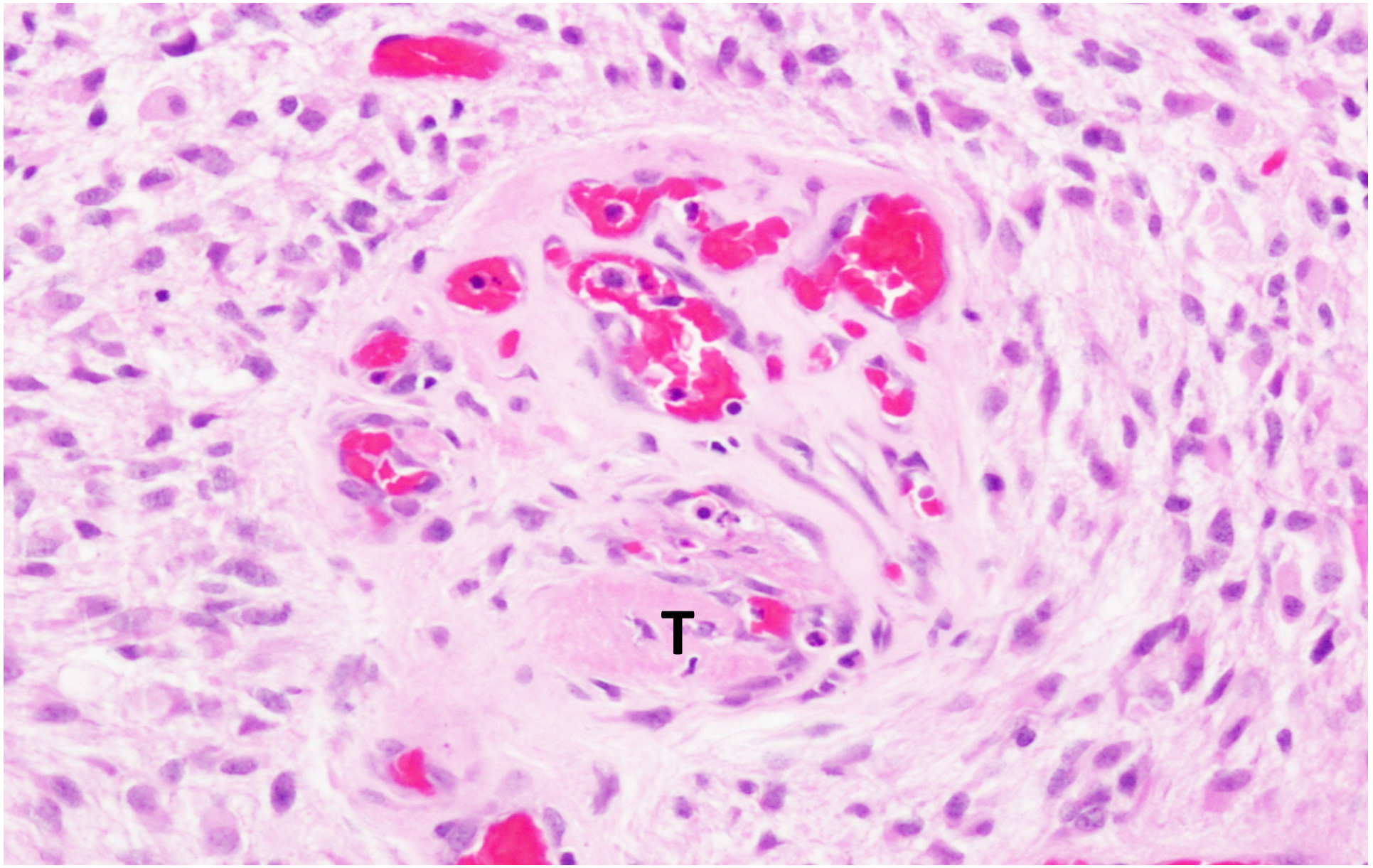
Glioblastoma

Extensive haemorrhages may occur in glioblastomas and evoke stroke-like symptoms

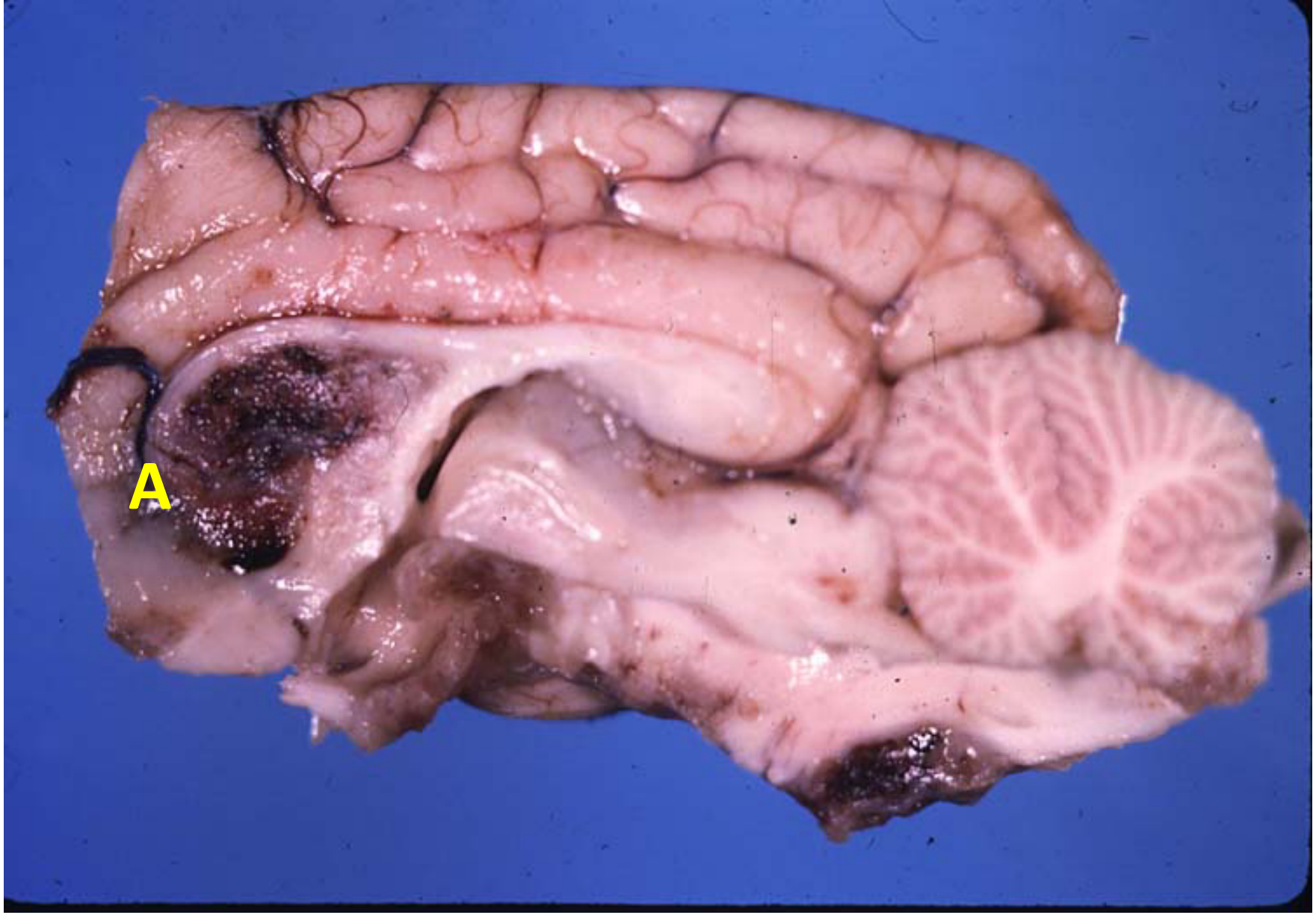
Cardinal diagnostic features are necrosis and microvascular proliferation (especially as “glomeruloid tufts”)

Show variable GFAP immunopositivity

Prognosis most consistently relates to patient’s age – younger patients (<45) have a better prognosis and patients >50 often follow an aggressive clinical course despite having a “lower grade” tumour



Glioblastoma “glomeruloid tuft” of aggregated abnormal blood vessels, one of which is thrombosed (T)



Astrocytoma (A) with a necrotic, haemorrhage appearance

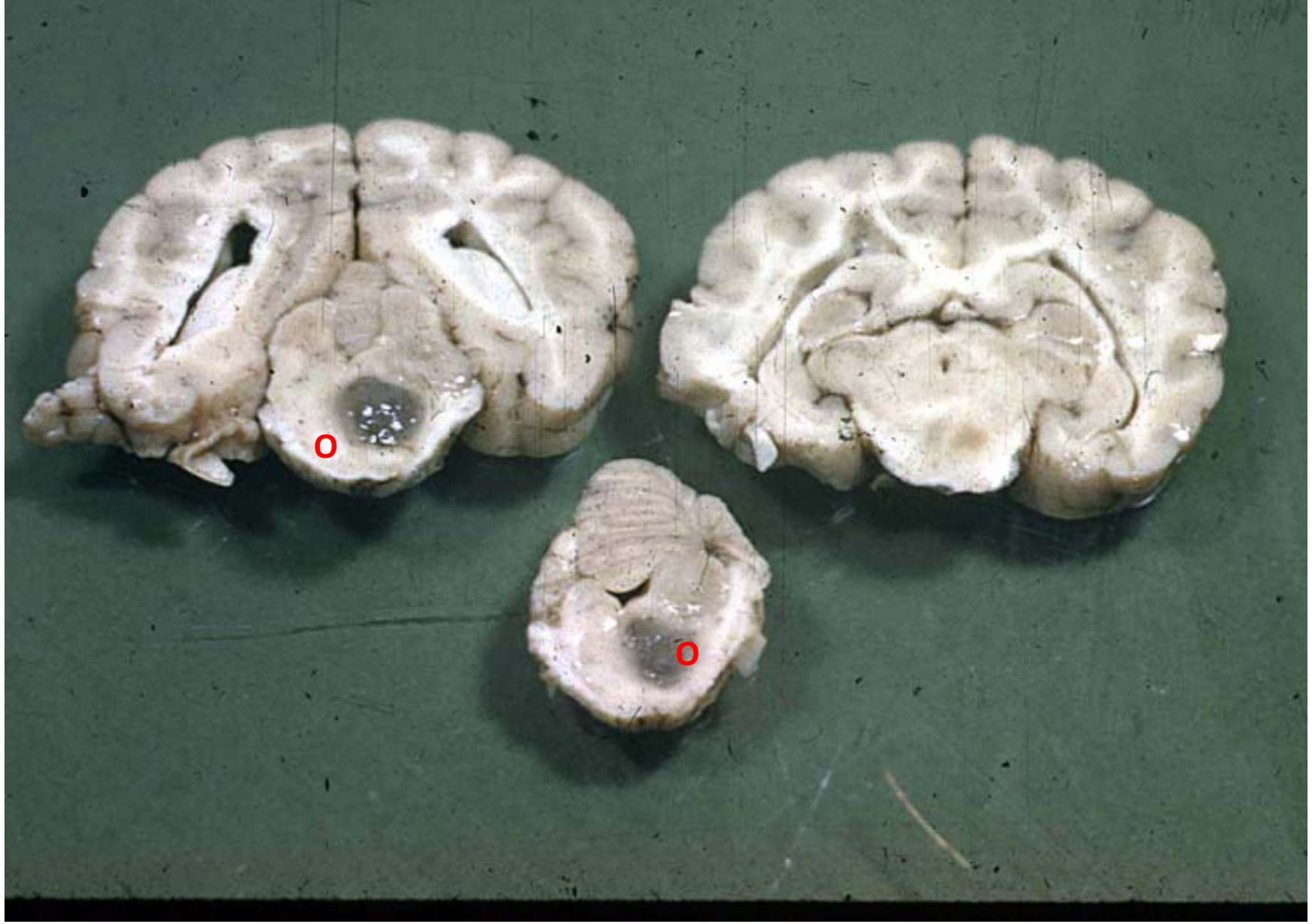
Oligodendroglioma

Diffusely infiltrating, low-grade glioma composed of neoplastic cells resembling oligodendrocytes

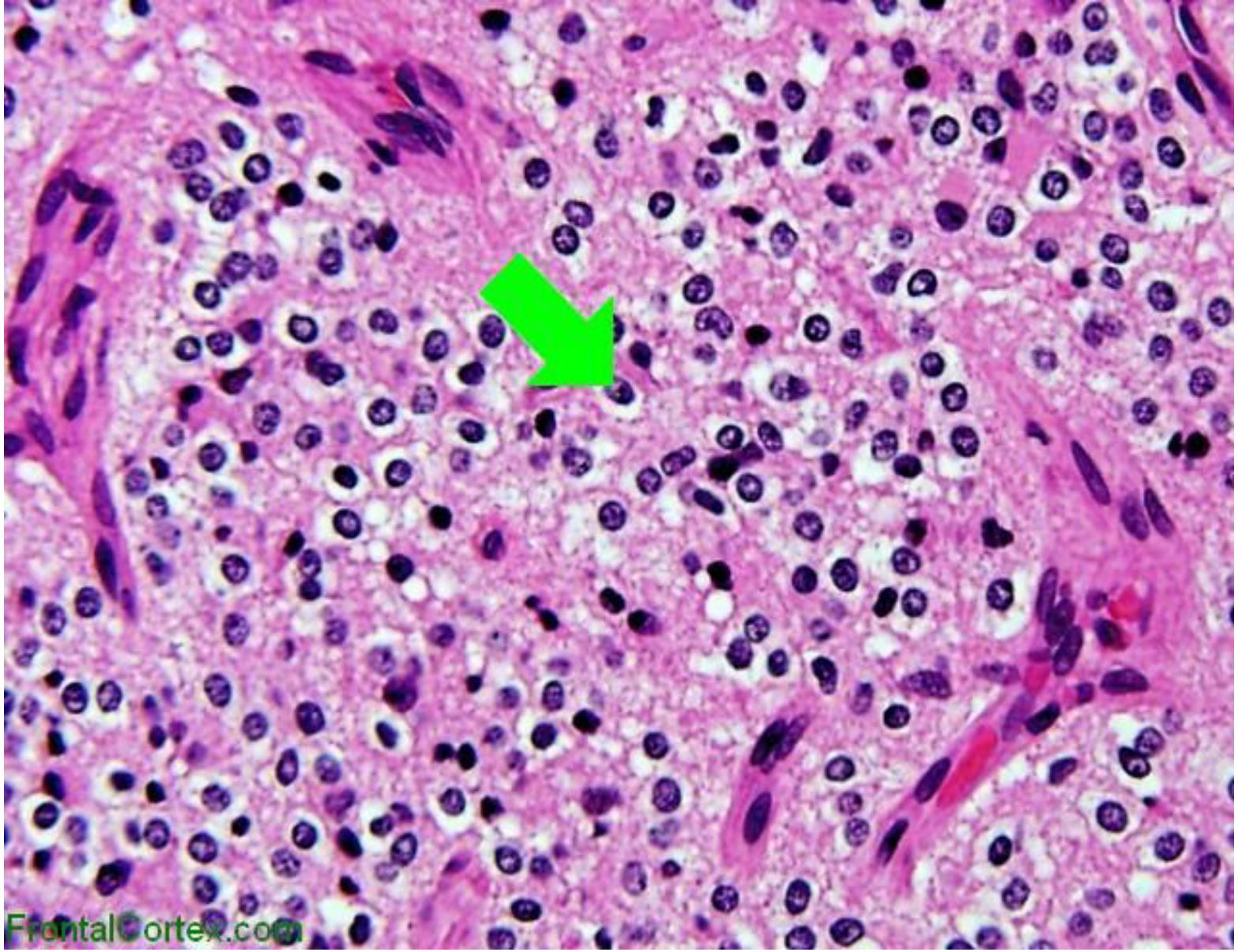
~2.5% of all brain tumours and 5% of all gliomas

Usually occur in adults with peak at 40-45 years of age

~75% present with seizures – also headache and other signs of increased ICP



Oligodendroglioma (O) – grey, glistening masses



Oligodendroglioma with small round hyperchromatic nuclei and a perinuclear clear halo (“fried egg” appearance)

Oligodendroglioma

Tumours often mineralised (calcified)

Most occur in cerebral hemispheres, especially frontal lobe, and involve cerebral cortex and subcortical WM

Monomorphic, diffusely infiltrating glioma with round to ovoid nuclei and a perinuclear halo ("fried egg appearance")

Slowly growing tumours corresponding to WHO grade II

Oligodendroglioma

IHC – Olig 1 and 2 are oligodendrocyte markers, but can also be expressed by other gliomas

Proliferation marker Ki-67 (MIB-1) has been used for grading and prognosis

Unknown whether these tumours arise from mature oligodendrocytes or progenitor cells

Molecular genetics – deletion of chromosome arms 1p and 19q is found in up to 80% of cases

Slow growing, with long post-operative survival, but most recur and malignant progression is not uncommon

Oligoastrocytoma

Diffusely infiltrating glioma composed of a mixture of oligodendroglioma and astrocytoma WHO grade II

These tumours either intermingled or occur as discrete masses

Previously thought to be “collision” tumours arising separately, but now believed to be monoclonal with phenotypic heterogeneity at the histological level

Ependymoma

Slowly growing glioma composed of neoplastic ependymal cells originating in ventricular walls or spinal canal

2 peaks of incidence – children <14 and adults 35-45

~60% occur in IV ventricle, leading to hydrocephalus and raised ICP, caused by obstruction of CSF outflow

Ependymoma

Cells resemble normal ependymal cells and hallmark histological feature is rosette formation around blood vessels – encircle vessels with processes projecting towards a centrally located blood vessel

WHO grade II

Generally relatively well-differentiated, with slow growth and little potential to invade

Complete resection often leads to long-term recurrence-free survival

Choroid plexus tumours

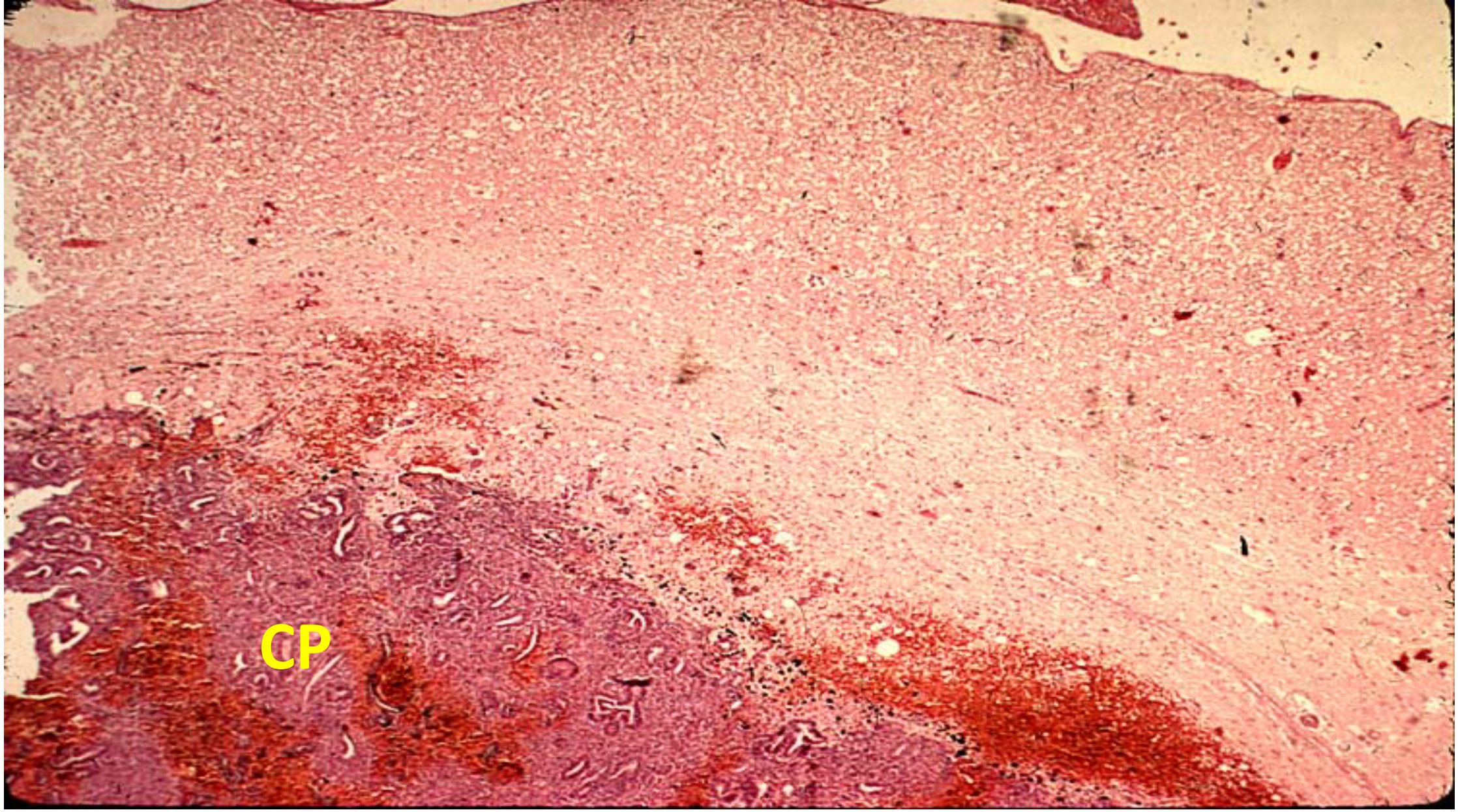
Rare, most occurring in childhood, especially in the first decade of life

Papillomas and carcinomas, the latter nearly always in lateral ventricles

Present with signs of obstructive hydrocephalus and raised ICP (headache, vomiting), exacerbated by CSF production by papillomas

Papilloma appears as a “cauliflower floret” and does not invade

Carcinomas fill the ventricle and invade the brain



Choroid plexus tumour (CP)

Embryonal tumours

~90% are medulloblastomas

Characterised by undifferentiated neuroepithelial cells

Classified as PNET (primitive neuroectodermal tumour) with capacity for neuronal and glial differentiation, perhaps sharing a common cell of origin from the subependymal matrix, but these tumours have distinct genetic abnormalities and show differential responses to treatment, suggesting the term PNET might eventually be replaced

Medulloblastoma

Most occur in childhood and account for >90% of embryonal tumours

Most occur between 3 and 10 years, with median age of 8 years

Preferentially affect males (M:F 1.6:1)

Favour the frontal lobes


MEDULLOBLASTOMA

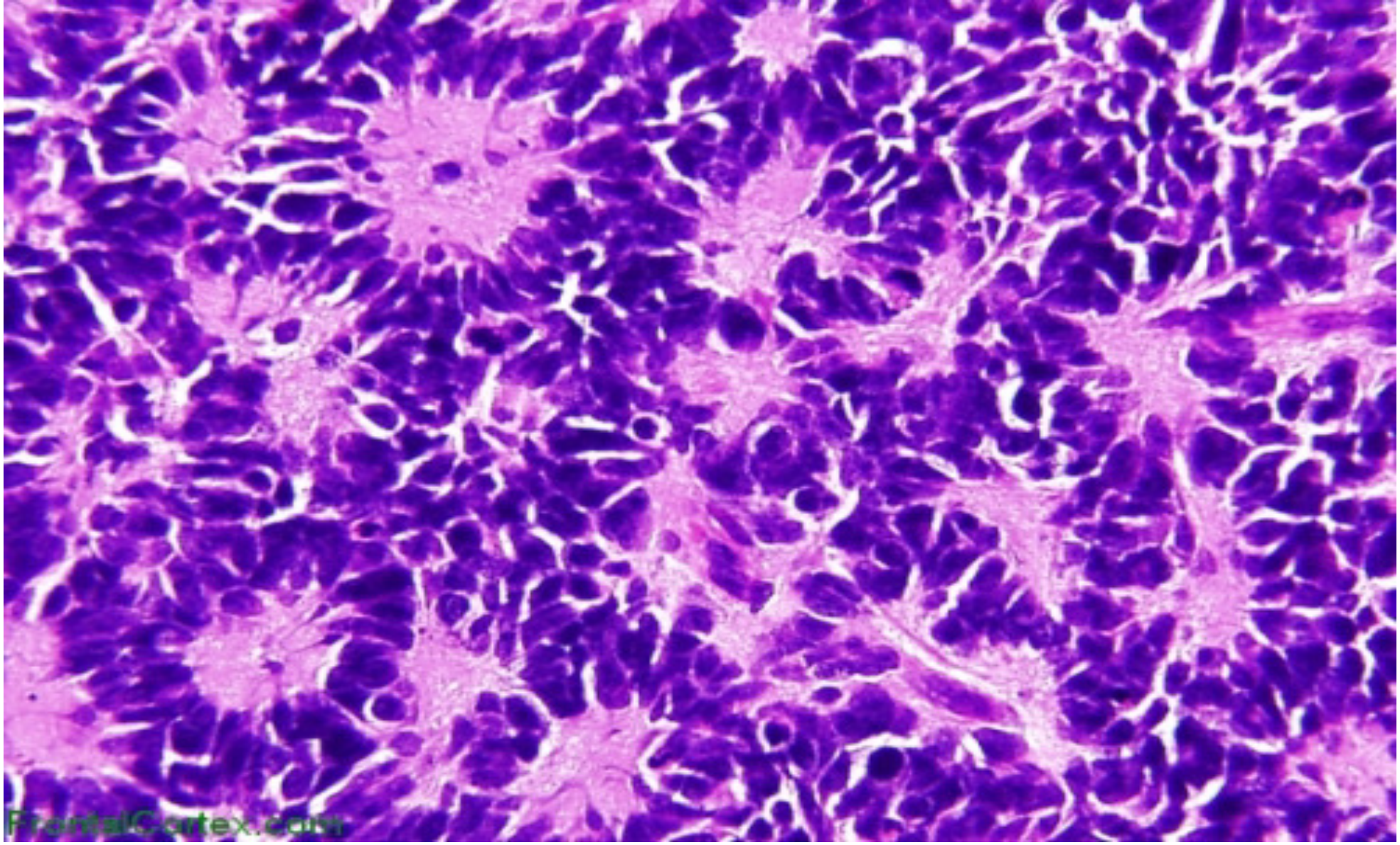
Medulloblastoma

In childhood, >75% occur in the midline (cerebellar vermis), occupying the IV ventricle, resulting in raised ICP as a result of acute obstructive hydrocephalus

Metastatic spread can occur within the neuraxis, but spread outside CNS is rare and usually late in the clinical course

Histologically, sheets of cells with round to ovoid, hyperchromatic nuclei and scant cytoplasm (high nucleus:cytoplasmic ratio), often found in rosettes

Arise from either subependymal matrix cells, external cerebellar granular layer, or both



Medulloblastoma with small round hyperchromatic nuclei arranged in a rosette pattern

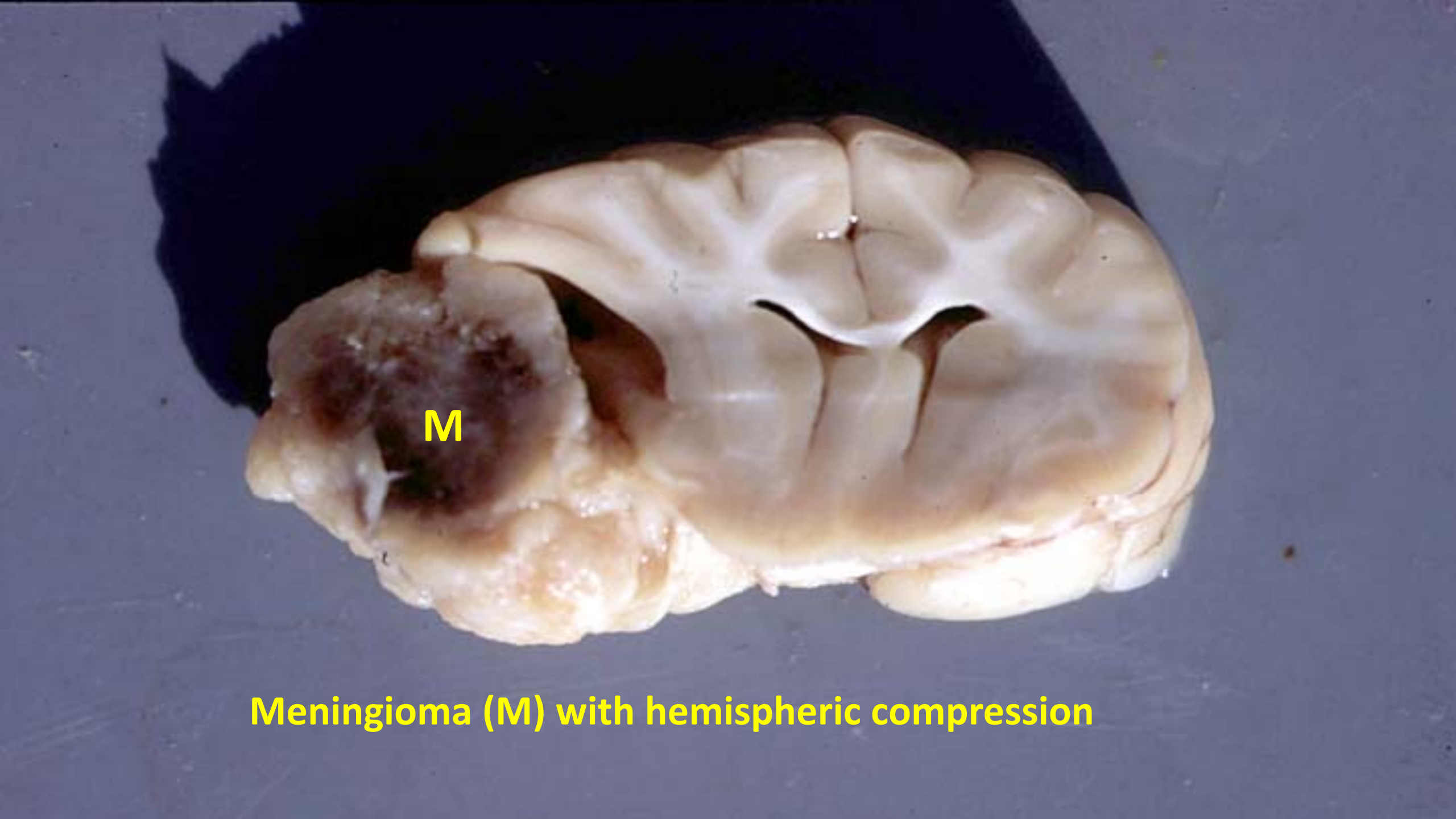
Meningiomas

Common and represent ~ 30% of all primary brain tumours

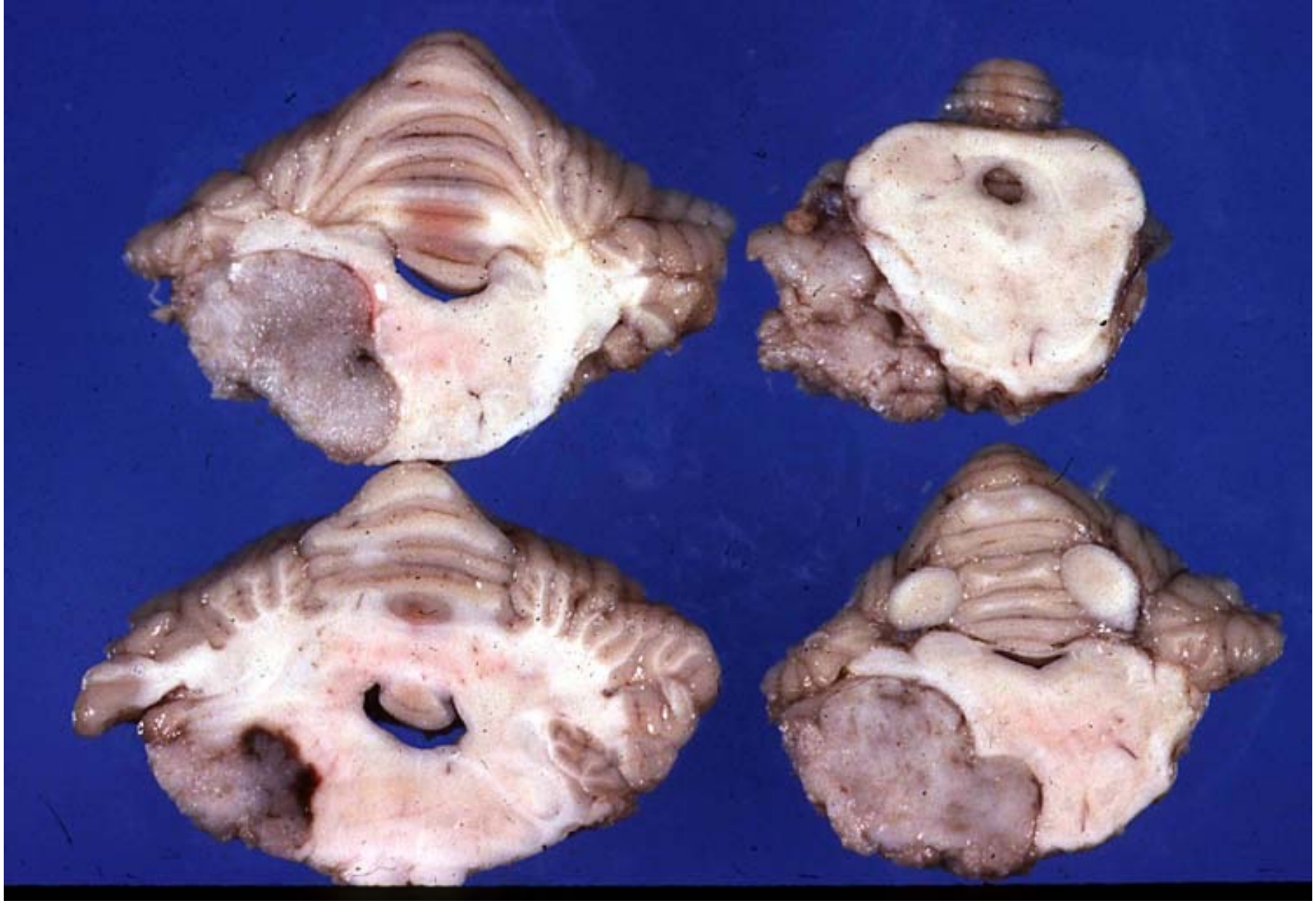
Peak at 60-70 years of age and females:males 2:1 (with involvement of female sex hormones a strong risk factor)

Occur anywhere along the neuraxis, and clinical signs thus variable and cause by mass effects

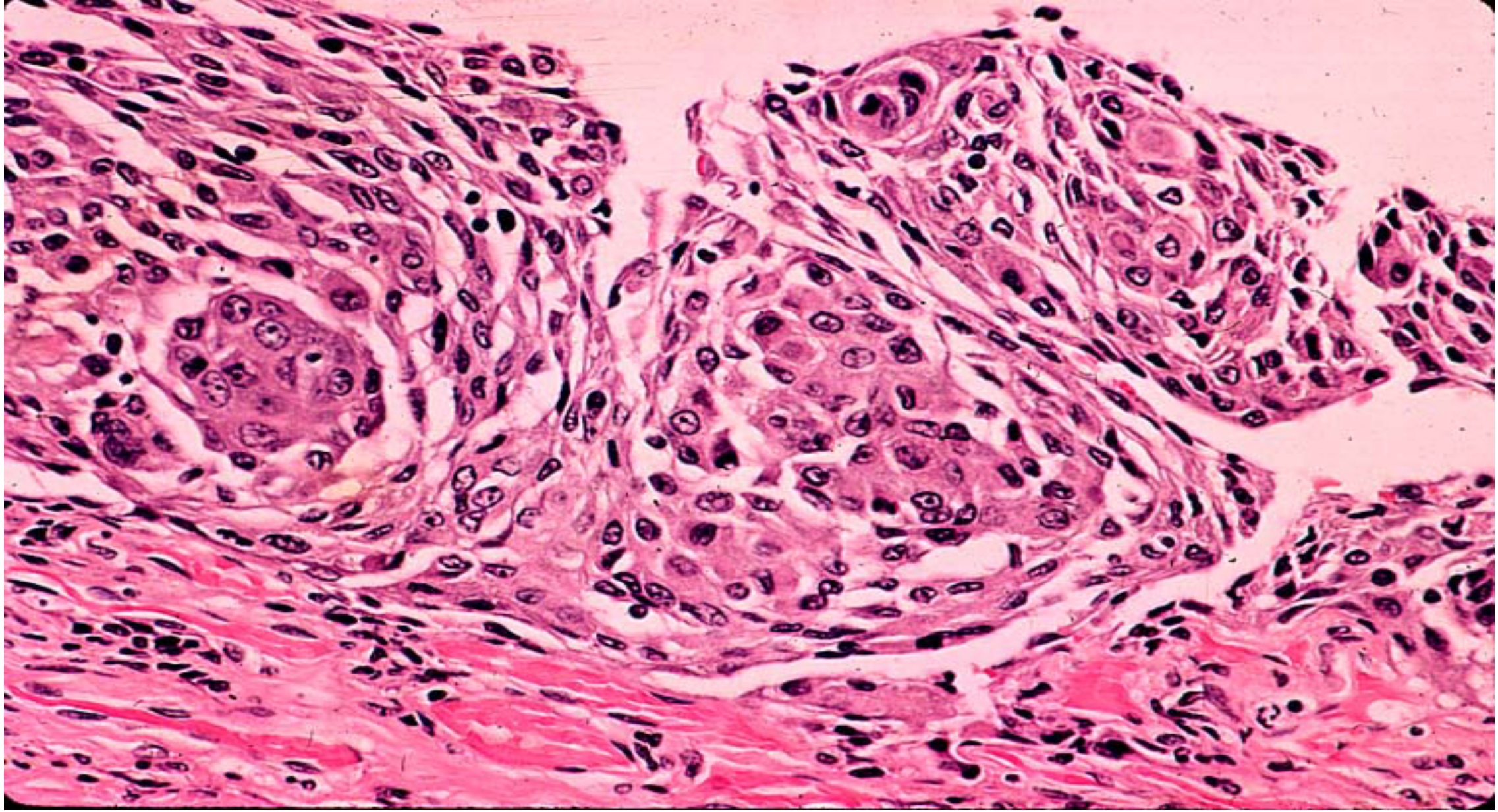
Commonly present when intracranial as headaches, seizures and personality changes + neurological deficits including hemiparesis, sensory deficits and ataxia, leg weakness and urinary incontinence



Meningioma (M) with hemispheric compression



MENINGIOMA



HISTOLOGICAL APPEARANCE OF A MENINGIOMA

Meningiomas

Spinal lesions compressing the cord may impede motor and sensory tracts

Peritumoural oedema can influence morbidity/mortality

Generally well-circumscribed, spherical growths, firmly attached to the dura – generally slow growing, compress adjacent cortex, and can be easily dissected away

***en plaque* meningiomas grow within and expand the dura in a diffuse manner and infiltrate adjacent bones**

Infiltration of the brain is relatively rare, but invasion of the dura, venous sinuses and bone is relatively common, even with benign tumours

Meningiomas

Show a large range of histological patterns and mixed patterns frequent

Most are benign and recurrence often influenced more by site and resectability than histological type

Histogenesis of meningiomas is controversial, but an origin from cell clusters capping the arachnoid villi is most likely source of meningothelial cells

Brain invasion (to be distinguished from extension along perivascular Virchow-Robin spaces) connotes a greater likelihood of recurrence

IHC supports dual a mesenchymal and epithelial-like nature of meningeal cells

Metastatic brain tumours

10 times more common than primary brain tumours

Typically occurs late in the clinical course, often when there are widespread systemic metastases

>2/3 of patients with cerebral metastases show neurological signs, including seizures, dementia, localised motor deficits, aphasia and headache

In ~50% of cases, may be primary or major contributor to death

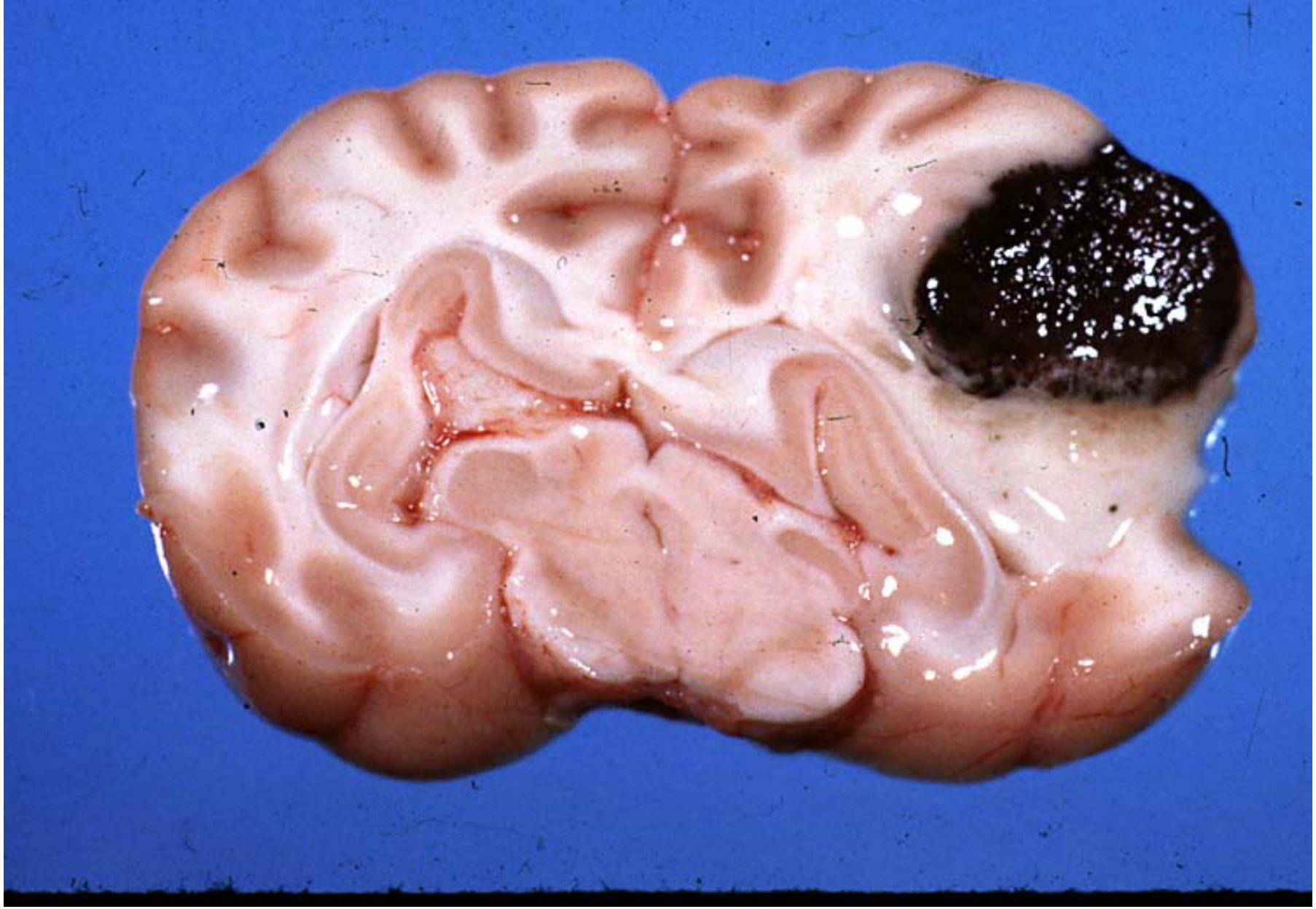
Metastatic brain tumours

~25% of patients with cancer have intracerebral metastases

Specific tumours have a predilection for brain (e.g. melanoma), whereas Hodgkin's lymphoma and carcinoma of prostate and ovary rarely metastasise to the CNS

Most common primary sites are lung (35-65%), breast (15-20%), skin (5-20%) and kidneys and colon (5-10%)

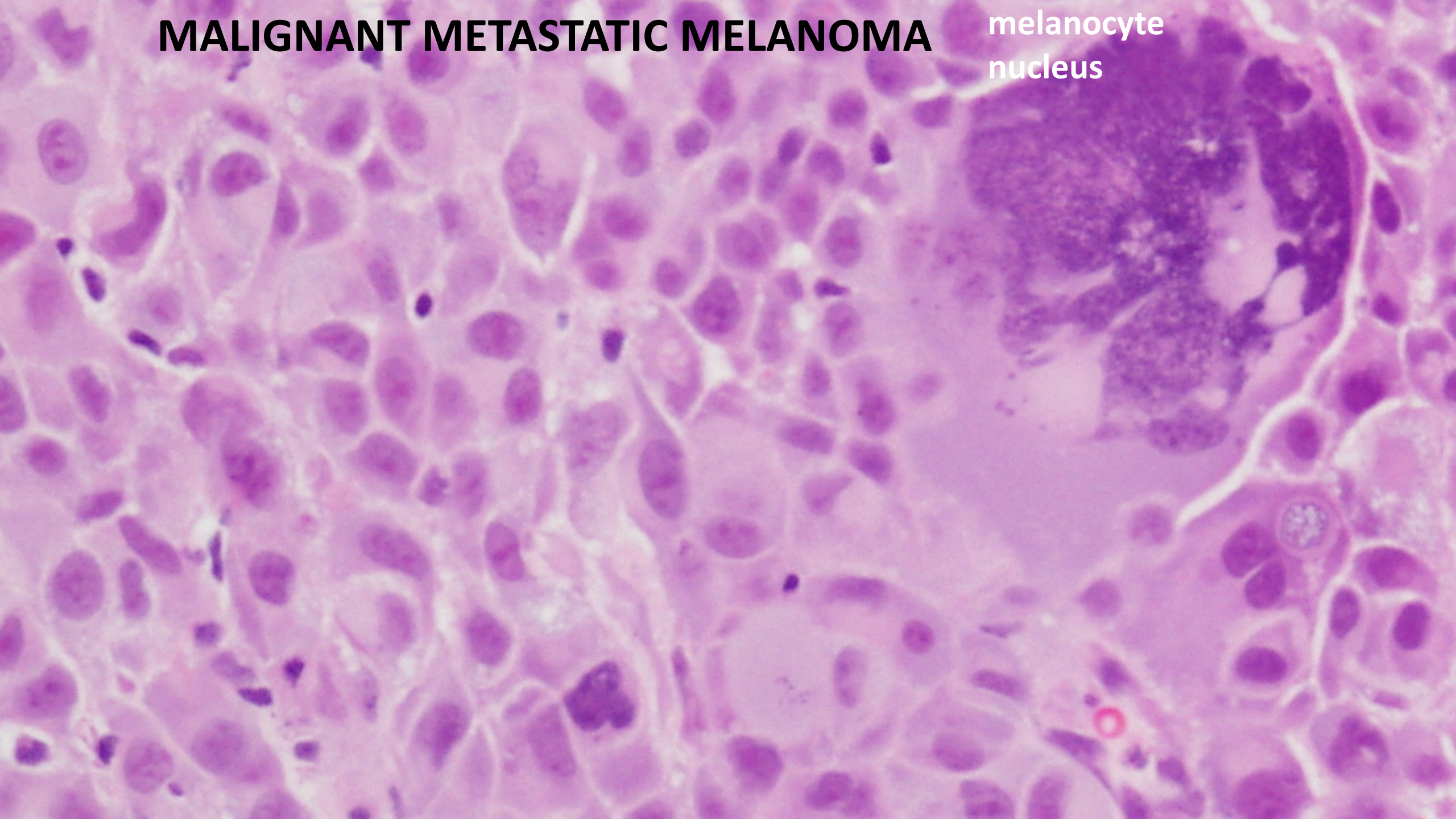
Metastases from an unknown site comprise 5-10%, but ~50% are eventually shown to arise from pulmonary carcinoma



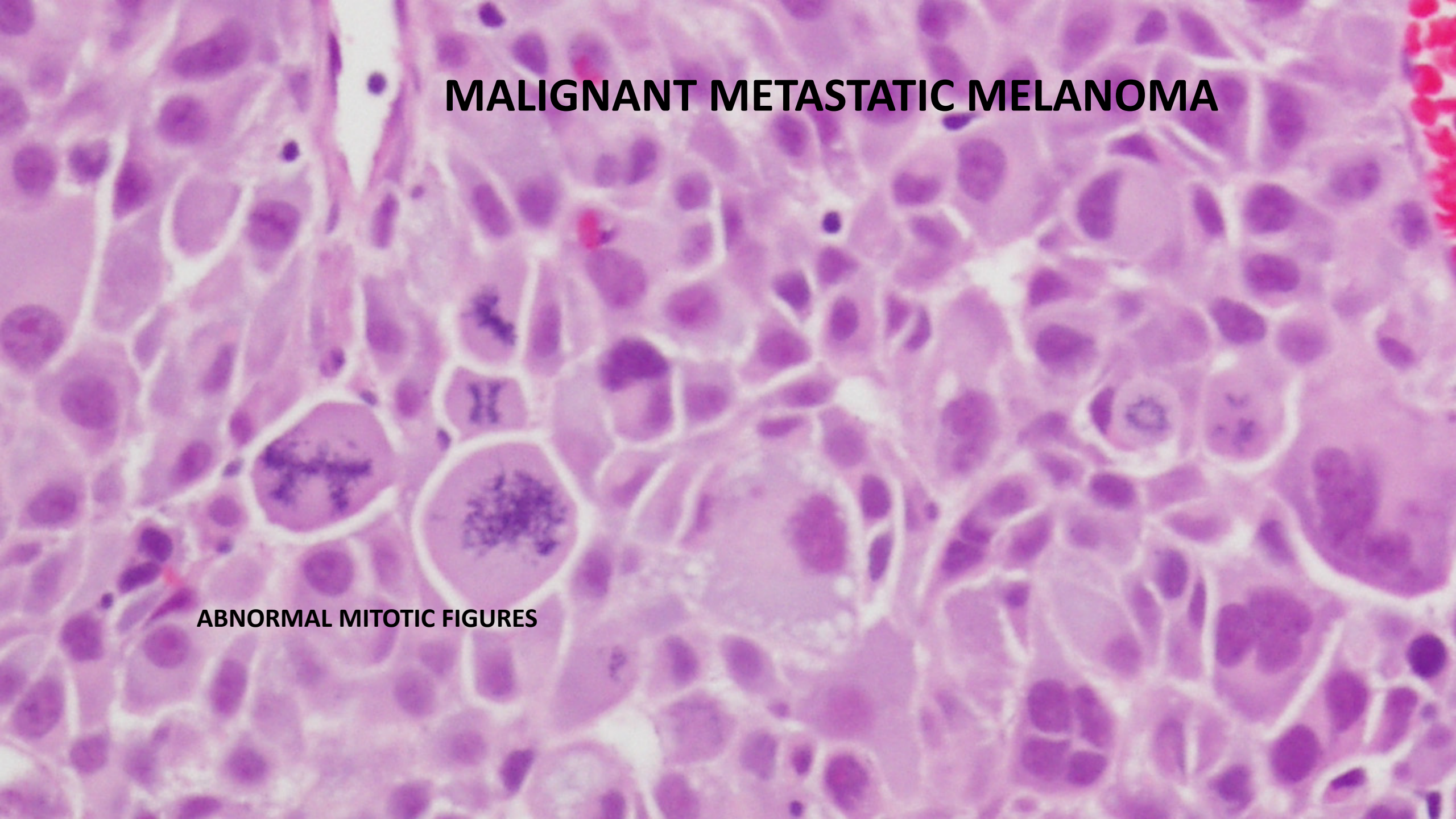
Metastatic pigmented melanoma. Note midline shift and distortion of the brain


Sheets of pleomorphic melanocytes in a melanoma metastatic to the brain
Binucleated melanocyte

MALIGNANT METASTATIC MELANOMA



MALIGNANT METASTATIC MELANOMA



ABNORMAL MITOTIC FIGURES

Metastatic brain tumours

Prognosis is poor (median survival < 1 year), which can sometimes be extended with surgical removal and radiation therapy

Most metastases are haematogenous and their distribution is proportional to the blood supply to the affected region

~80% occur in cerebral hemispheres (especially frontal and parietal lobes), 10-15% in cerebellum, and 2-3% in brainstem

Metastatic brain tumours

Metastases in spinal cord are rare, but secondary involvement from metastases in vertebral column are not uncommon

Less often, systemic tumours (especially breast and prostate) spread to the dura, sparing the brain parenchyma

~50-70% of patients have 1 or 2 metastases, but many patients have multiple metastases at autopsy

Melanoma and lung carcinoma more often have multiple metastases, whereas breast and GI tract carcinomas frequently present as a single mass

Metastatic brain tumours

Usually well-circumscribed, rounded masses that displace the surrounding brain parenchyma

Peritumoural oedema is often prominent and sometimes disproportionate to the size of metastases

Medium- and large-sized metastases often have a necrotic core

Melanomas and lung/renal carcinomas tend to have haemorrhagic metastases and present as intracranial haemorrhages

Histological features of metastatic tumours are usually similar to the primary neoplasm, but their may be less differentiation